because this isn't a yes/no, or this isn't a vote. This is a discussion. And so we have Harriet, Liz, then who is that? Is that Mel or Mel?

Was that you, Mel? Okay, it was Marv. And then Anne.

DR. NEMBHARD: Harriet Nembhard. Perhaps Gary or Frank, could you point out in the draft guidance, given the discussion already, what it is that is lacking or that may be specifically needs to be addressed? For example, is there some restrictive criteria in here that we need to be more specific about?

DR. HOLCOMBE: Frank Holcombe. The primary issue -- issues, probably, but the primary issue itself with this tablet is, where do you no longer have an ODT? You know, is there something that makes it not be an ODT? If one of the parameters exceeds a certain value, that brings us into disintegration time because I think everybody agrees the disintegration time is a part of the critical definition, even

though it's fairly general. A few seconds, rapidly, in the definition.

So disintegration time is one place that needs to be considered. The original products disintegrated, essentially, immediately. Not in a few seconds, but if you put them in moisture and they were gone. You put them on your finger and they were gone. That's no longer what most of the products do.

The other thing is the size. We presented 500 milligrams in the guidance, but we did not intend that to mean that if you have a 501 milligram tablet, it's no longer and ODT. It was just a formulation consideration. So large tablets that disintegrate really rapidly probably, you know, we wouldn't have a problem with.

However, there's still the question of what we're going to use as a cut off point? Are we going to use Bayer aspirin, which will dissolve in my mouth in about 35

seconds? Or are we going to use 30 seconds, or are we going to use 60 seconds? And how hard is that number? You know, is that a line in the sand or is that a line in the water at the beach, you know, that kind of analogy. Or is it a real number?

And if we had to pick one point, it would be the disintegration time that we need to have. That we need to come to some agreement on. And those are really the only issue for the product because formulation has given us products that are large and rapidly disintegrating. And small and rapidly disintegrating. And you know, anything in between.

So it's the idea of, is there a place in disintegration time where we can no longer say that something is rapidly disintegrating. 30 seconds is what's in the guidance. Do we need to change that?

Do we need to talk about it, you know, in a formulation context? Do we need

to include it with the other issues about is the tablet soluble or disintegrating? What other particles sizes? But guidance on what that number ought to be and how hard and fast that number ought to be, is really where we've been stuck for the past couple of years.

DR. NEMBHARD: It seems to me, though, in reading the guidance, that both of those are worded with sufficient latitude that it can already be finished, or is there something I'm missing? That's my question, essentially.

DR. HOLCOMBE: Uh-huh.

DR. NEMBHARD: The wording speaks to approximately 30 seconds or less. And by the USP disintegration test --

DR. HOLCOMBE: Uh-huh.

DR. NEMBHARD: And the size of 500 milligrams as a recommendation. So even that's not hard and fast. So --

DR. HOLCOMBE: Well, all of our guidance is recommendations, even though people

take them as law, sometimes. Most of the time. Because that's how we use them.

That's not really how we use them, but it's how people think we use them. But we use the word, approximately, because we have the -- you know, 30 is okay. How about 35? If 35 is okay, how about 39? Okay, pretty soon you're up to however high you want to go and that's a concern. This is already an average value, no more than. It's already an average value. So the question becomes, should that be approximately or should that be 30, I guess in response to your question -- specific question.

DR. MORRIS: Marv?

DR. MEYER: From a regulatory standpoint, don't you have to have some line in the sand?

DR. KIBBE: That's what they want.

DR. MEYER: Well, then make it -- I don't know if you can do a survey of all existing products and what's the slowest one.

Or take a panel of people who can't swallow tablets and find out how long they can tolerate having something in their mouth? These are all inexpensive studies to do. Or just pick something that's probably a few -- 30 seconds, 60 seconds beyond what you think most of them can achieve.

But you have to have something. I mean, when you call something highly soluble in the BCS, you pick 85 percent dissolved in 30 minutes. Very specific. Now it seems how we're going to have this -- like you say, it's going to be creep. Well, he had 65, but I've only got 68 or 69 or whatever. So I think you need some line. I don't know what that is. How long can people hold a tablet in their mouth? This is the question.

DR. MORRIS: Can I --

DR. MEYER: Go ahead.

DR. MORRIS: Can I just ask for a clarification from Frank before we -- and that is that the 30 -- I thought that the 30-second

disintegration was supposed to correlate somehow to a 60-second actual usage time. Did I read that wrong?

DR. HOLCOMBE: Right, you read that wrong.

DR. MORRIS: Okay. Well, we need a line. Next -- I'm sorry, were you not done, Marv? You had your hand up? So Anne, you're next?

DR. ROBINSON: Anne Robinson. So I think sounds like a reasonable number to me. But I also wonder whether perhaps some of this can be accomplished through labeling? Even though that's not, you know --

DR. MORRIS: That's our next question.

DR. ROBINSON: Right, I recognize that's --

DR. MORRIS: That's our next question, but that's okay. Go ahead.

DR. ROBINSON: One of the next questions, but just to keep that in mind, which is, from the standpoint of being able to see

that on the label and know what the approximate time of dissolution -- I said that again, didn't I?

DR. MORRIS: Disintegration.

DR. ROBINSON: Disintegration, may be useful.

DR. MORRIS: We'll just let Helen respond to her.

DR. WINKLE: One of the issues we've talked about in the office, time and time again, in fact, as we've been going through this, is the difference between the reference listed drug and the generic drug. You -- and Gary has already mentioned that reference listed drug often used a patented process whereby the product dissolves in three or four seconds. You now go to the generic and it dissolves in two minutes. Do you still get the same compliance from people, especially people who may have problems taking drugs? I know there's going to be a thing on special issues, but I think this is something we need to consider and look at

these issues and make some decisions.

This is a big question that we have on the sameness, here.

DR. MORRIS: Jerry's next and then you're next.

DR. GOOZNER: Me?

DR. MORRIS: Yes, you, Merrill.

DR. GOOZNER: I think my comment was directly on that point and maybe the labeling gets at this, but I would be less restrictive, rather than more. And let, you know, to a certain extent isn't this a physician and marketplace decision? I mean, if I could get access to a drug that melted in my mouth for 30 seconds, or 45 seconds, even though there was something that was 10 seconds that was available, then maybe I would rather have that. And I would be willing to put up with something, and if compliance is an issue, that's something physicians should be aware of, but I don't know that a guidance should pick some firm line in the sand unless it's -- you know, there might be

a completely outer limit where you say, it doesn't -- that's really not what's going on here.

But I would be less restrictive and just in the name of getting more product out there and more choices made available.

DR. MORRIS: That's good. I think we're looking for the outer limit, by the way. Art?

DR. KIBBE: I think you need to draw a line in the sand. And I think it would help you with the generic issue. If both products qualify as a Orally Disintegrating, that's the first tip. Then you do a bioequivalency study. Then you're done.

I think you could even set the criteria that you have to use. You know, it's 30 seconds in a USP apparatus with a number 8 sieve or a number 14 sieve, or something like that. And I don't think that would be onerous. I think the one thing that you should do is that preexisting products,

if they don't meet this criteria, they should still meet the QA or QC that they have and they won't be negatively effected. Because there's bound to be a few that are a little higher that 30 and I hate the concept of us coming up with a regulation that disenfranchises them. And the reason I say that is because as the technology moves, people are getting better at it. We're at a point now where I can't think that someone can't formulate rapidly disintegrating tablets and can do it in 30 seconds.

So I think you need to have a time frame that is equal to or less than 30 seconds in this apparatus, with this screen. And then grandfather the other ones, and then when anybody meets that, they are an orally disintegrated tablet for the purposes of pharmaceutical equivalence, right? Because we use capsules against capsules, and tablets against tablets. And then you go ahead with the same bioequivalency testing and you've

already -- now you've established that, you don't have to worry about somebody saying, well, one second's a lot shorter than 28 seconds. Well, it might be, but it's not significant in terms of the availability of the drug to the patient. And that handles that. Anyhow, that's what I think.

DR. MORRIS: Okay, and actually Jessie's going to --

DR. AU: Jessie Au. I would go for a line in the sand, but I don't know where this line ought to be. And I'll explain why I'm worried about this -- not having this line.

I'll go back to the earlier comment about safety and efficacy. Is there underlying -- if it's not disintegrating, is there underlying reason why it's not disintegrating? Does it require more saliva? Does it create a paste, a slurry? So the people you try to help, actually not being helped by this formulation.

So in my mind, it's the scientific

or technical part I'm concerned about. So if it's not rapidly disintegrating, there must be a reason why it's not. If is that reasoning going to be a safety problem? You know, people with no saliva. And the physician don't necessarily know how much saliva a patient will produce. So I think you need to draw a line in the sand, but I don't know which one -- where it is.

DR. MORRIS: That's a good point. I actually had one -- why don't you go -- go ahead, Keith and we'll --

DR. WEBBER: I'm just going to make a comment on that along with what Art has said -- it's Keith Webber. This is one of the discussions we've had a lot over this topic, is drawing a line in the sand and what is that line going to be. And based on some of the criteria for the reasons for having an orally disintegrating tablet, in terms of patient compliance, getting people who -- being able to dose people who may want to spit the product

out, that sort of thing.

If you set a line at, say, 30 seconds, is that going to be the right line in order to provide that dosage form with the compliance requirements that you're trying to achieve. And so there where do you -- you have to go back and look at what you're trying to achieve with that dosage form and set the line accordingly. So that's something we really have to keep in mind as we develop whatever line -- if we decide to put a line.

DR. MORRIS: Gary?

DR. BUEHLER: Gary Buehler. Yeah, I'm the line drawer, so it does -- I mean, Marvin is correct, it's incredibly easier if you just have a very -- like we do with bioequivalence requirements.

If somebody misses bioequivalence by a tenth of a percentage point, they lose. And there's no rounding, there's no give one way or the other with the bioequivalence

requirements. I makes my job very easy and there's just no argument. You just lose.

And now, is this an issue or a point that rises to that same level? As to whether a product is acceptable overall or not? And we would like people to accept generics. We want them to be happy they got generics; we want them to perform the way they expect to. And so this kind of falls in that line a little bit, and I understand what Merrill said, too. We want to make generics available and we want people to have access to them, but the reality is a lot of people get generics who have insurance plans and who are getting the reference product and then they get the generic because the insurance plan tells them they have to. And so we really do want the generic to perform in an equivalent manner or, at least, you know, acceptable manner.

So we have to keep that in mind. And you know, this is a very difficult issue.

That's why I said we've batted this around for a number of years in trying to make this decision. And that's why it's so difficult for us. You know, no line is easy, but no line is sort of no line. And if there's sort of, like, no limit then -- because people can argue with this and threaten to sue us and whatever. And it's right. If we have no line we have a difficult time to make a decision.

DR. MORRIS: Can I just say one thing before we go on, is that if everyone is agreed, we'll skip break and try to get the transportation here at 4:30. Or if there's strong objections, see Art. So could you --

DR. WINKLE: Just to -- I don't know if an hour is going to do justice to the next topic.

DR. MORRIS: That's a good point.

DR. WINKLE: There's three speakers that have to speak.

DR. MORRIS: Okay.

DR. WINKLE: And I feel like if the committee needs to go out of here at 4:00 -- by 4:30, and I could understand that need for transportation, and the rain, maybe we need to consider postponing the last topic?

DR. MORRIS: Okay, I agree.

DR. WINKLE: You know, if you could vote quickly on the next two -- on the next question --

DR. MORRIS: Well, why don't we see how far we can get?

DR. WINKLE: And see where we get to.

DR. MORRIS: Okay, but otherwise I agree. We don't want to short shrift it.

DR. WINKLE: Yeah, I don't think it would be fair, because these people have put a lot of effort into their presentations and stuff.

DR. MORRIS: So with that in mind, who would like to comment? Yes? So if we can be brief, please Pat and then Richard?

DR. TWAY: Yeah, one thing just to

keep in mind is, I didn't look at this just as a generic issue. Because, certainly, when that draft guidance came out, those on the innovative side also looked at it and so it's something we've got to think about for future, you know, not just from the generic perspective. This guideline will apply to all products and, certainly, we took it that way that, you know, you had a timeline. Whether it's 30 seconds or 60 seconds, there was a timeline.

DR. MORRIS: Richard?

DR. STEC: Rich Stec. Expedite and desire to keep it short. A lot of interest amongst the panel about establishing a line in the sand, but not sure where that might be. It maybe appropriate to consider performing a human factor's study in appropriate population to designate what they may be.

DR. MORRIS: Other comments before we try to -- okay, Marv?

DR. MEYER: If Gary Perry pays attention over there, yeah, I need to ask him a

question.

Yeah, if we establish, let's say, 30 seconds or some such thing, and there's already a brand out there that's 60 seconds, is it fair that the generic would have to be shorter than 60 or can we have a guidance that says the generic must be no longer than the disintegration of whatever the brand is? And if there's no brand issue, then go ahead with 30 seconds, from a generic standpoint.

DR. BUEHLER: That's one way to go. I mean, we have actually looked at sort of a paradigm similar to that, basing what we do on how the reference product performs. And you know, having some kind of a time break or time closeness parameter to the reference product.

DR. MORRIS: If we can summarize, then. The things that sound like we have consensus on are that there needs to be a line in the sand. Let's come back to what that might be. But that it has to include not only the disintegration time but also a particle size for

which we are limiting the disintegration, which is in the test methodology, right?

So the test methodology would then, for example, if we were to stay with the USP disintegration test, would be the conditions of the test including the screen size, which would then by default regulate the disintegrating particle size.

And in terms of -- I'm not sure we came up with a line in the sand. I personally agree with Art that it seems like you should be able to make something disintegrate in 30 seconds, but do we want to have a specific number? Or -- I didn't quite get a feel for --

DR. KIBBE: Art Kibbe -- remember, we don't vote on a piece of information that becomes a guidance. We give the FDA our best thought.

DR. MORRIS: Exactly. So do we want to give them a thought?

DR. KIBBE: So just let them go with

what we've already told them.

DR. MORRIS: Does that sit all right with everyone, or does any comments? All right.

So if we can move to the next question? Question 3, can labeling; i.e., instructions for use, be considered sufficient to define the dosage form? And this, I believe, is a voting question as well, right? Yes, yeah, so this is a yes, no, or abstain. And we are going to open this for discussion. I'm sorry? So that was Carol, Pat --

DR. TWAY: I think she's going to --

DR. MORRIS: Oh, Carol --

DR. GLOFF: I'm not --

DR. MORRIS: Carol Gloff.

DR. GLOFF: I'm not certain I really understand the question. Carol Gloff, yes. Sorry about that.

I'm not certain I really understand the question. Be considered sufficient to define the dosage form. To define it as an

orally disintegrating tablet? I'm not quite certain I'm following.

DR. MORRIS: If I can interject and -- let me try to speak for the writers and then they can jump in. But I think the idea was that so that the patient or health care provider would understand that that was the intent, that this was in fact an orally disintegrating dosage form and that meant that it had certain characteristics. Is that, more or less, the case, Frank?

DR. HOLCOMBE: Well, that's in general the case. The specific -- this question, in fact, the sequence of questions are actually in the context of, if you don't have -- and if you say "no" for the first ones, then you have to say something else. And this one was intended as, can you use the labeling only to say this is an orally disintegrating tablet. And that depended on how the previous two were answered.

DR. MORRIS: So sufficient in absence of agreement on the first two?

DR. HOLCOMBE: Right.

DR. MORRIS: Oh. So okay. So --

DR. KIBBE: I read it -- and I thought I understood what he just said -- and I was going to say, we've established how you define it in the previous thing. And then you use that definition whenever you refer to the term in the labeling. And we're done.

DR. MORRIS: So does that mean we don't vote on this? Yeah, no. Or that we all vote no?

SPEAKER: Either/or.

DR. MORRIS: Either/or. Okay, well, let's take a vote and see what -- just put it in the lap of the gods, here. Hang on a second. Are we ready?

So we're ready to vote. So please -- so okay, I'm sorry. So the question is, can labeling -- this is now, can labeling in the absence of any agreed specifications as to the definition of this dosage form that we've agreed should be

adopted, if you didn't have those definitions would it be sufficient just to put on the label that this is an orally disintegrating dosage form?

Did I say that improperly?

DR. HOLCOMBE: No, I think you said that okay. But the question becomes moot now.

DR. MORRIS: So do we just abstain?

DR. HOLCOMBE: I would --

DR. MORRIS: Or not vote --

DR. HOLCOMBE: I would not vote. It's moot.

DR. MORRIS: Just not vote? Okay, so since this -- Helen, what do you think?

DR. WINKLE: This just take -- since we're not having a break, that's the break. Yeah. I'm sorry?

So Jerry? Sorry, Merrill? You've got to move these signs. I just look at the signs. Yeah.

DR. GOOZNER: It's Merrill Goozner. It just seems to me that it's conceivable that

you could have a label that said, this one dissolves in 45 seconds, this one dissolves in 30 seconds, this dissolves in 15. You could have a -- you could use only labeling within a -- you know, with a much different guidance that gave very broad parameters.

What constituted this dosage form.

DR. MORRIS: Right. And I think that was the intent of the question.

DR. GOOZNER: And so --

DR. MORRIS: Yeah, if we hadn't agreed on something else, would that be sufficient. I think you're right, yeah.

DR. GOOZNER: And there's a part of me that says, well, maybe that's not a bad idea. But I don't want to contradict my earlier vote.

DR. MORRIS: No, no. You're -- so maybe we should vote, then, and just get it on the record.

Oh, sorry. One more. Anne?

DR. ROBINSON: Anne Robinson. I mean, maybe it's the wording of the question -- but I

mean, having the word "sufficient" in there seems to me to beg make the question -- I mean, I agree, I was one before who brought up the concept of including the labeling. And I think it's useful to have that, but "sufficient" is a word that I wouldn't think we need to vote on at this point.

DR. MORRIS: Please, Helen?

DR. WINKLE: Helen Winkle. I don't think it's necessary to take a vote on this, especially since time is so limited.

DR. MORRIS: And that really makes part A moot as well, I believe? Is that correct?

So that brings us to question 4, which has -- what, if any special issues, should be considered? For example, patient compliance, target populations, and conditions? So with that I'll open it for discussion. And I think I'll call on Harriet to re-state her taste masking very briefly.

And then -- just so it's on the

record.

DR. NEMBHARD: Harriet Nembhard. I would suggest that there should be some consideration of the taste or palatability of the product that's a part, at least, implicitly for the definition of orally disintegrating tablets. It seems it -- you know, as a consumer, you might expect -- I mean, to your point, it's not to say that it tastes like peanut butter or lemon drops, but that the taste is at least palatable. Or maybe you phrase that differently in terms of patient compliance, that it's not something that the patient wants to expel, or however you might want to phrase that. But some consideration of that issue seems to be implicit in the definition of ODT.

DR. MORRIS: So it shouldn't be an emetic. Are there any other special topics that -- yes, Jessie.

DR. AU: Jessie Au. I disagree with Harriet. I think our duty here is to look at safety and efficacy. That's where the

regulatory bodies come in. I think the marketing is not our responsibility. We shouldn't have to tell them what taste to do. You know, compliance I can see, but compliance only in the sense that they don't get choked on this or when they try to have the disintegrating tablet. But I don't think it is our responsibility to dictate that they have to have nice taste.

They will do the marketing research. They don't need us to tell them. If they want to make money.

DR. MORRIS: Other special issues that should be considered?

Well, if not, that closes this -- what's that? So Helen, do we have sufficient time to close this and keep going?

And so this brings us to the final topic. Which is -- sorry -- which is the use of inhaled corticosteroid dose response as a means to establish bioequivalence of inhalation drug products. And we're going to

have several presentations, starting, I believe, with Lawrence. I'm guessing, because he's up.

And people may mill in and out very briefly, Lawrence, but --

DR. YU: It's okay, I don't mind. Well, good afternoon everyone. I want to thank you for your contribution and the time and effort. We really had a great discussion this morning on bioequivalence GI locally acting drugs. We will certainly take your advice on biorelevant dissolution as well as the mathematical modeling back to the office. We'll discuss and consider your suggestion and the comments.

This afternoon, the last topic is on inhalation product. This is another very critical topic for us. Bioequivalence of inhalation drug product challenges and opportunities. Again, another locally acting drug product.

Back to last year, we issued a

critical path initiative. We identified bioequivalence of locally acting drugs as a critical area, which of the genetic drugs needs the working on.

Compared to systematic drugs, the locally acting drugs for inhalation products different because, as again this morning -- that this morning we basically talked about the gastrointestinal GI tract. Here, we talk about lungs. So that therefore, when patient takes the dose, do you have a lung deposition, and come to the systemic circulation. And also we have the GI tract and the liver. That's part of reason, again, that systemic exposure may not be predicting concentration and the location in lung -- in the lung deposition. That's why it's -- this presents a specific challenge to us.

With respect, the four factors affecting respiratory drug delivery, those factors include drug substance, physical

chemical factors including formulation, including device, and the patient compliance. Because the use of device is also critical.

In establish of bioequivalence, we are thinking about the formulation, whether formulation should be similar. We talk about device, shape and design. We're thinking about in vitro bioequivalence method. And we're thinking about comparative systemic exposure studies. It's comparative systemic exposure studies, indeed, pharmacokinetic studies to make sure that the test product and the reference product, they have similar exposure with respect to safety.

One of the particular items which is challenge to us, which we're here to discuss about, is basically in vivo studies with clinical or pharmacodynamic studies. For the reason because, as a response to very shallow, it's difficult to develop a sensitive method to demonstrate bioequivalence for those inhalation product.

FDA is actively exploring method or developing method to demonstrate bioequivalence for inhalation product. See this afternoon, we have two discussions, we have two presentations. One is by Wally from the Office of Generic Drugs, another is from Badrul from Office of New Drugs, present two models -- as my stability model as well as inhaled natural oxide.

With that short introductions, I turn podium to Wally Adams. Wally?

DR. ADAMS: Show me, how does this thing work? This one hear? That one? And that will take it back, right? Okay, good, thanks. Thank you, Lawrence, for that introduction. And good afternoon, ladies and gentlemen. I don't see -- as Lawrence has indicated, this afternoon what we would like to do is to provide two presentations to serve as an informational background for the Advisory Committee. And I'll be talking on asthma stability model for inhaled corticosteroid dose response.

Office of Generic Drugs, going back to the early to mid-1990s, did a lot of research on albuterol, MDI dose response studies, and the result of that work was a guidance that was issued to inform interested firms on the conduct of appropriate bioequivalent studies for albuterol, a short acting beta agonist.

At the present time, OGD is working on these two approaches to the establishment of a sensitive method for establishing bioequivalence of inhaled corticosteroids. And as -- there's clearly a need in the years to come, as there are a number of dry powder inhalers which will be going off patent that contain inhaled corticosteroids. And also some MDIs will be going off patent in either the near term or longer term.

So what I'd like to do is to discuss methods to establish bioequivalence, challenges to -- specifically to inhaled corticosteroid bioequivalents. Talk about

the asthma stability model and the pilot study which was conducted by Dr. Ahrens. Talk about crossover and periolic design. Estimates of sample size, and also the FDA's research on the asthma stability model. And in addition to that, briefly mention something about pharmacodynamic study data analysis, if there's time.

I believe that Lawrence may have presented a similar slide to this based upon the regulations which indicate that in order of decreasing accuracy, sensitivity, and reproducibility, if we look at three methods of in vivo studies, pharmacokinetic studies are preferred. If they are not appropriate to establish equivalence, then a pharmacodynamic endpoint -- a bioequivalence study with a pharmacodynamic endpoint would be next in line. And next in line after that would be a bioequivalence study with a clinical endpoint.

And in addition to that, there are

cases in which comparative in vitro data alone will suffice to establish bioequivalence of various products. That's a general statement.

Now, this is an idealized plot showing efficacy curves. I should say that inhaled corticosteroids are locally acting drug products and as a consequence of that, the pharmacokinetic studies are not appropriate to establish bioequivalence, but rather, some pharmacodynamic means is necessary.

The PK studies will indicate something about systemic exposure. But they do not necessarily relate directly to local efficacy.

So this is an idealized curve, as I say, and it shows the increasing efficacy as you go up the curve for a locally acting drug. And in addition to that, I've also got here in the curve a curve for the safety aspect. And in a bioequivalence study for

establishing local delivery equivalence, what we're interested in is trying to develop a study in which the study is conducted in the rapidly rising portion of the dose response curve.

And in addition to that, we would like to have a study design which has low variability. In order to increase the power of the study. The plot also indicates that there are safety concerns we would be concerned about for these locally acting drugs -- drug which is absorbed via the lungs or swallowed and absorbed via the GI tract.

And so there would be plasma levels -- measurable plasma levels of drug which are a concern for systemic exposure. So we include a pharmacokinetic study in addition to a pharmacodynamic study for local action in the standard request for bioequivalence.

Now, this slide I've taken from some material that Dr. Peter Barnes has presented indicating the general problems

with establishing dose response. And some of this has been alluded to earlier this afternoon. But for dose response, differences from placebo for each of the active doses are generally statistically significant. A dose response generally exists, although it's shallow. There's a lack of statistical significance in response between adjacent doses with a high variability of response. And in fact, it may take a fourfold or greater difference in dose in order to detect a statistical significance.

Now, I don't want to imply that a statistically significant difference is a criterion for bioequivalence. It's not, but it's simply emphasizes the fact that there is a problem with establishing a meaningful dose response curve in a bioequivalence study for inhaled corticosteroids.

There's another problem, too, which is that the pharmacodynamic effect may

persist for quite some time and may result in an investigator feeling that a crossover study is not feasible. Because they would have to wait until after the pharmacodynamic effect has washed out in order to give a crossover treatment. That is frequently not done, and many studies for relative potency, in fact, use a parallel group design rather than a crossover study.

And the problem is, in terms of bioequivalence is that the carryover between treatment periods can result in -- if it's an unequal carryover, it can bias the estimate of the difference between treatment means. Meaning that we would get an incorrect measure of bioequivalence.

So there's a problem with inhaled corticosteroids.

Now, I'd like to mention the Bussey et al. study, which looked at a dose response and a comparison between Beclomethasone Dipropionate, the CFC formulation, and the

newer HFA formulation. And in Dr. Bussey's study, he used subjects ages 18 and over, they were adult subjects. FEV-1 was 50 to 75 percent of predicted. And the treatments were Beclomethasone Dipropionate for six weeks at each of the dose levels. It was a parallel group dosing. He doses for up to 28 days prior to the start of the study in order to wash out any corticosteroid from these patients.

And he dosed at three dose levels for each of the CFC and the HFA products. Blinded to dose. But interestingly, I'd like to point out that you'll notice at the end, at the left hand bottom, indicates that in this study he used between 50 and 59 subjects per treatment group. This is far higher than what we normally think about in a pharmacokinetic study in which 24 subjects is quite common. Much larger than that. In fact, though, there were over 300 subjects in this study.

And I'm citing this study because it represents a very well controlled, carefully performed study conducted by this investigator. And in fact he did establish a dose response, but we'll see that there are some issues with regard to the results.

And this is the plots for the increase in FEV-1 -- percent predicted over baseline -- over a six-week period. And what we see is that there's a trend towards an increasing response over the first four weeks, and then as we get out towards six weeks, the responses tended to plateau.

And the Bussey paper indicated that there was basically marginal statistical significance between the 400 and the 800 microgram doses. And we heard earlier today that there was a difference between the 100 -- statistically significant difference between 1- and 800. I looked at this paper, I could not find statistical comparisons for any of these doses relative to the baseline.

And because there was a dose response, Dr. Bussey was able to conduct a Finney analysis of this data set. And in fact, it met the Finney criteria.

You'll see that there is a dose response to both the HFA's BDP, which is the QVAR, and the CFC-BDP product. And using this approach, it asks the question, what is the dose of each of these products that would give the same pharmacodynamic response? Increase in FEV-1 over baseline. And the plot shows that as result of that calculation, 150 micrograms of the HFA product would be equivalent to 400 micrograms of the CFC product. In other words, the CFC product requires 2.6 times as much dose to get the same effect.

Well, the interesting aspect of this, and the reason I wanted to present it was, if we look at the 95 percent confidence interval for this estimate of 2.6, that confidence interval ranges from 1.1 to 11.6.

That range is so wide that this number of 2.6, we don't really know where it is in that entire confidence interval range.

So the data are not clinically useful to adjust the data for this HFA product. And furthermore, the data are so wide that it certainly would raise questions in terms of ability to meet confidence interval limits, such as we think of for generic products. If we converted this to -- expressed that confidence interval in terms of percent, it would have a width of 40 percent to 440 percent, a huge range.

And that, now, was with a parallel study design. And Dr. Ahrens had the idea that it may be possible to improve the precision of that estimate.

Improve the power of the study by using a crossover study design. And how might that be done? Well, the basic approach used in the asthma stability model is to say, we want to do a crossover study, we don't

have the time to wait until the pharmacodynamic effect has been washed out from the first treatment, until we give the crossover dose. So rather, what would be done is to dose the patients up to the maximum of steroid response with a high dose corticosteroid. And then, put the subjects on for a period of three weeks on a particular dose of the inhaled corticosteroid.

He used oral prednisone 40 milligrams twice a day as a wash-in to bring the patients up to maximum steroid response. And then in a crossover design, he put the patients either on 100 or 800 micrograms per day of the drug. And followed their FEV-1 over time.

And then after that first period, he again gave a wash-in of the high dose corticosteroid to again take them up to the high plateau of response of the maximum steroid response. And then put them on the

crossover dose.

And when he did that, the data looked like the figure on the left in which we see that there's a high value due to the oral corticosteroid -- the oral prednisone, I should say, taking them up to a maximum response. And then putting them on either 800 or 100 micrograms per day. And you'll see that the 800, basically it dropped a little but maintained a fair plateau of asthma stability. Whereas the 100 microgram subjects were dropping down in response as they stayed on that dose.

And he was able to use that information, then, in order to do some calculations. And I want to go back to the previous slide in which the interest was in determining what would the sample size need to be in order to do a bioequivalence study -- a successful bioequivalence study. And the assumptions were these.

That the study would be done as a

two by two study design, it would use a Finney bio assay, he would look at a 90 percent confidence interval, and the bioequivalence interval on the dose scale would be 50 to 200 percent. Now, that's a lot wider than we normally think about for our normal bioequivalence limits of 80 to 125.

These limits were much broader than that.to 200. But that was the assumption built into this paper, and these calculations. And in order to compute sample size, the power of 80 percent.

Sample size estimates were based upon the standard deviation obtained from the ANOVA, and the slope at the end of the treatment period. S is a standard deviation for responses from ANOVA, B is the dose response slope, and a low S-over-B ration indicates increasing study power.

And what we see is, if we look at the right hand side of this plot, in which

the S-over-B ratio has been plotted as a function of sampling at increasing times over the 21-day period. We see that the S-over-B ratio drops. And so the calculations which were done for this investigation used the data at the three week time point. And did calculations of how many subjects would be needed to -- for a product to meet the bioequivalence requirements of 50 to 200 percent.

And calculations were done assuming either a parallel design study as indicated on the previous slide -- earlier slide -- or a crossover design. And just looking at the common AM FEV-1 endpoint, we see that using the parallel study design, there was some 1,400 or so subjects would be required in a parallel group study design in order to meet those bioequivalence requirements as defined in the paper.

On the other hand, if a crossover study were conducted, these study results

indicate that those criteria could have been met with 25 subjects.

It's a -- I don't have a point -- it's one of the very bottom points on that curve, is -- represents the data for the crossover study design using the morning FEV-1.

This was of substantial interest to us because we've been -- in OGD -- because we've been looking for some method which would represent a sensitive study design which could be recommended to firms to conduct a bioequivalence study. It needs to be sensitive in order to be meaningful.

Now, this slide, then, represents the FDA's study objectives based upon the pilot study which I just described. And we wanted to expand and fine tune the work which Dr. Ahrens had done. And so one of the questions we wanted to ask was, can that maximum steroid response be reached with a high dose inhaled corticosteroid rather than

oral prednisone. There would be large benefits to doing that, because it would avoid the large systemic exposure of the oral prednisone if we could dose with a high dose corticosteroid. That's one of the questions we're asking in this study, which is underway.

We want to characterize the dose response based upon three treatment levels. And I want to back up for a moment. If we look at this left-hand figure, that represents the decline in response with 100 micrograms. What we don't know here is, what would the decline in that response look like if the subjects were on placebo or no drug. We don't know that. And so what we wanted to do was to better define this dose response curve by adding a third dose.

Now, either we could do it in one of two ways. We could either include a placebo treatment in this study, or we could simply add a third dose of active drug. And

for ethical reasons, about taking these steroid responsive, steroid dependent subjects off of drug totally for a three or four week period would be a concern and we didn't want to do that. Therefore, we included three different active drug doses in order to establish a dose response.

A third bullet, study efficiency of the screening process for identifying subjects demonstrating a sufficient dose response. Where, it's critically important to try and enrich the study population in these studies in order that we include subjects who are dose-responsive. And that's one of the aspects of this study.

To examine the dose response of the primary and secondary outcome variables. The Ahrens pilot study suggested that the AM FEV-1 is one of the very most powerful endpoints, but there were a number of other endpoints, and so we're going to be looking at that issue as well. And we're also going

to characterize the dose response using both linear -- using linear and nonlinear and Emax modeling.

So those are objectives of the study. And some of the specifics are that these subjects in our study, which is currently ongoing -- the asthma stability model study -- will have persistent asthma, they'll be non-smoking. They must exhibit a dose response during run-in. Otherwise, they are excluded from the study. Run-in study periods will be a high dose inhaled corticosteroid run-in, which is going to be 220 micrograms times 4 actuations. Followed by a low dose run-in of 44 micrograms per actuation.

Essentially, what we've done here is, we are giving the subjects the highest label dose of the inhaled corticosteroids as a high dose run-in, and then we're dropping them down to the lowest possible dose -- of the lowest dose of this product, which is

Beclomethasone Dipropionate, HFA. I neglected to say that. We're giving them the lowest possible dose, which is a 44 micrograms X actuator.

And so therefore, we're looking for a drop in their FEV-1 as a result of the drop down to the lower dose. And there's a criterion we're using there of a greater than or equal to 7 percent decrease in FEV-1 as a result of that criterion -- that element of the study design.

And then the study treatment periods will include either -- there'll be four treatment periods, and they will include either an oral prednisone dose or a high dose inhaled corticosteroid. Two of those periods of subjects are going to receive the high dose oral prednisone, 30 milligrams BID, or the inhaled corticosteroid. There will be four randomized periods, it'll be a double-blind, double-dummy study. Each one of these periods on the various treatments

will last for four weeks, and we have four different doses: 44 micrograms, which is one actuation of the product; 2 actuations, which is 88 micrograms; or 352 micrograms. And each one of those dosed twice daily.

And I should say that on the study design which Dr. Chowdhury will be describing, we are using exactly the same test product, fluticasone propionate HFA. And we're using exactly the same doses.

So what we're going to have with these two studies is two very different endpoints. One a measure of bronchodilation, one a measure of inflammation -- the ENO study -- and looking at these two very different study designs and endpoints as a way of seeing -- of comparing the results of those two in terms of their ability to serve as a good study design for bioequivalence.

And looking at this from a graphical standpoint, there's a pre-study period of 7 days leading up into the high

dose run-in for 14 days, a low dose run-in for 28 days, and over that time period there has to be at least a 7 percent drop in FEV-1 in order for the subjects to go into the randomized portion of the study.

We then dose them with a high dose corticosteroid. And after that period, we then put them on the four weeks of the fluticasone propionate at either one of three doses, and the middle dose we're dosing on two occasions in order to determine intra-subject variability.

How am I doing for time, by the way? Should I keep going, or should I --

DR. YU: You're fine.

DR. ADAMS: Five minutes? Okay. Five minutes to discuss the proposed data analysis.

Now, the issue here is that we could either establish bioequivalence criteria on the basis of comparability in the pharmacodynamic measure that is on the Y axis, or we could establish bioequivalence on

the dose axis. And after we've gone through the experience with albuterol MDI back in the 1990s, a group at FDA -- Dr. Bill Gillespie at the time at FDA -- Stella Machato (?) and Don Sherman developed a method that we call the Dose Scale Approach. And it, in fact, makes comparisons on the dose scale rather than on the response scale.

And a point I'd like to make, and it may not be totally easy to see on this plot, which represents an Emax model. An idealized figure. But if we had two products in which we're up high on the dose response curve and the test and reference products, let's say, differed by 10 percent in their response, and we drew lines over and dropped them down, the difference in the doses between those two products that resulted in that 10 percent difference in pharmacodynamic response would be substantial. It'd be a big difference in those two doses. Whereas, on the rapidly rising portion of the curve, if

we had a 10 percent difference in response and went over, dropped it down onto the dose scale, we'd see that the doses that caused that 10 percent difference in response were much closer together.

And the point is that we do not want to set bioequivalence criteria on the response scale because, depending upon where the study is conducted on that Emax model, is going to affect the test to reference ratio. So therefore, we do not want to make comparisons on the response scale but rather, on the dose scale.

And this slide was prepared by Dr. Gillespie for an Advisory Committee meeting back in 1996. The general -- the specifics would vary depending upon just how the study design was conducted, how many doses are given. But in this particular case, which was based upon our albuterol experience, the zero dose represents baseline. And then 1 and 2 puffs -- 1 and 2

actuations of the reference product or dosed, and we prepare -- we fed an Emax model to that curve. Based upon the response of the reference product. And then, a test product can be given.

And in this case, you'll see that that middle -- I wish I had a pointer. But this curve right -- that point right there is due to one actuation of the reference product. And if one actuation of the test product is a higher response --

DR. MORRIS: Your clicker has a pointer, Wally.

DR. ADAMS: What? Oh, that thing has a -- thanks, Lawrence. Now I find out.

Okay, so in this particular hypothetical example, the test product dosed at one actuation had a response that was greater than the response of one actuation of the reference product. And you can draw a line and drop it down onto the X axis and as it indicates here, this dose of the reference

product that would result in a response equal to that of the -- from -- response from the test product is estimated by that value right there.

To make it a little clearer -- and this is my last slide -- this is another slide presented by Dr. Gillespie at the Advisory Committee meeting -- again, it's a hypothetical curve. But in this particular case, the Emax model curve has been developed based upon the 0, 1, and 2 actuations of the referenced product to establish our dose response curve. And then, the test product have a lower response than one actuation of the reference product. And as it indicates here, you can then calculate this number and get a relative bioavailability on the dose scale.

And the advantage of this method is, that it allows -- it compensates for the non-linearity. The study could be conducted in a different region of the curve and you'd

still get this same result. The same relative bioavailability. So it's an important aspect of our thinking in terms of how pharmacokinetic data should be analyzed for inhaled drugs.

And there are mathematical basis for this approach, which I'm not going to present.

So finally, I'd like to acknowledge the project advisory group for this study. It's Dr. Chowdhury, who is going to be presenting next; Sally Seymour, who's in the audience; Rob Lionberger, who presented this morning on a different topic; Bing Li, who's in the audience. And I also want to thank Dr. Lawrence Yu and Helen Winkle for providing funding for this research project.

And I also want to acknowledge two other individuals. One is Dr. Gerjavahl (?) Singh, who's in the audience. He was a co-project officer on this project before he left the agency.

And I also want to acknowledge one other individual. I should say that this contract study is being conducted at the University of Iowa by Dr. Ahrens. And he has a co-principal investigator, who is Dr. Leslie Hendeles, who is also in the audience.

I want to acknowledge both those individuals. Thank you.

DR. MORRIS: Thank you. Should we go with clarifying questions -- yeah. If there are just any brief clarifying questions, that we could take them now. If not, we'll proceed. So thank you, Wally.

DR. ADAMS: Yes, sir.

DR. MORRIS: Please, go ahead.

DR. CHOWDHURY: Thank you for being here so late in the day of a two-day Advisory Committee.

And also the audience here. It's very tough to be the last speaker in a two-day symposium and keeping interested. I'll try my best to do that.

I'll be talking about exhaled nitric oxide as a model for inhaled corticosteroids for ICS dose response. Inhaled corticosteroid has flat dose response on usual efficacy variables, such as FEV-1.

And this flat dose response has hindered the development of generic ICS. That typically would require comparison of drug products on dose response curves.

We're exploring various models and markers that can show dose response with ICS. You've heard one model, in the next 30 minutes I will discuss with you another model, which is exhaled nitric oxide or ENO, as I'll be referring to in my presentation. And ENO appears very promising.

Before I start, I'd like to acknowledge and thank some individuals. Dr. Adams, and Dr. Willy Purcell (?), who is currently at Watson and was formerly at the FDA. And Dr. Robert Meyer, who is at Merck and was formerly at FDA. And for both of

these individuals for providing scientific leadership to this project. And actually generating many of the background materials that I'll be presenting today.

And also thanks to Dr. Winkle and Dr. Yu. Now, here's the outline of my presentation. As we know, single ingredient ICS are approved for asthma in the U.S. Therefore, the disease of interest is asthma. I'll use one slide to introduce the disease to you. I'll then use two slides to discuss relevant regulatory framework for the development of NDA (?) products, and AND (?) product.

I'll then discuss the challenges in developing generic corticosteroids very briefly. I'll spend most of my time talking about why we think ENO is a suitable marker for ICS bioequivalence, or BE, studies. And we have funded a study to assess the feasibility of using ENO for showing ICS dose response. At the last part of my

presentation, I'll discuss the protocol with you.

Asthma is a chronic inflammatory disease, it is probably well-known to the audience here. And there are various cell types which infiltrate the lungs, resulting in wheezing, shortness of breath, airway hyperresponsiveness, and airflow obstruction.

And the current signs leads us to believe that ENO can also be considered as another characteristics of asthma.

There are two types of drugs used in asthma treatment. First are reliever drugs, which are used as needed. And second are controller drugs which are used continuously. ICS are controller drugs and are widely used in treatment of patients with persistent asthma.

ICS are marketed as either single ingredient products or as combination products with long-acting betagonist (?), or LABA, as fixed-dose combination products in

the U.S.

But new drugs are brought to the market in the U.S. by the NDA process, which you are very familiar with. And the essence of the process is to bring drugs of better-known quality, like CMC attributes. And safe and effective, a label, which are based on clinical studies.

Generic drugs are brought to the market by the NDA process. And a generic drug is identical to a previously approved drug, or the reference listed drug, or RLD, in active ingredients, strength, root, et cetera. Generic drugs are, in essence, copy of RLD. Sameness of the product quality of a generic and an AND or NDA drug is assured by CMC processes.

And the sameness of safety and efficacy of the two are assured by bioequivalence, which I will discuss subsequently.

Critical to the approval of a

generic drug is demonstration of bioequivalence to the RLD. Regulatory definition of BE is in the slide. The key operating principle in the definition of BE is demonstration that between a generic drug and RLD there's no difference in the rate and extent of availability of the active moiety at the site of drug action.

But for most drugs such as oral drugs, BE is demonstrated based on drug concentration in the blood, because the drug reaches the site of action through the system of circulation. This approach is not applicable for locally acting drugs such as inhaled corticosteroids, because the emitted dose does not rely on systemic circulation for delivery and action in the lungs.

To demonstrate identical rate and extent of availability of a generic drug and RLD, it is necessary to show bioequivalence on relevant clinical or pharmacodynamic endpoint. As you have heard before, the

relatively flat dose response curve of ICS, unusual efficacy measures such as trough FEV-1 makes demonstration of bioequivalence challenging.

And here is an example of an inhaled corticosteroid that shows flat dose response on trough FEV-1. Flovent is marketed in the U.S. in three dosage strength. There are three dosing recommendations based on asthma severity. In phase 3 studies, these doses virtually did not separate from each other on the typical measure, which is trough FEV-1 over the duration of treatment of 12 weeks.

Here is another example, which is a dry particle inhaler, actimoete (?) is mometasone. The trade name is Asmanex. Again, the same flat dose response curve.

Now, how does one show bioequivalence of inhaled corticosteroids? Just as a frame of reference, I'm putting up a picture of albuterol and a warfarin

generic, which Dr. Adams briefly touched on before. For an inhaled corticosteroid, the way we look at it essentially is total kind of a package approach, if you would call it. In the various areas where one needs to look at to ultimately conclude bioequivalence, these are drug product characteristics, in vitro performance, systemic exposure, and local action.

Let me expand on this very briefly. The generic ICS and the RLD should have the same formulation and device. Formulation meaning, they should be qualitatively and quantitatively same, meaning that actives, inactives are the same -- and be within 5 percent of each other.

The devices should be generally similar, and operation characteristics generally similar, allowing interchangeability.

The applicable in vitro performance should be similar, primarily being similar

emitted dose for inhalation and a similar particle size distribution.

The systemic exposure should also be similar, and is really in forms of safety and not efficacy. The ideal way of doing similarity of that are standard PK approaches using the standard PK parameters. If, for an inhaled corticosteroid, exposure is very less, one could use appropriate pharmacodynamic models such as HP access.

The generic and the RLD should have same local action. To assure that there is no difference in the rate and extent of availability of the active moiety to the site of traction in the lungs. This requires, as we heard before, a demonstration of dose response on the relevant clinical or pharmacodynamic endpoint so that generic and RLD can be characteristically compared on the slope of dose response curves. As we heard before, and I mentioned earlier for ICS, this has been challenging because there is no

established model that shows dose response in the relevant clinical or pharmacodynamic endpoint.

There are some models that we are exploring. You have heard Dr. Adams talk about one model, which was asthma stability model. And I'll discuss and present to you the other model which we are exploring, which is the ENO.

Now, ENO appears to be a good marker for use in ICS bioequivalence study. ENO is a clinically relevant marker of asthma, its response to inhaled corticosteroids, and the responsiveness behaves in a fashion that makes it suitable for crossover BE study. And the methodology and measurement are standardized and harmonized for the exhaled nitric oxide.

I'll expand on these points using data from published literature, and bring back to this slide again and kind of wrap it up saying why we think ENO is a good model.

Nitric oxide, or NO, has several important biological functions, such as regulation of vascular constriction, later degradation, neurotransmission, et cetera. In the airway respiratory tract, it acts as a selective pulmonary vasodilator. Source of NO in the exhaled air is upper airways, particularly sinuses, and lower airways, or the lungs. Once the nasal airway or the sinuses are excluded, NO in breath is originates all from the lower airways.

NO, or nitric oxide, is synthesized by NO sythase, or NOS. And these are found in several cell types. Let me go over that.

There are three types of NOS, which are numbered as 1, 3, and 2. These are distinct gene products, and the chromosomal occulations in the humans are different. And all three of them are expressed in the airways.

Functionally, NOS are of two types. Constitutive and Inducible. The constitutive

NOS is produced intermittently at very low concentrations, femtomolar or picomolar. Inducible NOS is induced by pro-inflammatory cytokines such as TNF, (inaudible) IL-1, which are, again, markers of inflammation important in asthma. And they're produced at larger concentrations, nanomolar. And they are there for several hours after exposure to an inciting agent. And importantly, inducible NOS is steroid-sensitive.

Here's a picture of NOS. And this one is NOS 1, or cNOS. Which is shown in an endobronchial biopsy specimen taken with a patient who has asthma, showing the expression here in the epithelial cells.

Now, this slide shows the levels of ENO, or exhaled nitric oxide, in various respiratory diseases. In asthma, it is elevated. And I'll show some data later on that shows it elevated quite high. Other diseases where ENO levels are elevated are pretty much clinically distinct from asthma

and can be clinically easily distinguished.

ICS reduces ENO in patients with asthma. ENO is quite sensitive to ICS. I'll show data from two studies, one here and the second study will be in the next slide.

This slide shows results of a cross- sectional observational study. Here is the ENO level in control subjects, ENO levels in patients with asthma not on steroids -- quite a high increase -- and here the ENO levels in asthma on steroids comparable to control.

Here is a study where 11 patients with asthma were treated with inhaled steroid, 18 microgram Budesonide or placebo for three weeks in a crossover design. And if we see the results, the baselines are right here for the ENO. With steroid treatment, the ENO level went down. Quite a large reduction. With the placebo, there was virtually no change.

The important point for us is the

reduction of ENO by ICS in patients with asthma shows dose response. I'll again show results from two studies. One in this slide and the second one in the next slide.

This slide shows results of a crossover design study where patients with asthma were treated with beclomethasone for 1 week, 3 doses used; 100, 400, and 800 micrograms per day. And there were five visits. Visit one was the baseline, visit two was the placebo, and then these three are the three doses. If you look at all subjects, there was a dose response. Perhaps not that steep, but there was. If you look at patients who were taken out of these who had high baseline ENO level, the curve was much steeper.

The second study showing dose response is presented here, and this was a parallel group design study. Patients with asthma were given placebo, Budesonide 100 or 400 once a day for three weeks. And ENO

levels were measured on days 0, 3, 5, 7, 14, and 21. The time course of ENO reduction was rapid, occurring approximately in seven days. A numerical dose response trend was seen during the first seven days. And then, the slope was flat. Between the two steroid doses, there was a dose response. And if you look at this four points, which creates the dose response curves -- and same here -- and the higher the dose of steroid appeared to have a steeper curve. And the rate of decline was more rapid with the lower dose of steroid, with the placebo being flat.

Another important point is that the reduction of ENO by ICS in patients with asthma is not affected by bronchodilators. Bronchodilators being albuterol, the classic drug as a short acting agent. And low acting bronchodilators such as salmeterol and formoterlol.

To make the point, I'll show two study results. One here, and the second one

in the next slide. And in this slide, I'm showing results of a crossover design study where patients were given fluticasone propionate plus salmeterol for two weeks. Or fluticasone propionate for two weeks. The doses were different here. Here is the baseline level of ENO, which is quite high. And the two levels, either with agonist or without, they're virtually very similar.

And this is another study. And this was a crossover design study. And patients here were given Budesonide plus formoterol for four weeks followed by Budesonide for one week or fluticasone plus salmeterol for four weeks followed by fluticasone for one week. And if you see the results, this is the baseline. Quite high here, no levels.

It came down with the treatment, either with or without steroid -- or without long acting agonist, formoterol, the numbers were similar. And same here, with or without

salmeterol in presence of fluticasone. The numbers were similar, showing virtually no effect of with agonist.

And lack of a bronchodilator effect of ENO is important, and beneficial in several ways. First, in ICS BE studies, patients will need to take rescue medications for symptom control. Particularly when they're washed off ICS. And risky bronchodilator use will not interfere with ENO changes in such studies.

And second is lack of effective bronchodilator will allow ENO to be used for comparing long acting betagonist plus ICS combination to test the isolated effect of ICS complement without the worry of LABA complement interfering with the ENO.

Another important point is the reduction of ENO in patients with ICS in patients with asthma is consistent, and reproducible. And to make the point, I'm showing results of a parallel group study

where patients were treated with Budesonide for four weeks, and then washed out for four weeks, and then given eight weeks randomized treatment with a steroid or placebo. Here's the baseline. After four weeks of treatment, the ENO levels came down. After wash out, it came up again, virtually going back to baseline. And then, when the patients randomized to either steroid or to placebo, the levels came down with the steroid or without steroid, it came up. Showing quite a bit decent reproducibility of the effect.

And the reduction of ENO by ICS in patients with asthma is fairly rapid. And reverses fairly rapidly as well. And this is one thing that shows that point. The ENO level coming down quite quickly with the steroid treatment and staying low as long as the patient is on steroid. And coming back quite rapidly once the steroid is tapered off.

A time course of ENO reduction with

ICS compared to other outcome measures such as symptoms, hyperreactivity of production is quite rapid. It's quite rapid compared to others. And one point to note that the expelled ENO does not correlate with pulmonary function parameters. However, it does correlate with other markers of inflammation.

So with this information, in clinical practice ENO is gaining some traction and is being used in asthma monitoring. And there's some points, I'll get to it in a later slide. But one point I want to touch on is the methodology of exhaled ENO measurement.

You may have noticed in the previous slides, the ENO values from various studies were quite variable. And this was because these studies were done at different time points, in different labs, using different methodologies. The measurement of ENO has recently been standardized and

harmonized. There's a European Respiratory Society document on this, and the ATS, the American counterpart, has subsequently a joined document, which basically standardizes the procedures. And we expect the standardizing of procedures will actually help in using this in our biostudy.

So going back to what I was mentioning earlier, there is quite a bit of use of ENO in clinical practice. And a lot of publications on that. And mostly revolving around the use of ENO of a measure of inflammation, as a measure of steroid treatment, compliance, and so on. And it's pretty encouraging, because ENO is becoming more recognized as a valid pharmacodynamic endpoint that actually is even making a sway in clinical practice.

So based on existing data which I shared some of it, ENO appears very suitable for use in ICS bioequivalence study. And I've showed you various characteristics of

ENO in patients with asthma, in the previous slides. And I've showed you that it is a relevant marker for asthma. I've shown you that it has increased in asthma, is responsive to INS -- ICS. It decreases by ICS. And it also decreases with clinically relevant doses, and not affected by bronchodilators.

It's a quite rapid onset and offset of reversibility, and the effect is reproducible, making it very suitable for use in bioequivalence studies. And as I mentioned earlier, there is quite a bit of standardized methodology for measurement which is harmonized.

So encouraged by these observations, we put forward an RFP for study exploring ENO as a biomarker for potential BE study. And ultimately funded a study to test this. And the study was contracted to a National Jewish Medical Center in Denver, Colorado.

So before I describe the study, I would like to acknowledge some colleagues of mine who are in the project advisory group. Besides myself, there's Dr. Adams, Bing Li, Robert Lionberger, and Sally Seymour.

So here is the study design and the conduct. Patients to be enrolled in the study would have asthma according to standard ADS criteria, should be reversible. Standard ages. And exhaled nitric oxide quite high, and the cutoff use in the study is over 45 parts per billion.

The study has four phases, which I'll get to in the next slide. And these are being called 1 through 4. Idea of the first three phases is to enroll patients who are likely to show ENO response.

And the phase 2, which is the main phase of the study, will test those response.

Let me show you the design and the conduct of the study using the slide. As I said, the study has four phases. The first

phase is a placebo running phase, where patients will be coming into the study, they'll be washed out of the ICS, and ENO will be measured every other day. The intent here is to have patients who have got ENO level above the cutoff of 45 parts per billion.

Then, the patients will go into a 14 day treatment with fluticasone 88 microgram twice a day.

Again, frequent measurement of ENO. And the expectation here is the ENO will decrease, and the decrease will be captured as something which we are calling as "responders" where the decrease is over 25 percent. Then, there will be placebo wash out again. And the expectation here is the ENO level will return to baseline or within 10 percent of it.

So the idea for this phase is to get patients with high ENO, show that they're responsive, and show they come back up again.

And then, on the final phase which is the phase 2, patients will be given 44, 88, 352 microgram as in the other study that Dr. Adams mentioned. With 88 microgram being repeated.

The major article of interest in the phase studies are changes from baseline in ENO with different doses of ICS, magnitude of those response, intra-subject variability in those response. And our anticipated outcomes are a large decrease of ENO from baseline with ICS. A good dose response, and a low intra-subject variability.

The number of patients to go through the study, expectation is approximately 80 patients will be enrolled in the placebo run in. Some will drop out because they probably would not have the elevated levels. And then with the treatment, again, some will drop out. Ultimately, will go into phase 2. The expectation is that 39 will complete.

The measures will be standard. ENO will be measured by FDA-cleared -- the NIOX instrument. In addition, other measures of asthma control such as spirometry and methacholine challenges will also be done.

So in conclusion, then, development of generic ICS has been challenging. So has been challenging the development of combination products of generic ICS, and low betagonist. As I mentioned earlier, standard BE approaches are not applicable.

Because of with the doses, it does not rely on systemic circulation for deliver and action in the lungs. And the relative flat dose response curve on typical efficacy endpoints have made demonstration of bioequivalence difficult.

The study is (inaudible) to develop models that can shorten the response and therefore two such models today. And I, and we, hope that these studies will succeed and lay a path for developing generic inhaled

corticosteroids, either as a single entity product or as combination products with low acting betagonist.

With that, I stop and thank you very much.

DR. MORRIS: Thank you. All of you, for those excellent presentations. There is questions for our speakers, here, and start with Mel.

DR. KOCH: Mel Koch. Just a clarifying question. The measurement of the NOS is made by NIOX instrument? What's the basis of that, electrochemistry or?

DR. CHOWDHURY: I am not a chemist, I'm looking at some chemist to help me here. Chemiluminescence.

DR. KOCH: Chemiluminescence. And that part per billion sensitivity? That's --

DR. CHOWDHURY: Yes.

DR. KOCH: Method's well-established?

DR. CHOWDHURY: The method is well-established. As I was showing you in the

earlier slides, initially back 10, 15 years ago some laboratory based methods were used. And you saw a lot of variability. And the ATS ERS got together and the method has been very well-established. There's actually position statement with the ATS and ERS. And the mission is they're commercially available after they're cleared. So that portion is actually very easily addressed.

DR. MORRIS: Marilyn?

DR. M. MORRIS: Marilyn Morris. I just had a question regarding the initial levels of exhaled nitric oxide for your study. You indicated that patients had to have levels of greater than equal 45 parts per billion? And I was wondering, overall, what percentage of patients would have levels?

DR. CHOWDHURY: Approximately half. And we are still in discussion with investigator, we already have discussed with investigator, and they have a large database at National Jewish where ENO has been measured over

years. And based on the existing database, the expectation is if they screen 160 patients, approximately 80 would have that number.

DR. M. MORRIS: So do you anticipate if a patient has levels less than that, that they may not show this dose dependent decrease in exhaled nitric oxide in these studies --

DR. CHOWDHURY: From my standpoint --

DR. M. MORRIS: And is this the reason why in some studies they haven't shown sort of a dose dependent decrease?

DR. CHOWDHURY: Yeah, if you see one of the studies which I showed showing dose response, I showed two studies. The first one, the higher the dose -- the higher the baseline ENO was, chances are showing the dose response was higher is simply a matter of that having a lesser or larger room to decrease. So we're choosing 45 sort of with that idea.

And it is a first kind of a test of our hypothesis. It is entirely possible that a lower baseline ENO may also do it. The

question becomes, then, the sample size may need to be increased. So we are going with that 45 number as initial test.

DR. MORRIS: Lawrence?

DR. YU: Yeah, I should have mentioned. I was in a hurry finish my opening remark, that this topic is just for awareness. So there's not question to ask you. We will come back hopefully in the next time with the recommendations seeking your input and advice. Thank you.

DR. MORRIS: Yeah, I should have mentioned that, too. And please, Art?

DR. KIBBE: In that case, I get to ask some interesting questions and then not make a recommendation. It seems from the information that we were given that there is a really poorly defined dose response in the actual measures of the clinical manifestations of the disease, right? That that's relatively flat. That a change in dose seems not to have a dramatic change in response, in that -- that's why you're

looking for a secondary marker. Right?

DR. CHOWDHURY: Let me just address this not as a question but just as a comment. Inhaled corticosteroids do have a dose response. It is quite flat. And if you go back and ask a patient, they know it very well. That if your patient has got, say, asthma which is poorly controlled, the first thing the clinician would do is increase the dose. And they don't respond. And then, we cut the dose, and the response stays.

There is a dose response. If you go to large clinical studies for approval of a drug where we use trough FEV-1, it becomes rather flat. But I have not shown data -- but in the development programs, again, there are often other models he used. Such as showing response to methacodine (?) challenge, or some other markers or asthma stability or exerbations (?), or use of oral corticosteroids. In those -- you see those response. Again, not necessarily all the

time excessively significant.

DR. KIBBE: So that what I hear you saying to me is that if you have a non-responsive patient and you initiate corticosteroid therapy they feel a real benefit of it. But if their dose was changed slightly or even dramatically, like go up by another 50 percent, they wouldn't necessarily feel or notice a change. That's where the flatness comes from. Is that not right?

DR. CHOWDHURY: No, that is not really true. I mean, patients often would feel a change of reduction or increase of 2 or 44. And that's the reason currently marketed --

DR. KIBBE: Two or fourfold.

DR. CHOWDHURY: Correct.

DR. KIBBE: But 50 percent, 25 percent difference wouldn't necessarily --

DR. CHOWDHURY: That is --

DR. KIBBE: It is relatively flat. Otherwise, we could you use that.

DR. CHOWDHURY: That's correct.

DR. MORRIS: But aren't you saying that the patient will feel it but the FEV won't show it?

DR. CHOWDHURY: Patients will feel it, and FEV will not often show it.

SPEAKER:: Right.

DR. CHOWDHURY: And for the purpose of approval, FEV-1 is still a surrogate of asthma control. It's an indirect measurement of inflammation.

DR. MORRIS: So the measure doesn't show it but the patient can feel it.

DR. CHOWDHURY: Yes.

DR. MORRIS: I think is what you're saying.

DR. CHOWDHURY: Yes.

DR. ADAMS: You know, and that's another aspect of this, too, which is that on the data which Dr. Chowdhury has shown, those are population means.

You know, those are average data. The individual subject is capable -- many

individual subjects will be capable of showing an increase in response with an increase in dose. But when you look at the average data, it may not be seen as markedly.

DR. KIBBE: Now, here's where I'm going to go down one of those dangerous roads. This particular dosage form is fairly well defined as a dosage form, because we are very careful to measure and accurately reproduce the particle size generated so that we get it into the right place in the lung, or else if it's the wrong particle size it will be exhaled easily or whatever. So we're tight on that. And we can measure the drug load produced in each puff, and those are relatively tight. And so the question that I have in the back of my mind is -- and I'm bringing it to the front -- is how -- where is the problem that causes an individual puff to not be equivalent to another individual puff, physiologically, that we have to measure for?

I don't -- I mean -- we're going to an exquisite level to get a bioequivalence

study which is actually a pharmacodynamic based bioequivalence study to evaluate two different products which the standard testing of those products is relatively tight. And maybe I'm not even on that, but I would expect that the agency expects a particle size analysis of each puff and a content analysis of each puff, and those are the two criteria that matter to whether or not the drug -- the active ingredient -- gets to the right part of the lung to start with. And so now, if there is no additional ingredient which Q1, Q2, and we're getting the same particle size and the same total load, and we're delivering it to the lung, then the real variability is how well trained the patient is who's using it. And then we're going to go and do what is a fairly extensive study using a pharmacodynamic second generation or two removed measure to establish equivalence.

I mean, are we beating a dead horse

with this study?

DR. MORRIS: Can I -- I think the way I read it -- and please feel free to comment -- I sort of the way I was looking at these, at both the asthma stability model and the ENO, was that the bioequivalent studies that are required now would be prohibitive in terms of the size of them and that this was a way in addition to a more accurate measure was to be able to do it with fewer -- for the asthma stability model, was to be able to do it with fewer patients. And the clinical study --

DR. KIBBE: And my heretical question really is, why are we doing it at all?

DR. MORRIS: At all? You're saying why at all. Right.

DR. ADAMS: You know, we've got issues with these products in that it's not simply the drug and the formulation. It's a device formulation combination product. And there can be differences in terms of the device that's used by the -- a test product manufacturer

versus the referenced drug manufacturer. There may be differences in the actuator orifice, performance of the actuator, maybe the metering valve differs in some regard.

But in addition to that -- you know, you talk about the same particle size distribution. And why -- we, in fact, by using the cascade impactor, we would know the aerodynamic particle size distribution.

DR. KIBBE: Maybe I'm missing something, but when the actuator works and you get a fog produced, and you can accurately determine the particle size distribution of that fog, and compare that particle size which is a bell skewed to the right, approximately -- it comes up skewed to the right a little bit. And you can compare those two between different product formulations, and you can compare the total amount of drug coming out, and you know the content because you know the propellants in question -- which are not even part of the actual dose, they're dissipated -- and whatever

adjunct is in there. Then, what variable am I missing that I have to do this study to make sure it doesn't affect something? That's where I am.

DR. ADAMS: You know, we -- you know, the agency has participated in a profile comparison working group in which it's looked at aerodynamic particle size distribution. And that's been very challenging, because when you look at the cascade impactor, that which is aerodynamic particle size.

A test and reference product are not going to be identical. And depending upon what your metric is, it may seem like it's the same mass, median, aerodynamic diameter. Maybe very close. However, when you look at the individual deposition on the various stages, they may not be as close as the MMAD might imply.

And so products will differ. And we don't know what the importance of those differences between a test and reference

product will be based upon in vitro data only. We don't have an in vitro in vivo correlation to know what the significance of those differences may be. The differences will be there. And so as Dr. Chowdhury's indicated in his slide presentation, our approach for establishing bioequivalence is one in which it's a weight of evidence approach based upon the sum of a number of different criteria being met in order to establish equivalence.

There's the formulation and device -- formulation being Q1 and Q2 the same qualitatively and quantitatively, the same. Device comparability to the extent that that can happen. There's the in vitro performance data, there's the PK data, and there's the (inaudible) local efficacy data. It's all a package, and it's only -- because each one of those has weaknesses, to stand alone and say that the products are equivalent, we put them all -- all this

information together and say that package of information confirms that bioequivalence has been established.

DR. MORRIS: Could I just -- one quick thing during the -- I'll turn it over to you. So I mean, the equivalence for the DPI devices is even more problematic, I know. And I think that sort of enters into it. But it seemed to me like the real win here is to combine the asthma stability model with the ENO. Will that work? Will you see the decrease in ENO after you ramp up in the asthma stability model?

DR. ADAMS: You're saying, would we expect that a test to reference product would show the same relative bioavailability in both of those study designs?

DR. MORRIS: Well, in other words, so my read was that the asthma stability model was actually to have a more sensitive and efficient way of doing the study. I mean, in terms of numbers of patients, you said you had the 1,400 patients versus 25. So could you use ENO as

your marker --

DR. ADAMS: Of course.

DR. MORRIS: In those studies.

DR. ADAMS: That could also be used. I mean, as Dr. Chowdhury indicated, the -- both of these study designs are two ways of looking at the same issue, which is one of equivalence. And we hope that both of these will work fine. We won't know until completing the study --

DR. MORRIS: Right.

DR. ADAMS: What the study power will be in order to --

DR. MORRIS: But the ENO is a marker --

DR. CHOWDHURY: Yeah, the issue here is that these are different designs, different models, and either or, if it wins, can be used in BE studies.

If you look at the asthma stability model, you are still using airflow. Some measure of airflow, which is more close to the basis of the approval of this drug.

However, being that, it may or may not be as sensitive as they want it to be. Whereas ENO, being a biomarker, looking at the existing data, appears to be equally promising if not more.

So these two doesn't have to happen together one or the other --

DR. MORRIS: No, no, no. I understand. But am I correct in saying that the asthma stability model, in a sense, can use any marker if it's an appropriate marker?

DR. CHOWDHURY: Understood. It can actually use any marker.

DR. MORRIS: Okay.

DR. ADAMS: You know, one --

DR. CHOWDHURY: It does.

DR. ADAMS: It does. It includes a measure --

DR. MORRIS: It does.

DR. ADAMS: We are measuring ENO that study.

DR. MORRIS: In the asthma -- oh.

DR. CHOWDHURY: I think your question is a hybrid. Can the asthma stability model be used, and rather than using FEV-1, can it be used --

DR. MORRIS: Yeah.

DR. CHOWDHURY: As an ENO. Answer is yes, and actually, ENO is being looked at.

DR. MORRIS: Good, that's good. Question --

DR. ADAMS: You know, one point I'd like to make is, the take home message -- one of the take-home messages here should not be that it looks as if a 25 subject study conducted at a crossover design with the asthma stability model will be suitable -- powerful enough to establish bioequivalence.

Recall back the -- one of the criteria was that the bioequivalence fall within 50 to 200 percent. Now, that's an exceptionally broad range, and it's far greater than the 80 to 125 that we normally think about. So those numbers are diminished

by the width of that proposed confidence interval --

DR. MORRIS: Sure.

DR. ADAMS: That Dr. Ahrens used.

DR. MORRIS: Yeah, that's a good point. But presumably your study will hone in on that.

DR. ADAMS: And it's critically dependent, too, upon the actual slope. And that's why it's important that we look at these three different doses, to get as good a measure as we can of the slope during that study. So we don't know -- you know, this is -- we're trying to fine tune the study, enrich the population, get a good measure of the slope, get a good measure of the variability -- that's why we're doing the replicate design at the 88 microgram dose. And putting all of these things together to give us added confidence in the performance of that asthma stability model.

DR. MORRIS: Sure, sure.

DR. ADAMS: And it's similarly on the

nitric oxide study. We're looking at various aspects, too, as Dr. Chowdhury indicated, to enrich the study population. And we have questions about, do we really need to follow the decrease in ENO over a four-week period? Maybe not. There's a learning process going on here in terms of what we may need to ultimately ask for in the study design -- in the actual bioequivalence study design.

Recognizing that these two studies are not bioequivalence studies --

DR. MORRIS: No, no. No.

DR. ADAMS: They're solely dose response studies. And they're based, too, upon a model drug.

What we're hoping to do is to develop an approach which can be used for basically all inhaled corticosteroids with whatever modifications in dose or whatever may be needed. But we're trying to put together a model. It wouldn't need to be fluticasone. It could have been some other

drug.

DR. MORRIS: Sure.

DR. ADAMS: Fluticasone was convenient.

DR. MORRIS: Jerry?

DR. COLLINS: Jerry Collins. What I thought I heard was that the population FEV in the flat range does not predict for clinical benefit that's occurring over that dose range, that there's still clinical benefit even though FEV is flat.

DR. CHOWDHURY: That's correct. And in these studies, the benefits are actually being measured.

DR. COLLINS: But just remind everybody that the agency's definition for more than 20 years has been, if you call something a surrogate endpoint, it has to predict for clinical benefit. So be careful when you describe FEV, because it doesn't sound like it meets the agency's criterion for being called a surrogate endpoint.

DR. CHOWDHURY: I'm not sure why you say that. Because FEV-1 is actually used quite extensively in clinical practice, and has been used over years and it actually does correlate quite well with real outcomes such as macerations and other factors.

DR. COLLINS: Well, what I heard is for individual patients, you can see some change that may have a dose response curve that correlates with clinical outcome. But for the population, which is what the current standards are in the existing OGD guidances, for the population FEV does not predict clinical benefit.

DR. CHOWDHURY: Well, I think -- I mean, I think one has to look at the data carefully and we, I think, are more careful in making that conclusion.

Because even in the population, if you look at this data which forms the basis of approval and other -- many of the studies which NHLVI (?) has done over years, FEV-1 is

one of the measures but there are many other measures. And they actually go in the same direction. And many of them are actually equally significant.

DR. COLLINS: If I submit a product --

DR. HENDELES: Parallel versus crossover --

DR. CHOWDHURY: Yeah.

DR. HENDELES: Parallel design might sound (inaudible).

DR. MORRIS: Actually, if we could -- if you could come to the mike if you're going to, so --

DR. HENDELES: Leslie Hendeles, University of Florida. I don't know -- now it's on. Part of the issue is is that the flat dose response is particularly a problem with the parallel design, which has been required in most of these studies because of the fear of the carryover effect. And what's happening -- and in fact what improves the power is the fact that the lung function is maximized to its best

before each treatment regimen, and there's a crossover, and what is being observed is a decline in the patient worsening. And so it isn't correct to say that FEV-1 is not a good marker. It is, and in fact it's a harbinger of asthma attacks, which is another endpoint.

DR. MORRIS: Any other questions? If not, let's thank our speakers again.

And with that, I think we're down to comments from Helen.

DR. WINKLE: In the interest of time, I'm just going to shorten my comments. I know everyone's anxious to get out of here.

I think the conversation about all five of the topics was extremely interesting. And at times very provocative. I think we in FDA need to take a lot of these comments back and apply them to our strategy as to where we are going on each of these topics. I think there's a number of them that we will need to bring back after we develop our strategy. Bring back to the Advisory Committee. And

seek further advice.

But I want to thank all of you for your input. I really, really feel that we learned a lot.

And again, we will be using that to either apply in our guidances or apply to our studies or whatever strategy we're going to take.

So thank you again.

DR. MORRIS: And let me add my thanks to everybody for participating, and for the honor of serving as chair. And all of your guidance over the years, Helen.

So with that I think we're adjourned, officially.

Is that right? Yes.

Thank you. Safe home.

(Whereupon, at approximately 4:46 p.m. the MEETING was adjourned.)

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