so back in the days when I tried to do this -- I mean, the GI compartment volumes can vary widely. Yes, they can. So -- and -- less so than others. So back in my day when I did these types of simulations, I really could get whatever answers you wanted. And I did a lot of work to look up physiological volumes. And they are quite variable.

DR. YU: Well, I agree with you. They're quite variable. For example, in test averages, small intestine transit time is 199 minutes plus/minus 78 minutes. Indeed, they are very variable, but when we look at those datas, we should look at from population perspective, from average. And so, not one individual. Yeah, I agree with you. Individuals, they indeed vary quite a lot.

And we did indeed -- actually, Rob and many of our students indeed use the mathematical model which I, 10 years ago -- early days -- you know -- we do have a software, Gastro Polaris (?), we utilize them

in our simulations in our studies. So that's why you can see continual publication from us in modeling simulation.

And whether we use those modeling simulation become regulatory standards, I guess we have to further investigation, further considerations.

And particularly -- and I'm hesitant to say that the model I developed become standard. So what you company has to used, which probably is --

DR. MORRIS: You don't seem that hesitant to me.

Let's -- Jessie, you had a comment. And if possible, we need to wrap up on question 1 so we can finish question 2. So let's try to summarize after Jessie.

So please.

DR. AU: Jessie here. I want to respectfully disagree with you, Liz. Because those that do simulation in this setting knows that you fix your boundaries. So if you're in

the middle, you can change something. But you really can't change transit time. You may have plus or minus -- there's going to be plus or minus for your reference compound anyway.

So -- all right, so that's -- I think you can do it. It's doable.

We've done it, we use it to design clinical trials with it. So it can be done, yeah.

DR. MORRIS: And -- go ahead, Marv.

DR. MEYER: These questions are difficult, but I'm focusing, just as we should be, on locally acting drugs. My view is, I think to be locally acting somewhere along the line they have to go in solution. With exceptions of drugs like chlorestyramine, and sucralfate, which don't go in the solution. But there are alternate in vitro ways to look at chlorestyramine, and sucralfate we have to use clinical.

So and I'm thinking of, well, let's take three cases. No systemic availability

that's measurable. And no dissolution by any reasonable sense -- you know. Hydrochloric acid in a Waring blender is probably not a reasonable surrogate. I think, in that case, you have to do the clinical. I don't see a way around that.

If there's no systemic availability, and you believe that whatever drug it is has to be in solution to be -- to have a therapeutic effect, then I think there's a chance for us to -- with a reasonable panel of in vitro methods -- to have a dissolution test that will serve as a reasonable surrogate. And by reasonable panel, we may have to go to some of the ones Jim Polli put in his list. We may have to do 4 pHs, 2 apparatuses, 2 rotation speeds, et cetera. Because you might say, well, that's extreme.

But ask a firm whether they want to do a 600 patient clinical trial or 25 dissolution tests. I think -- you know,

which they'll pick. So I think dissolution will have a role in that -- role to play.

Now, in terms of if there is systemic availability, although low. And the numbers were 4 and 2. I think you could probably still get away using in vitro -- sorry. Using PK data. If there is a different scene. Now, that's probably difficult to achieve, but again compared to a 600 patient clinical trial, a 4 percent AUC versus a 2 percent AUC of absorbed dose might still be a reasonable thing to do. And if you have that systemic availability, then you can look at in vitro dissolution and you have something to correlate it with without just taking on faith that drug must be in solution and therefore dissolution's going to be okay. So that's kind of the way I like to look at it.

DR. MORRIS: That's a nice summary as well. Well, if we could, could we -- let me try to summarize our question 1 consensus -- that

may be a densification of what we have here. But let's try and then we can modify it and then move on to question 2.

So basically if we start from the premise on both questions that we're starting with -- now, I'm talking about the process itself. Dissolution -- and normally we would go through absorption then it would go to the site of action. Systemically, here we're taking out the compartment in the center, as Liz says, although there still has to be absorption at the site. So with that as our backdrop, the consensus, I think, is that biorelevant dissolution in certain cases would be subcategorized, as Marv was just saying.

But might well take on a different scope than dissolution as we do it today in the sense that it might be a panel of biorelevant dissolutions, dissolution media, and -- which somebody would have to develop or at least adopt in conjunction with

external advice and sources.

That the combination of this with simulations of one variety -- whether these are true constitutive relationships or simulations that come from more statistically based modeling or other types of model would be the ultimate goal. If you could then draw correlation that way, supported by the physical data, and that if we categorize it a little further, as Marv was just saying, that obviously if it's no dissolution then it's no dissolution and if that's your first criteria, your first constraint, you can't -- there's no other constraints. That's it. So you have to find another way and that's probably clinical.

In the other cases where it's dissolution, well, you got dissolution but with limited systemic -- or, no systemic involvement -- then dissolution is the proper mech. And then it would fall back to our panel of -- our new panel of biorelevant

dissolution. And there'd probably have to be a new division in FDA, so biorelevant dissolution.

And finally, if there is systemic absorption yet it still is locally acting, that a combination of PK with the advanced or, let's say, amplified dissolution scenario would be the consensus of the panel.

Are there any other comments anybody would like to make before we go to question 2? Yes, please, Art.

DR. KIBBE: I think we've taken care of question 2.

DR. MORRIS: I think we -- pretty close. But let --

DR. KIBBE: If we look at a holistic answer to the issues that they're looking at, you use PK when you have systemic absorption and you're wanting to see if the different dosage forms are giving you higher systemic --

DR. MORRIS: Right, actually -- yeah. And actually, if we can come back -- if we can

go to question 2 and then have you just start with that point, just so we get it on the record in that direction. Because that's exactly where we should start. I think you're right, yeah.

So if we can go to question -- so, question 2 is, what role should systemic pharmacokinetics play in developing BE recommendations for low solubility locally acting drugs that treat GI conditions?

And Art, would you mind sort of starting that? Because I think that's a good place to start.

DR. KIBBE: For me, PK in this situation is since it's after the fact as it were in terms of where the drug is acting, is really a measure -- am I not close enough?

DR. MORRIS: Move closer to your mike. Yeah.

DR. KIBBE: I'm sorry.

I'm not as tall as Marv, I can't reach it. I'm vertically challenged.

(Laughter)

DR. MEYER: You can sit on my lap.

DR. KIBBE: Thank you, that's good. It is, for me, a safety answer. At the back end, you say to yourself, are these two dosage forms giving rise to the same amount of drug getting in systemically. And if -- and I think we have to be careful. If you go from 2 percent to 4 percent, that's a doubling but that's not significant, okay?

I mean, unless there is some clinical reason to think that there's a threshold of 3 percent that therefore now gives you all sorts of toxic, that's not what you're looking for. What you're looking for is some dramatic change which would affect not only how much is systemically and therefore might give toxicity, but how much is lost from the site of action that should have been there. Okay?

And I think when we start talking about modeling -- and Lawrence's model system is very good and I'm sure Jessie has some

things that she could tell him that would improve it, and we'd have a really good model. But if you look at modeling and you can take that into a play -- into account with the PK numbers in the model and get a real good understanding of what's at the site or at the biophase over a period of time, I think you're way ahead of the game.

DR. MORRIS: Other? Yeah, I think that's spot on. I sort of had couched what we had said in terms of dividing it into safety issues versus performance issues. And in terms of safety issues, the reason in fact that in new drug development, the companies do so many BE studies. I can't remember what the average is, but it's way higher than you would think. It's like 8 or 12 or something like that.

DR. YU: I think it's -- on the average, is six.

DR. MORRIS: Six, yeah, that's -- that would be low from my experience. But, yeah. You have more -- But that's the number they turn

in, yeah. We won't go there. But at any rate.

But the reason that you do that along the way is that they want to be sure that the formulation changes that are made, in fact, don't affect safety negatively.

So in that sense, changes in excipients that might -- whether or not these excipients are actually activating transporters or changing membrane permeability, whatever it is, it should be manifest in the PK. And that's the safety issue. I fully agree.

But for performance, as we were discussing earlier, as Liz said, since the site of action doesn't depend on being systemically absorbed, then by definition the PK studies would be of limited use other than -- yeah, go ahead.

DR. KIBBE: I'm sure you were going to go there, but except for the fact that a high absorption relative would draw down from the site of use and shorten the duration --

DR. MORRIS: No, right --

DR. KIBBE: Of effect --

DR. MORRIS: Right. Except for the fact that you want the drug to get -- you can't sink the putt if it doesn't get to the hole, is the scientific analogy, I think. Yeah.

And then finally, I guess if I'm catching everything and not necessarily in succession but completely is, to Marv's point, is that when there is a systemic absorption that does correlate to the site of action locally, then that might be of use to do a PK study. Is that your point, Marv?

DR. MEYER: I can't deny that, but my question is how are you going to correlate the systemic availability with the arrival of the site of action? So I don't think you'll ever --

DR. MORRIS: Right. Presumably --

DR. MEYER: Know that.

DR. MORRIS: That would be a clinical -- you know, determination. You know, somehow -- you know, to use an unfortunate

analogy -- you know, when it used to be that you would count the number of legs in the air and divide by four? You know, I mean, so there's got to be some assay for response to whatever the disease you're treating is, I'm assuming. So I'm assuming that that would be a clinical determination. Not a routine determination.

DR. MEYER: I mean, the fundamental question to me is, if I do a PK study and I -- albeit of small values of systemic availability -- and I use those numbers, to what extent am I missing the boat? Am I coming up with the wrong answer, that one formulation that's actually better than another gives a lower systemic availability. I don't have the answer to that, but if it -- if that's true, then the systemic availability of a poorly systemically available drug product doesn't work very well.

DR. MORRIS: No, that's right. Yeah. I was thinking the other direction, but yeah.

So yes, Liz?

DR. TOPP: I just have a question. So if really systemic absorption of locally acting drugs is sort of a side effect compartment, do we want to do complete PK just because we can? Or would it be sufficient to say, let's check -- spot check some time points to demonstrate that the innovator and the generic product really have identical absorption and that we really don't care if we have enough data to do full AUC elimination rate constant, absorption rate constant, whatever PK analysis.

I mean, would it -- so that's a question, that's not an answer. I mean, do we do complete PK just because we can, or do you say, no, in this case a complete PK profile isn't even relevant.

DR. MORRIS: Yeah. Maybe. Can we get a comment from Lawrence or Gary?

DR. YU: Well, actually, Gary and I were discussing. It's -- when you -- I'm not trying to -- we're seeking advice at this meeting for poly soluble drugs. So we're

probably not defending what we're going to do or not.

One of the key issues, what does a PK use -- you know, based on Jessie's talk and Liz, your talk at the beginning, you do want the sandwich (?) in terms of what's happening. And with dissolution and the pharmacokinetics. We want the simulation. If you don't want to do simulation, and then I from, as a scientist, you have to have a completed PK profile because otherwise you do not know what to do your simulation for.

And then, certainly, for safety reasons even -- hypothetically, it's for us to say, for example, you get a 2 percent absorbed or 3 percent absorbed, when you look at a 2 percent absorbed versus 4 percent absorbed, even though difference is a percent, not much. But in reality are -- is that you do not know what percentage get absorbed. Because those poly soluble drugs usually do not have absolute viable data

available. So therefore, you're really don't have a -- I'm not saying you always, but many cases you do not really have an idea what percentage get absorbed. And does this scenario, seems to me, you may want to go to the regular PK.

DR. M. MORRIS: Marilyn Morris.

DR. MORRIS: Marilyn, then Marv.

DR. M. MORRIS: Okay, sorry. So in thinking about this, then, what if we don't -- we're not able to detect drug in plasma. So then we have only dissolution data and it may be similar. And similar in some aspects, maybe not similar in all aspects. Where do we go then? Maybe that's the point where we have to consider doing a efficacy study, a PD -- some PD endpoint study.

DR. MORRIS: Marv?

DR. MEYER: I just want to talk about 2 percent, 4 percent briefly. If we assume that in the site of action, one formulation has 4 percent of the drug released in solution and

another formulation has 2 percent released, and the other 96 or 98 exits in the feces, is it still not relevant to be looking at 2 percent and 4 percent resulting blood levels?

DR. MORRIS: Anybody want to comment? Gary, you want to?

DR. BUEHLER: I'll take a shot. Gary Buehler. No, this is -- this is what Lawrence and I were discussing. I mean, if we're going to ask for PK, usually in the Office of Generic Drugs we're going to apply bioequivalence standards to the PK. So the 2 percent 4 percent question would be an issue for us.

If we're looking at very, very, very small amounts absorbed and we know that the drug has very, very, very small amounts and we're concerned about some small differences -- you know, then we can possibly look at it for safety.

But if we're looking at measurable amounts where we can apply bioequivalence criteria, we probably will. Especially if we

can use those criteria in combination with some dissolution information and make a decision on bioequivalence in that way. Kind of using the --

DR. MORRIS: And I -- oh, sorry --

DR. BUEHLER: Subtraction method.

DR. MORRIS: No, and I think that actually -- or maybe you were going to say the same thing I was, probably. Because I was going to say, you're -- that really speaks to Art's point. I think what we -- what the consensus was -- stop me if I misquote you, but the consensus sort of was that if there was no absorption then -- you know, why bother.

If there is absorption, for the reasons of safety, of course, but also for the reasons that the availability might be affected by prior absorption, it would still be prudent to do PK study on it. Is that what you --

DR. KIBBE: Art Kibbe. That -- I agree with you, that's exactly my point. And

we've seen drugs where their window of absorption is higher up in the GI tract and their affect is locally lower in the GI tract. And depending on the formulation, if it releases sooner or later, they could change the amount of drug available during the absorption window and that would affect the load of the dose that actually got to the fluid in front of the biophase. That's what I was -- that's the second part of what I was concerned about.

I think that if the drug has no measurable absorption from the GI tract, dissolution is the thing that we should use and the pH profiles, dissolution or -- is enough to assure us that there is a sufficient load of drug in solution in front of the tissue it's supposed to affect. And then we're done in terms of the dosage form delivering the therapy.

DR. WEBBER: Just to clarify, are you comfortable with a zero tolerance on -- this is Keith Webber, yeah -- a zero tolerance on

absorption for making that decision? I mean, like, zero absorption?

DR. KIBBE: I'm comfortable with measurable.

DR. BUEHLER: Well, and especially if you're not concerned about the toxicity of the active ingredient. If -- you know, you have other data in hand that show you that very little amounts of this drug won't hurt you.

DR. KIBBE: Sure.

DR. MORRIS: Okay, any other comments before I try to corral this? So -- yeah.

If not, it seemed to me that our consensus, again, is very consistent with what we discussed before. But that if the compound has absorption -- significant absorption and that level can be something that we'll leave to further discussion, but obviously considerations of toxicity would certainly enter into it. Then, from the standpoint of presenting the material to the -- the same amount of material to the

site of action in the GI tract would dictate that PK study would be advisable.

If there's not measurable absorption, however, there's no real logic that would teach us to do a PK study. With the exception of the -- of a change in formulation that would include something that was known or suspected to be an absorption enhancer.

And I think that's really all I had in terms of the general consensus. Did I miss anything? Anybody would like to add to that? Of course, we like to model.

Carol, yeah.

DR. GLOFF: Yeah, you didn't miss anything from my point of view, but I'd like to add one thing looking forward.

DR. MORRIS: Sure.

DR. GLOFF: I think we're in the right place right now with the information that we have available. I think as additional information on biorelevant, dissolution media,

et cetera and additional data become available, we may be able to move more toward more circumstances where we would just need the dissolution data.

But for right now, I second, third, fourth, whatever the question about, if it's measurable, should -- in the bloodstream -- should we also be looking for if the concentration in the bloodstream is changing. Not only from a safety perspective but also, although it's more theoretical in my mind, from an efficacy perspective as well. For the local concentrations.

DR. MORRIS: Yeah. No, actually that's a really good point. Obviously, the whole -- we're talking about biorelevant dissolution media and panels as if we can go order them from -- you know, someplace and we can't right now.

So but with that, is that it? Do I have to read something? Ah, yes. Oh, the next item on the agenda is lunch. So we will

now break for lunch. We will reconvene again, in this room, in one hour from now at 1:43 p.m.

Please take any personal belongings you may want with you at this time. The room will be secured by FDA staff during the lunch break. I don't think they're armed. You will not be allowed back into the room until we reconvene.

So thank you.

(Whereupon, at approximately 12:31 p.m., a luncheon recess was taken.)

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

(1:37 p.m.)

DR. MORRIS: So if we could reconvene, please. A short announcement with respect to the travel arrangements of the committee -- we have and update at 3:00, at the break. People are madly working on it as we speak.

Is that okay? I think your car is being towed, Art.

DR. KIBBIE: If it is, you're buying me a new one.

DR. MORRIS: Well, there you go, so. So we should -- we can reconvene. We're going to begin with the open public hearing and we're going to hear from Paul Dorinsky, who's an M.D., the VP of Global Respiratory Clinical Research at the Pulmonary division of TEVA.

And, Dr. Dorinsky, if you can bear with me one minute, I just have to read this opening statement. You can stand, though, it's okay. Nice suit.

So 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. Our goal in 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, 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're 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 topics during breaks or lunch. Thank you.

And with that, if Dr. Dorinsky can begin?

DR. DORINSKY: Thank you very much.

I'll go ahead and move to the regular way -- there we go. Thank you very much. I'll start this again.

Just by way of brief introductory comments. Inhaled corticosteroid containing products are quite voluminous: An estimated $31 million prescriptions per year, accounting for approximately $7 billion annually. And therefore, we agree and think it's very important that guidelines be established for generic drugs that are clinically and scientifically robust, but also achievable in the clinic.

Just briefly, I'm going to spend a moment or two just setting the stage as far as background, that I'm going to briefly

overview. Some of the dose response data that is available in the literature from inhaled corticosteroid use. The implications that that flat dose response actually has for evaluating inhaled corticosteroid bioequivalents, and then suggest an alternate proposal for evaluating bioequivalents of steroids.

In general, the approach has been based on a test dose of drug -- that two different dose levels -- with the reference dose of the same drug, by comparison. With the attempt being to establish dose response using, in general, Finney bioassay. It's important to recognize -- and we recognize that this is -- the study's done in this way. You have internal study validity and that the dose response itself establishes assay sensitivity, and also, unequivocally establishes the dose relationship between the test and the reference drug.

However, it's important to

recognize that most of the steroids available on the market have had dose ranging studies in which they've generally been conducted in distinct populations with a small range of steroids, rather than single population receiving the entire range of steroids. So it is dose-response, but in a somewhat limited way. And it has also been shown that even the lowest dose of inhaled corticosteroids have very significant efficacy that's near the maximal effect of the drug.

This was first pointed out, or well pointed out, in a study by Szefler, and all of the mice study in which Beclamethasone (?) and Fluticasone were evaluated at a variety of doses that you see. And one of the things that was established in that was that the near maximal efficacy with a variety of endpoints, including FEV1 and PC20, occurred at very low doses. And that nearly 80 percent of the effect occurred at the

lowest dose.

The highest dose did not significantly increase the efficacy for these and other parameters across the range of doses that were studied. And the dose response seen in these studies was extremely shallow.

There have been numerous studies done, and I'm not going to get through all of them and only show this to point out a few things, looking at various steroids, various sample sizes ranging from 6 to 10, to as many as 250 patients per arm. (inaudible) cross a variety of endpoints from A&P challenge to CL nitric oxide, FEV1, allergen challenge, late phase response, and oral corticosteroid.

And one of the themes that emerged from most of these studies, when looking at actual dose responses in these studies, several of which were crossover studies, was that the dose response, when it was established, was actually very small in terms

of actual clinical differences between the dose. Again, establishing the dose response was quite flat.

And for many endpoints, that are listed over here, for example, Sputum Eo measurements of lung function. FEV1 in this study, Allergen Challenge, and oral steroids sparing. There was no dose response noted at all, in the course of these studies.

There have been several studies that have been done where a dose response was observed. Probably the one that was most prominently noted was the study by Busse, et al, in a group of patients evaluating CFC and HFA BDP at cross doses from 100 to 800 micrograms per day. And this did in fact establish a dose potency ratio between the lowest and the highest dose.

It was significant only between the lowest dose and the highest dose, an eight-fold difference. And when looking at end doses in between the highest and lowest

dose, for adjacent doses, I guess, the actual differences were small.

Romain Pauwels, a number of years ago, did a year-long exacerbation study in patients with asthma, comparing 200 and 800 micrograms a day of Budecimide (?) with Formoterol. And the primary outcome of that study was exacerbations. They did establish that there was a significant dose response between the highest and lowest dose of steroid, with or without the addition of beta antagonist Formoterol in the study.

But, again, it was a very large study -- approximately 1000 patients -- and was a year-long study looking at exacerbation rate. And there was no dose response established for FEV1, symptoms of Albuterol use.

Eric Bateman et al. a number of years ago, published the results of the gold study, which was, again, a very large study with a fairly complex design over a period of

a year in which patients were escalated to sequential doses of either Fluticasone alone or Fluticasone plus Salmeterol. After a period of 12 weeks, and over the last 8 weeks or each treatment period, asthma control algorithm based on peak flow symptoms, nighttime awakenings, and rescue Albuterol use was evaluated.

There were improvements in both treatment groups with or without Salmeterol, being greater in the Salmeterol plus Fluticasone, group. However, all the dose response was observed, between sequential doses, was relatively small or was small, especially at the top end of the dose range. And there were a significant number of patients that remain on control at the end of the study, indicating that regardless of what was done, there was going to be no additional response to treatment.

So to just briefly summarize this point, although some of the studies were able

to discriminate between ICS dose levels, no design, and in particular no endpoint, has been able to reproducibly be used for establishing ICS dose response. And even when those studies that did evaluate -- were able to demonstrate a dose response, oftentimes the magnitude of response was quite small and the differences, though statistically significant, were clinically quite small.

Now, just to turn it for the last couple of minutes, there is an implication in terms of assessing bioequivalence, using the Finney bioassay, for example, based solely on the fact that the slope of dose response is shallow. This is just a hypothetical drawing showing two different levels of dose response. One that's approximately .45 and one that's substantially less than that. And these are the 90 percent confidence intervals around that. As the dose response flattens by just pure mathematics, the slope of the

dose response will be associated with a larger confidence interval.

Given the fact that the confidence interval that's generally accepted for bioequivalence is .08 to 1.25. It has very significant implications for powering of studies, which has shown, again, hypothetically, on this slide. This is a series of power calculations where sample size is on the X-axis, power on the Y. Based on the established dose response slope -- and this could be for whatever endpoint is used. And what is hopefully clear from this is that this is a dose response slope of .06, and this is a dose response slope of 1.0.

Even at the highest dose response level, in order to get 80 percent power in a confidence interval of .08 to 1.25, assuming a constant level of intrasubject variability a sample size of approximately 175 patients is needed. With a dose response of .06, again same intrasubject variability

assumptions, in order to achieve a confidence range of .08 to 1.25, approximately 500 patients are needed.

To put this a bit more into perspective, dose response slope, for example, in the mice study for BDP, and for FPs in Methacholine response, was quite a bit less than this. Values of .18, and .07, respectively.

So because of this and because the dose response is flat. Because it would be extremely difficult to do studies and achieve the very tight confidence intervals, we propose a somewhat different way or an alternate way of evaluating bioequivalence. Trying to retain two key features, namely the ability to have assay sensitivity in the study itself and to definitively establish the relationship between a test and reference drug, while providing an adequate assessment of safety and efficacy in the relevant patient populations.

So specifically, once the in vitro characteristics have been established for 505(j) products, we propose that this be composed of three parts: Clinical pharmacology study, crossover study in healthy volunteers of patients for each dose in order to establish an equivalence for AUC and Cmax, with this traditional 90 percent confidence interval limits of .08 to 1.25.

Instead of relative dose response efficacy, we would propose that randomized parallel group studies of 12 weeks or longer be proposed. One study for strength, with the inclusion of either a placebo comparator, or an active comparator to establish assay sensitivity within the study. And then, in order to establish the relationship between the test and reference ICS, to have it powered for non-inferiority with appropriate assessment of safety and adverse events.

And I know I've run out of time, so I think with that, I'll stop.

DR. MORRIS: Thank you. And, Ken, are there any questions? Clarifications, for our speaker?

I have just one brief one -- Ken Morris. I couldn't quite tell from the table, there were a lot of data there. Does the -- is FEV the only endpoint that was used, or, I mean, was spirometry used in any of that stuff?

DR. DORINSKY: FEV1 was used -- well, some of them are derived from FEV1, like late-phase response, which was FEV1 based measure. A&P challenge with doubling doses was used for the -- not to call it an A&P challenge -- and in several of the others, exacerbation rate and this complex definition of asthma control. Some of which, of course, include -- not the exacerbation, but some of which, of course, include measures of lung function, as well. ENO was also evaluated in a variety of (inaudible).

DR. MORRIS: Thank you. Any other

questions? If not, thank you very much.

Where's my script? So that concludes the open public hearing, and 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, the Advisory Committee FDA believes that it is important to understand the context and this is -- I read the wrong one at the beginning. I read the wrong one before, so we have to start the meeting over.

So Lead in Pharmaceuticals, I think, is the -- yeah, at the conclusion. 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 return its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

Thank you.

So with that we move on to the second topic of the day. This is Drug Classification of Orally Disintegrating Tablets, or ODTs. And we are going to start with Frank Holcombe's presentation. He's the associate director for chemistry of OGD. And with that, I'll turn it over to you, Frank.

DR. HOLCOMBE: Okay, thank you. Thank you all for coming here to listen to this and to potentially help us in trying to decide how to provide guidance for this particular class of products.

The issue here is that we've had orally disintegrating tablets as a distinct dosage form for approximately 12 or 13 years now. And the dosage form includes an expected functionality, but he definition is fairly general, so there are questions that remain about the extent and the scope of products falling into the dosage form.

The development of guidance is

important for characterization and evaluation. In evaluation because the review staff has to decide whether or not it's the right dosage form and whether or not it meets the -- what we expect from that dosage form. However, because of the general nature of the definition -- because of some level of disagreement about its particular characteristics, we've had difficulty in coming up with what we considered to be an appropriate guidance -- or appropriate guidance, both for industry and for ourselves.

A little bit of history. Well, more than a little bit of history because there's several people on this current committee who were not on the committee when this issue was addressed some years ago in the context of dosage form nomenclature. But the initial products that were submitted as NDAs were produced by lyophilization. They were actually formed in the packaging, which

was a blister cavity.

They were cake-like, meaning they were porous. They had a glassy state. They were quite fragile. In fact, some of the initial products could not withstand being picked up from the sides, by the fingers, because they would either hydrate or collapse.

They were low weight because, after all, we're evaporating stuff from a blister cavity in a package. And they were actually designed to dissolve or disintegrate on contact with saliva.

They were intended as a treatment advantage. I think that was clear; they were a treatment advantage for target populations. This target population included people who had trouble swallowing, and these could be for a number of reasons. Pediatric populations, because they just didn't want to do it. Geriatric populations because they had trouble swallowing or because they had,

on compliance issues, general compliance issues of people who just didn't want to swallow it, or had some physical problems with swallowing a tablet. And, also, for convenience.

The definition says that you can just put them in your mouth and they go away, essentially. And so, this basically means an anytime, anyplace kind of administration availability.

They were considered a new and distinct dosage form, which is why they were called orally disintegrating tablet. Because the administration -- I'll start at the bottom here. Administration and use was distinct from previous products. The physical form was a tablet, even though it was more like a wafer than a tablet. It was considered to be a tablet -- and because the manufacturing technology to produce this product was somewhat different from the other kinds of tablets that were available at the

time.

The definition that you read here, it says: Solid dosage form containing medicinal substances which disintegrates usually -- usually -- within a matter of seconds when placed upon the tongue. Rapidly is another word in there which is a little bit big, but I think everybody knows what we mean by rapidly. That means pretty fast.

To show that this wasn't some kind of an arbitrary thing, there are a lot of other tablet forms that are based on the method of use. And some of them are listed here. Altogether, there are about 20-some different tablets in our data standards manual. Some based on the method of use, some based on the method of administration, and some based on formulation.

Well, that would have been fine had, you know, the world not marched on. And I've titled this set, Technology Development. Really, what it means is that people found

other ways to make this kind of a product. And, primarily, they moved into direct compression technology, for a number of reasons. It's a much simpler process than lyophilization. It's a much shorter process than lyophilization, generally. It's way less expensive than lyophilization, and it avoids patented or licensing issues in the use of the technology itself. It's also, pretty much -- lyophilization is pretty much, you set up your plant or you hire somebody to do it for you because you don't want to devote your plant to simple lyophilization, when there aren't that many products.

The move to direct compression allowed some things. It allowed common tablet excipients, which everybody had in their warehouse. It led to a larger tablet than a lyophilized product, but it also led to a more robust product, which means you could touch it. If you were careful about your packaging, you could package it in a

bottle instead of a blister pack. You could do a number of things physically with it, which you could not do with the original products.

Because you no longer had this tiny, little, fragile wafer, you had to do some things with your formulation. But the disintegration was aided in the newer technologies by the use of soluble binders, the use of effervescence, which are like Alka Seltzer, basically, and superdisintegrants (?), which absorbed a little bit of water -- a little bit of saliva, a little bit of moisture -- expanded tremendously and, basically, broke the tablet up through physical forces.

I'd like to say that, because of the use of these aids, you could pretty much control the disintegration time that you were after. You run into some challenges, though, because not everybody controlled the disintegration time through the use of these

technologies. And orally disintegrating tablet, in our minds, should represent a dosage form that's easily and readily distinguishable from other tablets. And, you go back to the definition, part of that is that it disintegrates rapidly, usually in seconds.

Also under challenges here is the trend to compress tablets led to larger tablets because, if you need to put in additional binders, if you need to put in disintegrants, if you need to put in sodium or potassium carbonate, you need a bigger tablet. You need to compress it. You often lead to longer disintegration times which, in itself, can lead to potential compliance issues, particularly with the people who have trouble swallowing in the first place and people who have either mental or physical reasons for not wanting to swallow a tablet.

This growth in tablet size and disintegration and technology leads us to a

question, which is: When is a tablet no longer an ODT?

This is an important issue in product labeling, but it's a critical issue for 505(j) products, what we commonly call a generic or an abbreviated application, because one of the requirements, as you saw on a couple of presentations this morning -- Lawrence's, specifically, I believe -- is that there's requirement that the product be the same dosage form as the reference listed drug.

You can't really tell whether or not it's the same dosage form. Then there's the question about whether or not it ought to be a NDA, a generic product. So in an effort to put together guidance for both the industry and ourselves, we've been through any number of drafts, any number of versions. Early considerations included things like disintegration times up to 60 seconds, which probably doesn't fit "rapidly," in a matter

of a few seconds. But applications that had come through or we were looking at, with the newer technologies, we were looking at 25, 30, 45, 50 second disintegration times. And so we felt early on that perhaps we shouldn't go below that level.

And some versions of our early guidance also included labeling descriptions of the product characteristics and instruction for characterization against preference listed drug, or against the definition.

I say these are early considerations, they went away as we worked through some of the issues and we wound up with the current draft guidance, the one that was provided as background, which basically has two things in it. It has a general discussion of the intention of the dosage form, which says it should disintegrate or dissolve rapidly in the saliva without additional liquids. And then there's the

general discussion of expectations for dosage form. And that includes general product development considerations. It includes a recommendation for in vitro disintegration time of no more than 30 seconds. It recommends the use of USP<701> disintegration test method as the approved or acceptable method. There are some other things like, as you heard from USP yesterday.

Methods that are equivalent or better can be used but we didn't know about any of those. Because this was important to us to have a standardized method because one of the things we discovered early on was that the disintegration time was both formulation dependent and method dependent.

You had a dynamic method, such as the USP method, which basically takes the tablet and does this to it in water. Then, some formulations that erode, disintegrate faster that way than if you just put them in a test tube. Or if you put them on an

apparatus that is more static than the USP method.

Applications had submitted static methods, they had submitted USP method, they had submitted variations of the USP method, and ranges of dynamic methods. And we discovered that when we ran these same products in our laboratory, using different methods, we got different numbers, as you might expect.

We also suggested a tablet weight limitation of 500 milligrams, not as a limit, but as a consideration because the bigger the tablet, unless other things are done to the tablet, the longer it takes to disintegrate. You can control most of this stuff by formulation, but if you got a gram and a half tablet, it takes a lot of stuff to blow it apart in a few seconds just with the saliva that's in your mouth.

Back to the USP method for just a second. The other thing that we were

concerned about was the use of proprietary methods. USP method is a public standard. It is available for anybody who has the USP and it also is something that people are used to using. All of the other methods that we saw were either patented methods or were dosage -- actually, product-specific methods that were developed for a particular NDA, or ANDA. And we are not -- we could not recommend those methods openly.

Well, we could not recommend them at all openly, or covertly, to other companies to use.

So we put out the document as a draft. And we got comments that are about 24 -- the document, it's on our website and was distributed for background, dated April 2007. And we got back approximately 24 comments on this, which really isn't all that many. And some of them were duplicates, which always happens when you seek public comments because companies submit comments to

their trade associations, who then submit them to the docket, and the companies submit their own comments to the docket. And sometimes it's a little difficult to know except for the fact that the wording is identical whether or not these are the same comments.

But at any rate, the comments that we received back covered the three basic issues that we had addressed, not counting the product development considerations aside. One was a tablet weight, and comments said, several ODC products are already larger than 500 milligrams. There are also a few applications that have been approved that are above 500 milligrams.

Comment was made that this limitation would restrict use for high dose drugs. The general example was oral antibiotics that was because 250 to 500 milligrams is often a dosage form that used -- a dosage level that's used. By the

time you've built a tablet around that, that would disintegrate in your mouth, you're up in the 700, 800, 1000 milligram range for the tablet. With nothing you can do about that -- it's just what it takes.

Several of the comments emphasized that all of the problems that we were anticipating could be resolved by proper formulation work in the product development.

The second area that was commented on was the disintegration time. And this is sort of a combination of all of them. And I've just said it should not be 60 seconds. Some people said it should be higher, some people said it should be lower. Some people said, we don't care. And that, anyway, that's not the point. Several people said USP<701>, the disintegration method that's in the pharmacopeia was not an appropriate method. And that ranges -- and the rationale for that ranges from the fact that the USP is the dynamic method of putting something on

your tongue. It is not, particularly, a dynamic mechanism unless you then chew on it or roll it around in your mouth for a while. And that's not what the instructions say.

Others said that the USP method was actually designed to let you tell whether something was disintegrating in a few minutes or several minutes, not in a few seconds or several seconds. And so it just wasn't an appropriate mechanical design for that kind of a measurement.

And the other comments on disintegration time involved the fact that there are no good in vivo/in vitro correlations for the disintegration time. There are some correlations. They're not general, they're product specific. They are formulation specific and they work really well when you have very low weight. Highly soluble from tablets, but as you start getting larger tablets, higher doses, the in vitro/in vivo correlations fall apart in many

case, assuming you're using the same disintegration method.

The fourth comment about disintegration time is that in vitro criteria are not relevant to successful use of this product. And while this, I think, is probably pertinent, it doesn't keep us from measuring in vitro characteristics for most other products. Probably every other product and most of those have not a lot to do with successful use of the product except, perhaps, the assay.

There were several comments on in vivo evaluation, which said it should be required. Including a century evaluation and palatability study. And I think many of the NDAs do actually address this kind of thing because they looking for focus -- for panels to decide whether people are going to like their product or not.

There were also other comments that said, in vivo evaluation before palatability

has nothing to do with whether the product should be approved for medical use. So basically, we had comments that said, we like your guidance. We think it's a good idea to have a guidance, but the things that you are talking about are wrong. And so we're back here, looking for some help in trying to decide where we want to go with this kind of a product.

Let's see here, that goes to the question, so really the issues that we have are that we believe there ought to be some guidance that identifies this product. We ought to be able to write some guidance that identifies this product. But there's a lot of discussion and non-agreement on whether those criteria ought to be specific criteria or whether they ought to be general criteria. We evaluate everything when it comes in the door, which, really, isn't guidance to anybody.

And how can move from where we are

now with a few particular recommendations and some general discussion about how to go about developing and building the products, which we called orally disintegrating tablets. From the draft guidance that we have to that -- to some verification of that guidance or, perhaps, some other type of guidance.

Internally, we have discussed that a guidance for this type of product, it doesn't set some specific criteria is not really a guidance really for the industry or our own staff. And would be better addressed with general papers on product development in the literature.

And so we're here to ask, you know, for comments and opinion and guidance on how to build a guidance for this kind of a product. Thank you.

DR. MORRIS: Thanks, Frank. Are there any clarification question for Frank? So I'll start with Harriet, and go to Marv, and then back to me.

DR. NEMBHARD: Harriet Nembhard. Thank you for this background. I just have one further background question. Without being specific about names of drugs, in general, are there drug products that are of orally disintegrated tablet form that don't have a different tablet form, or alternate form. That is, is only comes in the OPT formulation? Is my question clear?

DR. HOLCOMBE: There may be. For a couple of years, there were, because of exclusivity issues, that you could not have a generic product because the NDA had some marketing protection. To my knowledge right now, I don't believe there is an NDA product that doesn't have a non-lyophilized -- that isn't either an non-lyophilized product or doesn't have an ANDA that is a compressed tablet. So the answer to the question is, most of them are --

DR. MORRIS: Can I interrupt for a second? I think I heard you weren't

distinguishing whether it was generic or innovative. You're just saying, was there an ODT that wasn't in a conventional tablet or other formulation, whether it's a generic or not.

DR. HOLCOMBE: Early ODTs were all wafers. They were all lyophilized. Subsequent ones have been compressed. That's not the question?

DR. MORRIS: No, actually, Gary, you may want to step in here.

DR. BUEHLER: I think we're not sure. I mean, normally the ODT comes after the normal -- the regular compressed tablet or capsule is approved. We're not sure -- I mean, I'm not sure if there could be some dosage form developed initially as an ODT, but I have to say we've not had that question before, and so I'm not really sure.

DR. HOLCOMBE: I don't know of any that were initially an ODT that were application based.

DR. MORRIS: Pat, do you want to comment?

DR. TWAY: Yeah, I can only speak from my own experience, where we have several ODTs and they were always, initially, standard tablets. So the first registration was the standard tablet, and then the ODT came in as a second generation or something more convenient for the patient or so that both existed.

DR. NEMBHARD: Okay, it just strikes me that it might -- it might matter in the wording of the guidance if there was already a non ODT form or not. It just depends on how you want to write it. It just occurs to me as a starting point, it might matter whether the form already existed without ODT or not.

DR. HOLCOMBE: In the context of changes from the original product?

DR. NEMBHARD: Exactly, depending on how you may want to make the definition to distinguish the ODT form from the previous form.

DR. MORRIS: And yeah, Marv?

DR. MEYER: A couple of questions. If, when these ODTs disintegrate, do they also subsequently dissolve in the mouth? Or some do and some don't? Do the swallow?

DR. HOLCOMBE: Some do, and some don't.

DR. MEYER: So the particles are swallowed?

DR. HOLCOMBE: The particles are washed down. Whether they're actually -- when they're swallowed, either voluntarily or involuntarily, they're swallowed by saliva buildup in the mouth.

DR. MEYER: So if I took a Bayer aspirin tablet and put it on my tongue and just let it sit there, it would ultimately disintegrate, probably.

DR. HOLCOMBE: It would -- a Bayer tablet would disintegrate. In fact, that's how I take them.

DR. MEYER: But that's not an --

DR. HOLCOMBE: But it's not a ODT,

right.

(Laughter)

DR. MEYER: Which brings me to maybe a revolutionary idea. Do we really need that classification? It's a tablet. Some tablets can act like it. Some ODTs can act like a tablet, in that they have to be swallowed and then start to further disintegrate and dissolve. I don't see that we need the category.

DR. HOLCOMBE: We have talked about that. I don't think we have come to any conclusion about whether we can get rid of the form, or not. Now that we have it -- now that we have products in the market, I'm not sure that we can get rid of the form.

DR. MORRIS: So can I -- my question, actually -- and then, Pat, I'll come back to you -- but was actually a follow-up in part to what Marv's saying. Are there any ODTs that are intended to be absorbed bucklely? I mean, are there differences in routes of administration that are -- or do we not know, I guess is the

question?

DR. HOLCOMBE: The bioequivalence requirement for ODTs is that they are systemically absorbed through the GI tract, not through the oral cavity.

DR. MORRIS: Right, so --

DR. HOLCOMBE: So the answer to your question is it will for the IR products, falling back for the products that -- they should not be buckle absorbed.

DR. MORRIS: Which then, I guess, brings us back to -- actually, do you --

DR. WEBBER: I'm just going to say, I recall seeing dextromethorphan orally disintegrating tablet. I don't recall specifics, but I know that that product is generally locally absorbed.

DR. MORRIS: Pat, did you want to?

DR. TWAY: From an industry perspective and, at least we thing for the patient --

DR. MORRIS: Could you talk a little

more into your microphone?

DR. TWAY: Oh, there is a desire to have a category of orally disintegrating tablets because it's really geared, as Frank pointed out, in many cases, to people who can't swallow a tablet, that can't take water. People who have, potentially, migraine headaches, so they're nauseous, so the last thing they want is to drink a glass of water. And so you really want to be able to put it on the tongue and have it disintegrate. And I personally agree, frankly, there should be a time in your guidance.

You know, quickly. Rapidly, is the term. And so it meets a medical need for certain classes of patient, not I just put it on my tongue and sit there and see if my Bayer aspirin ever dissolves. So in the labeling, it would tell you to put it on your tongue and it dissolves rapidly. And that it gets -- you know, it addresses needs of some patient classes. People that chemotherapy --

that have problems, that type of thing.

DR. MEYER: Kind of following up on that, if -- probably not as good as an (inaudible), but if I take --

DR. MORRIS: Please, can we make sure to state your names again?

DR. MEYER: Mark Meyer. Perhaps not a good analogy. If we take a sprinkle capsule, a control release capsule, that's called by the FDA a capsule or control release capsule. Now, if it's recommended you sprinkle that on apple sauce, is that a new dosage form that we say, this is an applesauce administered sprinkle? Or is it still a capsule?

DR. TWAY: Pat Tway. We do have sprinkles, and they're called sprinkles, for children.

DR. MEYER: Where are they in the orange book? Are they under "sprinkles" or --

DR. TWAY: I don't know the orange book. They're not -- well, ours aren't in capsules. Ours come in a sachet and they're

sprinkles, so it is a unique dosage form.

DR. MORRIS: And Keith's here.

DR. WEBBER: Thank you. I just wanted to clarify your comment, Marv, that, well, you were saying -- you were questioning whether we needed to have that specific dosage form. But were you questioning whether we need to have the dosage form or whether we need to have --

DR. MORRIS: I think classification is.

DR. WEBBER: Do we need the classification or do we need to have products that have those characteristics?

DR. MEYER: I think we need to have the products, but I think the FDA could probably regulate them by just calling them tablets. I may be wrong, I haven't given it a lot of thought, but it sounds to me as if it had many of the same characteristics as a tablet.

DR. MORRIS: Anne's first, then Art can go.

SPEAKER: Thanks.

DR. ROBINSON: Anne Robinson. Yeah, I think from both -- you know, one could argue about how they're classified and I think that's what we're getting to, but I think there's certainly a need for these kinds of products. And to make sure that their -- both patients and physicians understand and can identify those differences is really critical.

I had a separate question, actually, besides that, which was, do the -- I'm not sure what the right term is, but the -- when you're talking about compressed, this is more of a clarification question. When you're talking about compressed tablets versus Lyophilized, is that what I think of as the strips?

DR. HOLCOMBE: No. The compressed tablets are just your conventional -- you put powder or melt into a cavity and you stomp on it and make a hard tablet out of it.

DR. MORRIS: Art, I think you're next, then.

DR. KIBBE: Thank you. Art Kibbe to disagree with Marvin Meyer.

DR. MEYER: You like it.

DR. KIBBE: I love it. First, I think if the industry is going to promote a product, even though it is a tablet. Everybody looks at it and says it's a tablet and they call it a special kind of tablet, then the public ought to have somebody help define what that term means. And I think you're it. You know, tag, you're it. The FDA does those kinds of things. So that the companies won't be making claims diverse -- over a wide range and the public not understand what those claims mean.

It's just like the term that we throw around all the time, lite. You know, lite beer, lite this, like that. And it has no real good definition. So what I think we need to do is establish when a company can legitimately claim that they have made a tablet which could conveniently be used by a patient, disintegrate rapidly on their tongue

so that they don't have to take it with a glass of water, or whatever.

I would recommend an old fashioned test for rapid disintegration, where you take the tablet, drop it into the top of a 100 mil cylidical (?) graduate and it disintegrates before it hits the bottom.

DR. MORRIS: Well, that's a good point and I think -- let's try to make sure we get clarifications from Frank before we go into the discussion. So with that, the next -- who's next?

Oh, was Carol? Carol, you are next.

DR. GLOFF: I guess -- I didn't have a clarification question. I actually was going to side with Art, rather than Morris. So I'll hold that until later.

DR. MORRIS: So I think we have -- oh, you were going to -- okay, yeah. Go ahead.

DR. KOCH: I guess it's -- now enough clarification but on --

DR. MORRIS: Mel Koch, right.?

DR. KOCH: Mel Koch. On slide seven, where you list the classification of orally disintegrating tablets, and on the list you have the orally disintegrating delayed release which is a bit confusing, if it's rapid before it hits the bottom of the cylinder.

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

DR. HOLCOMBE: Usually you can hear me, so. But the -- there's no requirement that it be dissolved. It's orally disintegrating and so there -- you may have residue after the tablet has come apart. In fact, USP disintegration test even allows you to have a mass of powder, after the test is complete.

There's no intention in the definition, or the products, to require that everything be dissolved. In fact, most of the initial products, as you're heard this morning, what probably 40 to 60 percent of today's product -- or drugs that are being studied are insoluble or are virtually

insoluble.

So what you wind up with is -- depending on the formulation and the particular tablet product, some stuff that's dissolved and some level of residue that's left. For the early products that were five milligram micronized products. And you would never know that that was there. For some of the later ones, with Sipe (?) that were manufactured with methylcellulose, you obviously would have some kind of residue that would be swallowed.

DR. KOCH: Maybe a follow up on that is, if you have a product like that, then you have additional labeling with regard to alcohol.

DR. HOLCOMBE: We probably would, for this case now.

DR. MORRIS: You're pro-alcohol, I take it. Are there other clarification questions for Frank before we start? If not, thank you, Frank. I suspect you shouldn't go far, but --

So if we can put the questions up, I think that the consensus, in terms of whether or not we should the classification is sort of been addressed.

So the first question is, given the constraints that we talked about with respect to the disintegration, not necessarily dissolution. The non-buckle absorption and the tablet denotation. What properties in vivo or in vitro, do you consider critical to this dosage form? And keep in mind, for those of you who don't have the questions memorized, like me, there are several questions that are going to play into this. The next one is should physical or functional properties be a primary factor?

So it's the -- now we're talking about either I in vitro or in vivo properties at this point as opposed to the materials property specifically. We can get to that, I don't think there's any danger in overlapping there.

So with that, let me open for discussion the question, what properties in vivo or in vitro do you consider critical to this dosage form?

Oh, that was easy. None. Okay -- no, no -- yes, Anne?

DR. ROBINSON: I mean, I think the obvious one which Frank talked about is the dissolution time.

SPEAKER: Disintegration.

DR. ROBINSON: Disintegration time. Thank you.

DR. TOPP: I think there's --

DR. MORRIS: Let's remember to state our names.

DR. TOPP: I'm sorry, Liz Topp. I think there are actually, in my opinion, there are actually two and one of them is disintegration time, of course. But the other one, I think, is size. That -- you know, I would be willing to have a rapidly disintegrating tablet the size of a golf ball if

I could guarantee that it would disintegrate in a short amount time in my mouth. But I'm not going to have an orally swallowable tablet -- even if I can say that -- tablet that's the size of a golf ball.

You know, so I want much more rapid disintegration time than I would want in a tablet intended for oral use. But I would be willing to tolerate much larger sizes or conceivably tolerate larger sizes than I would in a tablet that I needed to swallow.

DR. MORRIS: Okay, and you're speaking of volume, not dose, when you size?

DR. TOPP: Yes, right. Physical size.

DR. MORRIS: Not mass, but volume.

DR. TOPP: Right.

DR. MORRIS: Right, physical size. And what about dose? I mean, the 500 milligram dose that was in the graph guidance I think is, in part, supposed to be getting at that but it also has the element of the solubility of the drug itself.

DR. TOPP: Can I jump back in again? This is Liz Topp again. I said what I said, previously, a little bit flippantly, but I thin there really is a safety issue involved here. Because, you know, there's the issue of a choking hazard. This is a patient -- we're talking about patient populations who are not able to swallow. And so I think, you know, the combination of size and disintegration time, you know, we really do need to insure a fairly rapid disintegration time or, you know, an elderly person or a child that's got this larger device in their mouth may well try to swallow it, intentionally or inadvertently, and then there really may be safety issues associated with that.

So I think the issues of size, of volume of the tablet, and that, combined with disintegration time, are critical.

DR. MORRIS: Art?

DR. KIBBE: Art Kibbe. Just to agree with you, one other small factor is that I think

we ought to look at the size of the particles it disintegrates into because if it just breaks apart in two or three big hunks --

DR. MORRIS: Well, if it --

DR. KIBBE: No, I'm serious. It's a convenience for the patient. I mean, if you really want to get down to those specifics, the critical issue is how quickly it disintegrates. Most tablets that we've made over the last 30 or 40 years disintegrates into relatively small granuals. And I think the size is pretty well where they go.

So I don't want to get too worried about it, but if you want to put in size constrictions, that's the next step in the size constriction.

DR. MORRIS: And to follow up, so when you say the granual size it disintegrates into, is this for functionality or for just consistency?

DR. KIBBE: Just easier to swallow.

DR. MORRIS: Just easier to swallow.

And I guess the other thing I was thinking about when I was reading the background material is whether or not there isn't some sort of combined variable -- whether it's dimension-less or not, I don't know -- but combined a variable that includes the particles, the solubility and the granual size -- the resulting granual size in the sense that you could have -- or disintegration time, in the sense that you could have a golf ball if it was massively soluble in a heartbeat, whereas if the golf ball is composed of materials that are insoluble, and even if they break down into relatively small particles, it may be harder to swallow because of the mass of particles that persist would be significant.

Gary? I don't know who was first, Frank or Gary? Well, obviously Gary -- he's your boss, right?

DR. BUEHLER: Gary Buehler. I just wanted to provide a little perspective into this discussion and kind of why we're here. I mean,

this is -- actually, as Frank said -- has been going on for a very long time. I don't know how many years ago we brought this to the committee, about the time frame.

And we've kind of batted around, and poor Frank has drafted I don't know how many guidances on it. And one -- I agree with many of the comments, but I'm in the business of generics, you know, making low-cost alternatives available for people. Many of the really nice mechanisms for creating ODTs are patented and especially the one that's the wafer-type dosage form that sort of just kind of goes away, right away, and would pass, I think, Art's test of dropping it down a cylinder.

And so with them being patented, that leaves one company having that mechanism. And so if that should become a rigid requirement for an ODT, there would be no other ODTs for that particular dosage form or that particular product, for however long

the patent lasts.

And so the reason we're dealing with these other, maybe -- I don't know how you want to characterize them, as maybe less elegant dosage forms or the ones that take longer to dissolve and create, maybe, a little bit of a slush in your mouth when you finish, is because companies have attempted to formulate these products in a different manner and not using the patented technology that, you know, they're basically trying to design around.

And so our question here is, you know, these products are important to a lot of people. There are a lot of people who cannot swallow tablets. They just absolutely cannot swallow them.

And to make convenient dosage forms available for these people, the question is, how strict do we make this limitation on the ODT? And if we take a really hard line, that will wall out pretty much many of the other

products.

And you know, the question is, will you take a tablet and kind of create a little slush in your mouth. It maybe takes 30 seconds or 45 seconds to dissolve, but it costs you a dollar instead of five dollars.

And so that's what we're dealing with in OGD, and that's probably why we keep bringing this topic to you folks. Because it's a difficult decision.

DR. MORRIS: Yeah, thanks. And just -- let me just -- if I can couch just what Gary -- I think what we're -- at least with question 1, we're just talking about what properties would be critical. Not necessarily the magnitude of the property. So -- but at any rate. I think Art and then Carol, or Carol and then Art? Who is it?

DR. KIBBE: I'll give it a shot. Art Kibbe. I wasn't suggesting that particular test as the be all and end all, but that particular test was a advertisement for a Bayer aspirin

tablet. So that was a tablet that was intended to be swallowed, and yet it could disintegrate in that time frame. So I think the issue really is safety for the patient. That is, the tablet can be reasonably large, if it disintegrates rapidly into easy to swallow, small particles, okay?

And I didn't say, you know, 100 micron, but you can -- we'll pick it. The number that the FDA can come up with. And I think to give that designation to something that takes a minute or two to disintegrate isn't doing justice to it. So if you agree on 15 seconds, fine, but, you know, I'm not saying what that is, either. But those are the criteria.

DR. MORRIS: And Carol?

DR. GLOFF: Thanks. Carol Gloff. I think what Gary had to say was very helpful. I have been sitting here thinking, I think that the important property is disintegration. Disintegration time, it needs to be rapid. I'm

not personally very concerned about the volume, if you will. I recognize that a larger volume of the tablet or the wafer or whatever for some people might be more problematic than others. And then, to be perfectly honest with you, they'll -- their doctor will have the choice of not prescribing that for them, then. Or they prescribe it once and then it just doesn't work well for them.

But I think if it's going to be an orally disintegrating tablet, I don't want somebody -- I want a guidance that doesn't leave the person with something -- a big blob sitting there in their mouth.

Also I think it's perhaps beyond the scope of this question, but if their reference was to the USP disintegration test, I don't remember the specifics of that test, but there must be some requirements as to what is defined as disintegration. I doubt you can have two or three big chunks sitting there and that's considered disintegration.

But I could be wrong and please feel free to correct me.

DR. MORRIS: No, actually -- and it's Ken Morris -- so actually in the disintegration test there's a cylinder with a screen in the bottom.

DR. GLOFF: Yes, okay.

DR. MORRIS: And it's the screen size that will determine the smallest particle that will be retained. And everything has to disappear within -- depends on the -- it could be six seconds. I mean, it could depend on the dosage form.

DR. GLOFF: So with that said -- and again, I recognize we're not quite at that point in the questions yet, but something like that seems to me would be appropriate because then at least it's small pieces in somebody's mouth.

DR. MORRIS: I had one -- I'm sorry, Harriet, please?

DR. NEMBHARD: (inaudible)

DR. MORRIS: Well, it -- no, because

I'm going to change some little bit of direction.

DR. NEMBHARD: I wanted to add specifically to the question the property -- the in vivo property that I consider critical would be taste. Particularly, for children, I think. So I'm just speaking as a mom. I won't name products, but there are a couple that, you know, whereas I previously had a battle each morning getting my five year old to take. You know, I'm willing to go an pay twice as much, okay? For a product that disappears and has no taste. And I consider that even though the label is orally disintegrating tablet, I get that, but there seems to be also some implication about the taste -- at least from the consumer's standpoint -- with that label, as well, that I think could be almost as critical as the speed of dissolving.

So you know, if it dissolved quickly but, "Mommy, that tastes yucky." You know, that wouldn't satisfy my as a purchaser

of that product and have it, you know, be satisfied to have that label of orally disintegrating tablet.

DR. MORRIS: Ken -- go ahead, Mel?

DR. MEYER: I'm next.

DR. MORRIS: Marv?

DR. MEYER: I think, as far as taste, that's going to be very hard to regulate. You know, what would you put in the guidance? Must taste like -- and your kid might like peanut butter and somebody else might like a lemon. I don't know how you'd regulate that?

But my question was, many years ago we only had disintegration. And we abandoned it because we recognized it wasn't going to predict this bio availability because particles fell through the screen and then sat there. Now, I don't know, maybe these products are such that that's impossible. But if it isn't impossible, it's the particles themselves that are subsequently swallowed -- remain intact. I don't know why

you don't have a dissolution test?

DR. NEMBHARD: I understand.

DR. MEYER: There is a dissolution test.

DR. MORRIS: Frank?

DR. MEYER: Oh, I didn't see that.

DR. MORRIS: Frank?

DR. HOLCOMBE: I'm sorry, Frank Holcombe. There also is a dissolution test. These -- well, what we're talking about here today are the things about ODT. All of the things that you'd think about a regular tablet are already requirements.

DR. MEYER: Oh, okay. I'm sorry, I didn't see that listed.

DR. HOLCOMBE: No, it's not in there.

DR. MORRIS: No, it not. And if I can get -- Ken Morris, I'm sorry. Two things: One is that actually the taste masking issue is -- virtually all of these have some taste masking. So even though it's not something you can regulate, per se, but I've served on these

taste panels, so -- they're not pleasant panels to serve on, by the way, but there's a lot of effort that goes into taste masking. It's not always successful and it depends on the properties of the compound. And the more soluble it is, the worse it is, usually.

So the question I have is sort of tangentially to that, but it was in vivo -- or the comment I had. And that is, that when considering a disintegration test because, as Gary says, we don't want to be prohibitively restrictive but, on the other hand, it's got to come apart some time.

There is the differences in mechanical stress that applied to something that's in your mouth, as opposed to the disintegration. They're very different. And I know there have been other techniques tested in terms of something that's put pressure on and then you infuse water into it and look at the stress that it takes. So there are other sort of alternate testing

mechanisms.

But I don't think any of them are practical as a routine test right now. But that doesn't mean they couldn't be, if they were to be developed. So that's just an in vivo related comment I have. Is that there's really quite a different stress state that you're exposing the dosage form to when you put it in somebody's mouth.

Even if they not supposed to chew it, there's more mechanical stress.

Any other -- oh, I'm sorry, Liz.

DR. TOPP: Sorry -- Liz Topp -- I just have a quick rebuttal to Harriet's comment with regard to these in vivo things. With the area of these esthetic things, like taste and mouth feel, I think that we should be about the business of making sure the dosage form is safe and efficacious. And that it works.

And whether you like it or not, is not a regulatory issue, in my opinion. But if you don't like then patients shouldn't use

it or buy it, or should ask their doctors for a different prescription. But I think, from a regulatory perspective, our focus should be on whether it's safe and efficacious, and not on whether it's nice, or tastes good, or feels good.

DR. MORRIS: Yeah, I'm not sure if there's any patient compliance issue that ever arose that included regulating taste, but --

DR. WINKLE: Well, yes, and several of the drugs that we have for counter-terrorism, we've actually gone back and made sure that these had pleasant tastes, especially for children. Because when you want them to take potassium iodine or something like that, in case of an emergency, you've got to make sure that they're going to take it. So we have looked at some products, like I said, in counterterrorism, to make sure the taste was palatable.

DR. M. MORRIS: I may have missed this. This is a question for Frank.

DR. MORRIS: This is Marilyn Morris.

DR. M. MORRIS: Oh, sorry, Marilyn Morris. It -- you mentioned that in vitro/in vivo correlations for disintegration were not good. And the 30 seconds was an in vitro time for disintegration. About what does that mean in vivo?

DR. HOLCOMBE: It depends. That's a favorite FDA statement, but in this case it really does depend. Because if you're in the populations that these products were originally created for -- and I will say that the products are moving away from those populations as convenience products, primarily, or line extensions.

It might mean that the 30 -- let's say 30 seconds. It might mean 10 seconds in somebody's mouth that has a lot of saliva and it might be a minute and a half in somebody's mouth that doesn't have very much saliva.

I haven't looked at this -- I haven't collected this information recently, but the early studies that I looked at had

standard deviation, this is disintegration time in vivo, had standard deviations that were approximately the size of the main.

DR. M. MORRIS: And in most of the tests that you've done, is 60 seconds a reasonable time frame then for most of the products that you've seen?

DR. HOLCOMBE: Most of the products that we've seen are not that long. However, we have seen some depending on the size and depending on the early technologies -- early compression technologies that were that long. Companies have gotten better with their formulation efforts and the first 30 or 40 of these products that we saw were -- probably 60 or 70 percent were down below 30, and all the rest were below 60. And that's basically where the 60 seconds came from. And the use of better explosion technologies, if you will, since that time is where the 30 seconds is coming from. The current 30 seconds.

DR. M. MORRIS: Thank you.

DR. MORRIS: Yeah, explosion technology, that may be an unfortunate, after just talking about the bioterrorism, but that's okay.

Well, if we can -- let me try to summarize this. In terms of what in vitro/in vivo considerations were, by consensus, the important number one -- maybe the number 1 through 10 is disintegration time -- however, the other corollary to that is it's disintegration to suitably small particles. That is particles that would then facilitate being swallowed, as opposed to just creating a different geometry to choke on.

And also the size. That is the volume of the dosage form itself should not be necessarily excessive. I'm not sure how we'll put it, what excessive is on that, but it has to be some combination of factors including the size relative to how rapidly it will disintegrate and, perhaps, even the solubility of the API itself, given it's

load.

And I think those were really the big issues. The taste masking, if you don't mind, we'll defer that. That actually comes up in the last question, which is patient compliance.

Is that -- this is our -- we only have two discussion questions, the beginning and the end. And then we vote on the middle two, so I think these discussion will serve us well on the next two questions.

So if there's no more discussion, can we go to Question 2?

Excuse me, so the question is, should physical and or functional properties -- for example, size, formulation, and disintegration times -- be a primary factor in determining conformance to this dosage form? So we can open this up for discussion?

DR. KIBBE: Should we push the button first?

DR. MORRIS: I think, actually, we discuss it and then we vote and then we lie about why we voted. No, that should never --

DR. KIBBE: Art Kibbe. We had a -- I think a draft guidance yesterday that said we pushed buttons and then we discussed.

LCDR NGO: No, I think we discuss it first, actually. And then raising their hand was before.

DR. MORRIS: I think, yeah, I think we just neglected -- we got a little departure from protocol in that we didn't raise our hands before we did something.

LCDR NGO: Before we went around the table.

DR. MORRIS: Before we went around the table. So after we push the buttons, we raise our hands, and then you sluff off your sport coat and we tell everybody what we did.

But if there's no discussion to be had then we can go right to a vote.

But if there -- if anybody would

like to discuss, as I said, I think our discussion on the first question serves us well on this one, but certainly if anybody would like to add anything, now is the time.

So if not, then we can -- are we ready to vote? If we could vote? So the question again is, should physical and or functional properties -- for example, size, formulation, and disintegration times -- be a primary factor in determining conformance to this dosage form? And the choices are, yes, no, or abstain.

Okay, so we have all our votes in. So this will be an easy exercise. Will everybody who voted yes raise their hand, please?

Will everybody who voted no raise their hand?

And will everybody who abstained raise their hand? Thank you.

And so now we'll go around for the record and have you state your name and your

vote and any elaboration you'd like to add. Let's start with Carol.

DR. GLOFF: Carol Gloff, yes.

DR. COLLINS: Jerry Collins, yes.

DR. GOOZNER: Merrill Goozner, yes. Actually, I will elaborate because I was awful quiet this morning and I didn't have a chance to raise an issue. But I'm just fascinated once again by what Dr. Buehler said from the FDA, which was that essentially -- if I understood correctly -- this is about products coming in where people are trying to engineer around process patterns, in order to get a generic drug. And you know, I find that a whole lot of science gets discussed in order to essentially accomplish what is essentially and economically driven decision. And it was -- the same was true this morning, as I listened to a very complicated discussion which was fascinating to me.

You know, about whether or not we actually could get good data about what was

happening, you know, whether it be BK (?) or these dissolution studies and, you know, I'm a lot smarter now than I was then about it. But when you really got right down to it, it was because over around -- over in the Office of New Drugs there's a whole bunch of data that has all of that information already about the originator product.

But we can't get access to that and so therefore, we have a company that has the right to come in and create a generic drug. At least by the patent laws of this country. But you know, we want to make sure that it's safe and efficacious and is doing the same thing in the body. And they can't get access to the data that they need in order to do it. So they have to reinvent the wheel and do it all over again.

And we don't know if it's going to be done well, or not? So again, it was sort of driven by economic concerns rather than science, even though we need to help the FDA

have a science to do it because of their roadblocks that are in the way.

So I just thought I wanted people to know what was going through my mind this morning as I sat rather mute for the whole discussion.

DR. MORRIS: Thank you. Art?

DR. KIBBE: I forgot the topic at hand. No, I voted yes. I have to say my name? Arthur Hamilton Kibbe.

DR. MEYER: Marvin Meyer, I voted yes because I feel if you're going to insist on having this extra category of tablets, you have to define what they are.

DR. KOCH: Mel Koch, yes.

DR. NEMBHARD: Harriet Nembhard, yes.

DR. TOPP: Liz Topp, yes.

DR. M. MORRIS: Marilyn Morris, yes.

DR. ROBINSON: Anne Robinson, yes.

DR. MORRIS: Ken Morris, yes.

DR. AU: Jessie Au, yes.

LCDR NGO: For the record, that's 12

yes, 0 no, and 0 abstentions.

DR. MORRIS: Thank you. And that takes us to the next question. So this is Question 2A, promising a 2B. And the question is -- why, did I miss something? Oh, here it is. Oh, okay, it's a sub-question. Okay.

So now that we have voted yes that we should include physical and or functional properties, the question is, if so -- knowing the answer is yes -- so since we have approved that, how specific or restrictive should the criteria be?

This is a little bit of an open-ended question. So now we've said that we've agreed that there are certain things that we think are important to know to be in conformance with this dosage form. We've agreed that they should be determined. And now the question is, what sort of restrictions or how specific should we be in dictating these limits?

So we'll open this for discussion