wants to say anything of concern, let's do it that way, that if there are serious concerns about this, let's discuss them. If there aren't, let's assume that there's consensus on this in the affirmative and we'll go ahead.

DR. ANDERSON: Mr. Chairman, I don't really have any concerns. I view this sort of like--this study has been going on for a long time and I sort of view this as walking into a quantum mechanics exam after not having taken the course.

I don't disagree. I'm still trying to sort out the issues and define the problem. So I would like to not vote on any issue but rather to express my confidence in the people who have been doing this, studying this for all these years.

So that my maybe abstinence from voting, if we vote, is not to be construed as disagreeing with it but not having enough information to make an intelligent judgment about this.

DR. BYRN: Other comments?

[No response.]

DR. BYRN: Why don't we go ahead with the general idea without any vote that there's an affirmative feeling on the committee on discussion topic 1? Let's discuss the other topics and then at the end let's come back and we'll go over discussion topic 1 and we'll determine whether all

the provisos we put on it through the rest of the day make people less comfortable or more comfortable.

Okay, so let's go ahead with Roger's scenario that was presented, Kim, just the next transparency, which was--and maybe Roger could walk us through that as a hypothetical. This would be a hypothetical study?

DR. WILLIAMS: Well, I think the committee now is going to get into one of the tougher questions and let me see if I can explain it this way.

I call it what's in the box? And what's in the box would be what the agency would recommend in terms of some drug products that would be recommended to have replicate study designs.

So Kimberly, I've got some graphics and Steve, if they help the committee, I'll put them up quickly. And if they don't help the committee, you can take them down real fast.

Now I would say this is the box that's recommended by the agency in the general guidance that Vinod talked about. The way the agency conceived it was sort of put everything in the box and then take some things out.

Now as you can see, we took a lot out. We took out long half-life drugs, anything that needed a steady state study, anything that had a safety or blood concern, anything that was subject to BCS Class I, Biopharmacy

Classification System Class I, which I think we're estimating now is about 10 percent of all the drug products. Non-oral dose forms. What's that last one?

Oh, we wanted to take out particularly for pioneers anything that wasn't related to the pivotal study to the to-be-marketed dose form. So we would never want to say to a pioneer that some of those early studies that you do to optimize your formulation would be subject to individual bioequivalence.

Food effects is off the table. And then we wanted to give--you know, all of these things are recommendations so any sponsor who wanted to come in and talk to us about why they didn't think they needed to do a replicate study design would certainly be appropriate.

Now I think this should be clear. We started with everything and then we take a lot out.

Now the next one sort of starts from a different thing, which is that the box is empty and you put certain things in it. I think here now I tried to capture the thought that Les spoke to from the expert panel, which is that you put certain things in the box. And some other things that you could think about putting in that box are listed there in terms of the Biopharmaceutic Classification System II, III and IV.

There's one in there that speaks to that root mean

square error that I talked about earlier today, that if you do a replicate study and it's less than .15, you'd be okay. There may be some other things that could be put in the box.

Now the last overhead actually captures both thoughts, where now we say we're putting things in the box and we're taking things out of the box.

Now Steve, I appreciate that this may not be helpful but I hope it helps the committee begin the discussion.

DR. BYRN: Let's leave this up and let me ask Les Benet to--as I understand it, Les, your committee put in the box modified release drugs, right?

DR. BENET: That's correct.

DR. BYRN: Did you not put in highly variable IR drugs?

DR. BENET: That's correct. We could not reach consensus because the only category where the expert panel could reach consensus was on modified release drugs.

And let me come back to the point raised in question number 1 because there we expected you have a rationale for seeing a potential subject-by-formulation difference. There is a complete rationale in modified release drugs.

So we felt that that was the one category we all agreed on, but we also said in our second recommendation we

would like to see these highly variable IR drugs carried out that way but we cannot recommend that it be required by the agency.

DR. BYRN: Am I to understand, too, that by implication, your panel answered affirmatively to the first question?

DR. BENET: Oh, yes. My panel is 100 percent for topic number 1 and feels in answer to everything else here, you know, that this will work, that modified release products should be the stalking horse to provide the kinds of information that would be useful to the scientific community in learning whether this would be something that would be useful.

And I think my committee would also say, in answer to the rollback question, if it's not useful, if we come out with all that kind of information and there's nothing there, you stop it.

DR. BYRN: Okay. Now you didn't put in also--your committee did not put in BCS Class II, III, IV drugs?

DR. BENET: That's correct.

DR. BYRN: You specifically discussed those and didn't think they should be in there?

DR. BENET: No, we could not reach consensus. We specifically discussed lots of things but we could not reach consensus.

DR. BYRN: Okay. And what about the RMSE 0.15?

DR. BENET: That's something that you have to actually run the study to find out in the first place.

DR. BYRN: Okay. So I think what we ought to discuss is among ourselves now it's clear that we have an expert panel that is favoring modified release drugs in the box, everything else out of the box.

I think we should discuss first whether we think highly variable IR drugs should be in the box and then these other issues.

Yes, Arthur?

DR. GOLDBERG: I have a question for clarification. Does the agency believe the data that we saw this morning on the Levothyroxine is a subject-by-formulation interaction?

And the other question, does the data we saw this morning on the sorbitol in Ranitidine, was that a subject-by-formulation interaction?

MR. HUSSAIN: With respect to sorbitol--

DR. WILLIAMS: This is Ajaz--

MR. HUSSAIN: Ajaz Hussain, FDA.

With respect to sorbitol, our hypothesis was that sorbitol would tend to decrease radiant extended absorption of a low permeable drug like Ranitidine and sucrose might help improve that.

So we're in the process of testing that hypothesis and hope by the end of next month we'll have a complete analysis. Until then I can't comment on that.

DR. GOLDBERG: Let's assume that the data you had now stands. You don't do anything else. Would that be considered a subject-by-formulation interaction?

MR. HUSSAIN: No, not at this point, no.

DR. GOLDBERG: And what about the Levothyroxine?

MR. HUSSAIN: Levothyroxine, I'm not fully familiar with that but based on the differences in dissolution, I think there were differences so I'd rather not comment on that.

DR. BYRN: Bill, can you comment on that?

DR. BARR: Sure, I'll be glad to.

DR. BYRN: Introduce yourself.

DR. BARR: Bill Barr, Medical College of Virginia, the individual who presented the data on the Levothyroxine.

In this, to me it's clearly subject-treatment interaction. If you have people who have a long transit time, there will not be a difference between these two formulations. That was the majority of individuals.

On the other hand, if you do have people who have a short transit time, you will have differences between those two formulations such that it would be clinically relevant. And I think that meets all the qualifications

that we've talked about in terms of the subject-treatment interaction if there indeed are physiological variables that will make a difference between individuals in the response to two different formulations.

I think that is the definition that we've used, so I think it fits those criteria.

Now one could argue that had you simply looked at the in vitro dissolution, you might have been able to pick that up but the truth is nobody did.

DR. BYRN: Kathleen?

DR. LAMBORN: Actually that was coming very close to my question. My question was would some of the other measures that are currently required to get bioequivalence have detected that without the requirements of actually clinically looking at subject-by-formulation interaction?

DR. BARR: As I commented, if you looked at the in vitro now retrospectively and said yes, with this new information we have we should probably not let products on that way and call them bioequivalent, I think that you would pick that up. But the point is no one did without these kinds of data.

And furthermore, there were two studies that I know that were identical to this that people didn't pick it up simply because they weren't looking for it. The data were identical. They saw the same interaction in studies

that were done almost identically that were submitted to the FDA and they thought they simply were outliers, although the mechanisms seemed to be exactly the same with the same product.

DR. BYRN: Now Robert's going to ask a question but Levothyroxine is an considered an IR product?

DR. BARR: Yes, very much so. Well, I'm not sure; if you looked at the reference drug that we looked at, you may disagree with that based upon the solubility. But the intent, I think--there are three generics that we've looked at the in vitro and they were virtually all the same, very much IR drugs.

DR. BYRN: So the question, the issue and why we're talking about Levothyroxine is that that would be a highly variable IR drug and we're trying to decide whether to put it in or out.

I think Bob is first and then--

DR. BARR: Let me just comment that I'm not sure it would be highly variable if you look at a specific product. I think that in general, the drug itself might be considered to be an NTI drug but not necessarily a highly variable drug.

DR. BYRN: Okay. Now is it variable from product to product or it's not even highly variable in that regard?

DR. BARR: I don't remember the exact amounts but

we did look at intrasubject variability in terms of this one term and we found that I think the intrasubject variability for the reference drug was something like about .3 and the intrasubject variability for the generic drugs was something like about .1 or .2.

So they would not be considered highly variable, I think, for the generic drugs, which performed better than the reference drug in this case.

DR. BYRN: Okay.

DR. BRANCH: Just before leaving that project, Bill, I had two questions of clarification.

The first was did you actually measure intestinal transit times in these people?

DR. BARR: No, we didn't. We plan to do that.

DR. BRANCH: So this is speculation in terms of the transit times?

DR. BARR: That is correct.

DR. BRANCH: And secondly, in those people who had an elevated TSH level, did you actually look and see whether those people had lower thyroxine levels, because you were presenting mean data, not the individualized data and you're really focussing on the outliers. Was there any relationship between the actual plasma levels and the TSH response?

DR. BARR: They did look a little bit lower in

those cases in terms if you looked at the combined sum of those. The problem, of course, is that this is a steady state level that we're viewing, whereas the TSH is really that day that it picked up. So it would be two successive days.

So it's really much more sensitive than that mean level that we're looking at steady state. I think we probably would have seen greater differences had we done this as a single dose study perhaps.

DR. BRANCH: So as a sort of general comment, it would be really helpful as examples are identified where a subject-by-formulation interaction is being imputed is trying to find the mechanisms and whether they have clinical consequences.

DR. BARR: We certainly agree. Unfortunately, this was a funded study, that these results just happened to come out and there really are no funds really to go back and do those kinds of studies that I'm aware of. That's one of the difficulties we have in terms of really getting at some of the more concrete mechanistic implications.

DR. BYRN: Roger?

DR. WILLIAMS: I don't want to interrupt the committee discussion.

DR. BYRN: Okay, Mary? Mary and then Judy.

DR. BERG: Dr. Barr, sorry to keep you up there so

long.

In regard to the TSH that you showed this morning, there is a question of circadian rhythm with TSH levels; in other words, the chronobiology. And were all those samples taken roughly at the same time? Because we know that TSH peaks literally after midnight. So I was curious, since you showed mean data--

DR. BARR: They were taken at exactly the same time. All the replicate samples--

DR. BERG: Because that's actually a very important point to note when doing that kind of study, because that is a biomarker then, that TSH really becomes, and you want to know in relationship to when the dose was taken, your sampling of the blood samples--

DR. BARR: Each of those were, according to protocol, taken exactly plus or minute one minute apart from each other.

DR. BERG: But I'm talking about with regard to the timing as such and taking into account the chronobiology of the TSH itself.

DR. BARR: All I can tell you is that each TSH level was taken at exactly the same time for each individual and the same time for the same individual each time it was taken.

DR. BYRN: Judy?

DR. BOEHLERT: Don't go away. Maybe I'm missing something here but it seems to me we're perhaps overinterpreting this data because when I looked at the dissolution data, these products do indeed behave in very different manners. And what we probably have is a nondiscriminating dissolution test. If, indeed, the products had been equivalent under dissolution conditions then maybe you would not have seen a subject formulation difference.

And so we're saying it's a subject formulation difference when I really think it's a basic difference in the products themselves, in the way they dissolute.

DR. BARR: Well, I think it's how you define subject-treatment interaction. What we see is a true subject-treatment interaction. Whether or not it should be there in terms of other regulatory things like in vitro dissolution is a second question but this is a formulation which behaves basically the same or gives the same bioavailability in most cases, but because of the formulation differences between this, which in this case can be identified as being a slower dissolution--at least we presume it can be--then that does produce an interaction in the subset.

So it fits the criteria. How we might change it? It may not take a bioavailability study to change that but

point is it took one in order to get that information. And I think that's where we are today and that's why I strongly support going ahead and looking at this.

I agree very much with Dr. Sheiner that if we don't do the study, if we don't look at these things, we'll never see them. The reason we've never seen these, we've done two studies. I went back in the literature for Cyclosporine looking for these and they're there. There's one study that I mentioned to you that people had looked at and thrown it out because they didn't believe it was there.

Until we examine this from a scientific method, until we go out and prospectively look for these, we're not going to know whether they're there. And to throw this out now and say we don't know they're there; therefore we won't look--to me, just doesn't make sense.

So I think this is a good example of having found information simply because we looked.

DR. LAMBORN: I have another question for clarification. We heard this morning from Dr. Lesko about some instances when you would expect to have subject-by-formulation interactions and instances when you wouldn't and I can't do a terribly good translation between those factors and that list.

So as we move forward to trying to at least get some sort of consensus, could somebody help me a little bit

with how that set of risk factors fits with that?

DR. BYRN: Okay, Ajaz?

MR. HUSSAIN: Yes. Let me go back to what Larry presented. In a sense, the likelihood of seeing a subject-by-formulation interaction would increase when there are multiple risk factors present--immediate dosage forms.

And if you look at Class II drugs, BCS Class II drugs, they exhibit low solubility and that would be a risk factor. And Class III drugs are low permeability drugs. Class IV are low solubility and low permeability.

So in a sense, there's the hierarchy of increasing "risk variables" that we think might lead to subject-by-formulation interaction. Modified release would be an additional set of factors.

I just wanted to add with BCS Class I also, what we have recommended is for rapidly dissolving Class I drugs, we are suggesting bioavailables, not for all BCS Class I drugs. That's a clarification.

DR. BYRN: Ajaz, would you recommend that we put those in the box, BCS Class II, BCS Class III and BCS Class IV? You don't have to answer it if you don't want to. That's information for the committee. Your response is important information.

MR. HUSSAIN: When we were working on BCS and examined biowaivers for Class I drugs, we were not willing

to assume lack of subject-by-formulation interaction, even for BCS Class I drugs when dissolution rate was either slow or slightly different.

For example, Levothyroxine, if that was a Class I drug, that would not escape the stringent dissolution requirement that we have placed.

So the willingness to assume that there's no subject-by-formulation interaction, we were not willing to do that for those classes of products, and for many reasons that Larry pointed out.

DR. BYRN: Roger?

DR. WILLIAMS: Sorry, Steve. I'd just like to add to some of the comments.

First of all, you mentioned the Tennessee study with sorbitol and sucrose. We did do that as a replicate study in a broader population than just healthy males, so we will have some information as to whether there is a subject-by-formulation interaction from that study. We don't have it yet.

Second of all, maybe I'd just like to add to what was thought there in terms of Bob Branch's question. If we wanted to roll forward into an expansion of waiver of in vivo studies, we could probably only do it by getting the data for those question marks that are in the box in terms of BCS II, III and IV. We will never probably waive an in

vivo study for a modified release drug product.

Another comment to state is modified release drug products are a fairly small fraction of the universe. I'm going to guesstimate that if we get 200 bioequivalence studies in the course of a year in the Office of Generic Drugs, only about 10 percent of those are modified release. So it's really a very small universe.

Highly variable drugs, if I may add a final comment, if you think about it, it really relates, I think, to question 3. Highly variable drugs and the possibility of scaling is sort of a benefit to industry. And as a matter of fact, I think that we have the further thought that a subject-by-formulation interaction for a highly variable drug isn't such a public health problem. I think we've had that discussion internally. Because of the marked widening of the goalposts, it just doesn't matter.

So if we want to think about carrots and sticks, I would put the highly variable in the carrot category with the understanding that we use the individual criterion to allow market access, which I believe is question 3.

DR. BYRN: So Roger, you're in favor of putting in--I think, to translate what I thought I heard you say, you're favoring putting in BCS Class II, III and IV, say, to increase the number of compounds in the study, and the highly variable is more the carrot for industry than it is

critical for this study.

DR. WILLIAMS: If you allow use of the criterion. I'm afraid to answer that question without looking at Kimberly. Can I give an opinion as an agency?

MS. TOPPER: They can take it for what it's worth.

DR. WILLIAMS: Well, I like the way the box is shaping up. Let me put it that way.

DR. BYRN: Oh, we need the box because I think our main question or one of our main questions is what's going to be in the box. I think we need that.

I think we've heard from all the experts pretty well. Are there any questions? Let's discuss among ourselves what goes in the box.

I think we heard from Les Benet, just to summarize, that modified release, that the expert panel reached consensus that modified release should be in the box but nothing else.

Then we heard from Roger that BCS Class II, III and IV, it would be helpful if those were in the box to increase the number of compounds in the box and also I guess there was a carrot there of providing some information that might lead to regulatory relief. So that would be an advantage.

And then highly variable IR drugs is a lower priority.

So what's the sense of the committee? We don't have to decide this now. We can go on to some other topics but that's the question.

Yes, Bob?

DR. BRANCH: I was under the impression that the expert committee had advocated recommending or supporting the other groups of drugs being done but on a more voluntary basis.

So I guess my question--is that a further option that we could adopt the expert opinion approach?

DR. BYRN: Les?

DR. BENET: That is correct, Bob. It was the recommendation, a unanimous recommendation of the panel that we encourage those kinds of studies but that it not be a regulatory requirement.

DR. BYRN: Is there reason to believe that there would be substantial numbers of those put into the study?

DR. BENET: Well, we are starting to see studies now. A few years ago we had no data. So now we have the FDA datasets. We were presented in Montreal with a lot of additional interesting studies.

So I think we are going to see that kind of data. I think if we have a regulatory requirement we're going to see more. I think we're going to see it because scientists are interested in it and people want to know those

questions. And in some cases it is viewed as being the kind of information that would be very useful to a company to have, so from their own point of view, they will want to know this.

DR. BYRN: Roger, could I just ask historically if there's a voluntary request for data by the agency, does that usually materialize?

DR. WILLIAMS: I can't say that's been my experience, but maybe I can clarify for the committee.

First of all, none of these things that we're talking about are requirements. Requirements have to be expressed in regulations. All our guidances are recommendations. We sort of add teeth to a recommendation by saying if you want to come in with an alternate approach, please do so with justification.

But I think there could be an element that we would do via some clever wording in the guidance that would make it a little more voluntary for some of these drug substances.

DR. BYRN: Go ahead, Judy.

DR. BOEHLERT: I just ask a question that perhaps has been answered but these guidances, do they remain draft during this two-year interim period? It would seem to me a draft guidance is even more of a recommendation than a real guidance.

DR. WILLIAMS: Judy, I don't think we can do that. I think we have to finalize them because the reality is you don't have to follow a draft guidance at all.

But I do think the recommendation could be something like if you want to look at these, we recommend it but if you choose to deviate, you don't have to submit a justification. I've come to some nimble words there that I would have to check with our lawyers but I think we're getting to something.

DR. BYRN: I think what Roger's proposing is that we would put modified release in the box and we would use appropriate wording to strongly encourage the BCS Class II, III and IV to be in the box.

Is there further discussion on the committee about that? Kathleen?

DR. LAMBORN: I'm sorry but I'd like to go back to just a restatement of the issue of, in a sense, the goal of the experiment. Obviously more data is good. I mean as sort of the statistician, I have to say more data is good.

But do you anticipate when you complete the two-year period looking at the number of cases in which you saw a certain characteristic or what do you anticipate beyond just "Let's look at the data; what's the focus of what you want to learn from this experiment?" Can you define it a little bit better?

DR. WILLIAMS: Again Kathleen, an excellent question and I think we're going to get into that very clearly in topic 6. But let me say for now, let's say we saw in some of these replicate datasets large subject-by-formulation interactions. I think we would start to engage in the process that you saw Larry present, looking at excipients, looking at subject population, looking at drug substances--I think there's another factor in there--and see if we can come to a hypothesis as to what's causing it.

Some of the things we might also do is just to see if we could replicate the observation. You know, did we see it by chance or is it really there?

So I'm getting to sort of what I'd like to talk about in topic 6. I think that's what you're asking about.

DR. LAMBORN: If that's what you meant by further research programs. The thing I'm having trouble with is if the goal is to identify cases where you have subject-by-formulation interaction and then look for the characteristics that go with that, then you have to assume that there are going to be enough cases--you know, you don't gain information--well, you gain some information, for instance, where you have no subject-by-formulation interaction but again if you have instances where you have very little likelihood of it, the burden of the additional information relative to what you gain from it is less.

And then linked to that also is the question, which has come in a variety of ways, which is if, in fact, this interaction is going to be related with subgroups, what do we know about the likelihood that you're actually going to be able to identify the interactions, given the few number of individuals that you're planning to have per study.

So again it goes to what are we going to hope to get when we get done, realistically? I mean we can hope for anything but what we realistically expect to be able to get when we get done.

DR. WILLIAMS: Well, Kathleen, you're asking some terrific questions, which I always say are covered a little bit later on for some of them. And I think we're getting right into topic area 6.

You know, in some ways we're talking about an observational period that is not a controlled public health experiment. I mean if I had endless resources, I'd like to design formulations, you know, hundreds of different formulations in hundreds of different drug substances and do replicate studies in broad populations. I can't do that.

So the reality is we're trying a perhaps not quite as optimal path from a clinical trial, a statistician approach, to say over a multi-year period we may get 400 replicate studies, which would be maybe eight times what we

have now. We would be looking more in the general population or even specific populations than what we do now. We would have a broad range of excipients.

And I guess it goes back to some of what Bill and Lewis said, you know, if you don't look, you won't find.

On the other hand, I'm sensitive to what industry calls--what do they call it?--a data-dredging? Fishing expedition.

So I think we're sort of a situation: can we do this as a public health agency? And I think if you think about it in a very interesting way, it's a very novel experiment. It's certainly something we never did for efficacy or safety. We just did it.

DR. BYRN: One idea I had, Roger, when you were talking about the protocol, if protocols were written to this level of detail and then discussed with the expert panel, it would be a way to define--address some of these questions that Kathleen is--I'm not sure we can address them but if a protocol were written by the agency with some flow charts and decision trees in it and then the expert panel reviewed it, then that may be a way to provide some assurance that it wasn't a total fishing expedition, if you will.

DR. WILLIAMS: And Steve, I don't have to point out to you that we have the Product Quality Research

Institute, which is also a forum for some of this research.

DR. BYRN: In fact, it occurred to me that that could be a very nice forum for some of this research.

Okay, so what's the feeling? We're still trying to--the general idea, I think, we're discussing is that modified release, as Kimberly has checked, goes in and then again, just to repeat, BCS Class II, III and IV stay in, with some type of wording that doesn't require them to be in but strongly encourages their inclusion.

Do you want to go on to the next topic? So that seems reasonable.

DR. WILLIAMS: Jeff is looking perplexed. I can do it, Jeff. Give me a chance.

DR. BYRN: Okay Roger, do you want to explain this question, just introduce this question, explain it for us?

DR. WILLIAMS: I don't think there was an accompanying overhead on this. Was there, Kimberly? I think we go right into the next topic area.

Oh, yes. Now I actually think this is a very critical public health question, which is could we use the individual criterion to allow market access? And in the agency guidance that Vinod spoke to, the General Guidance for Orally Administered Drug Products, if you look at number 3 you'll see that we would say to a sponsor, "If you specify in your bioequivalence protocol which criterion you would

like to use, you could use either an average or individual criterion to allow market access."

And if we allow the individual criterion, we would allow scaling, because that's an elemental part of it, and it really refers back to the carrot that I offered for highly variable drugs. If you really think you have a highly variable drug and you specify in your protocol, we would allow market access with scaling.

And I will emphasize for the committee these boundaries can get quite wide--you saw that--because of the variability of the reference. And it also relates to your faith in this criterion to perform, if you will, adequately.

It also leads into the further question, which is Dr. Beice's question about constraining the means, but I think we wanted to start with this one first because if you said no, there's no point in talking about constraining the means.

DR. BYRN: Yes, Robert?

DR. BRANCH: I basically have a problem with the issue of this total study design. The focus right now has been on saying you're going to make arbitrary decisions using one model or another model and you're going to focus that back to try and then understand mechanisms.

But the public health issue is do either of these make a difference to people? If you're introducing this as

an experiment, this is the only time you will ever have an opportunity to find out if there is any difference in outcome.

So I would urge that some thought be given to this question of the overall study design because you're going to have some drugs that are going to be passed on one, failed on another criterion, other drugs that are going to be failed on the first one and passed on the second, and which is right? Which is actually in the population's best interest?

If you are currently working under one procedure, it would seem to me that if you maintain that and don't change the rules in terms of the approval criteria, you will at least be able to assess what's the impact of those drugs that fail these new, more expensive higher criteria. Does it really matter?

This will involve some additional study and focus, and that's part of the nature of the research, but it seems to me that you really need to clearly define your experiment before you start-- does society use your measures that are coming out of your experiment to actually make regulatory decisions? I would feel uncomfortable in trying to do that without a very clear clarification of what you're trying to do.

DR. BYRN: Is Larry Gould here?

DR. GOULD: Oh, yes.

DR. BYRN: Larry, could you put up that slide that had the broad reference and then the two narrow--you know the one I'm talking about?

DR. GOULD: Which one did you want?

DR. BYRN: The one that had the narrow--the broad reference and then two narrow--doesn't that directly relate to this question? If you could put that up and then let me ask you a question or two about it. I think it might relate to this.

In this bottom case, is this a case where you could have--the reference would be the reference compound.

DR. GOULD: Yes, the pioneer compound.

DR. BYRN: And then two bioequivalent--under this scenario you could have two bioequivalent generic products.

DR. GOULD: Yes.

DR. BYRN: That were not the same or close to the same but both were ruled bioequivalent to the reference. Is that correct?

DR. GOULD: Yes. As I pointed out when I gave the presentation, I exaggerated for the sake of making a point but the point remains, and that's inherent in how the criteria are defined.

Now whether that's a likely scenario or not is not something that I know enough about data that have been

submitted to tell you that. But nonetheless, it's in principle possible.

DR. BYRN: Obviously if that were possible, that would be a concern with allowing IBE data to approve drug products, right?

DR. GOULD: Yes. But that's also a point that Laszlo Endrenyi has made. The problem is this trade-off.

MR. SHEINER: You could have that now and not know it.

DR. GOULD: True.

DR. BYRN: That was Lew--

MR. SHEINER: Lew Sheiner.

DR. BYRN: And that point's well taken. I think I was just responding to Robert's concern that if we answered affirmatively to discussion topic 3 without knowing more about the situation, we may be getting ourselves into trouble. Is that your concern, Robert?

DR. BRANCH: I guess so. I'm also trying to step back a bit, go back one step and say one of the key elements of the whole interaction between the generic industry and the FDA is to get public confidence in the system. And the whole of this exercise, as I see it, is to try and improve that level of confidence or to go through to an improved level of confidence.

We had a statement earlier on about the fact that

in the epilepsy population there may be a perception that generic equivalence is not there for every patient, but there's very little solid data to support it.

So it seems to me that if we're going to be looking for the issue, we're going to take a much harder look at our current levels or current approaches to bioequivalence--appropriate? Should they be modified? Should they be individualized for narrow therapeutic drugs? Should they be tightened, which is essentially what this individualized is, is tightening the regulatory requirement.

Out of that experience is likely to come some observations. Now the question comes back, and it's been raised repeatedly: What's the relevance of these observations? Do you set your criteria at 10 percent, 5 percent, 20 percent, 30 percent? Should it be individualized to the individual drug, depending on the efficacy-safety profile of that drug?

It's not a simple story but it seems that before we go into applying the regulatory rules of a new approach, we should at least look and say does it make sense when you start seeing the data?

So I'm just urging us not to use information that is being analyzed in the form of an experiment as a regulatory tool until we know what it means.

DR. BYRN: Other comments by the committee?

Actually, I think discussion topic 4 is addressing what I was just asking.

Other comments by the committee?

[No response.]

DR. BYRN: Okay, it doesn't sound like there's a lot of support. Are there some concerns on topic 3?

[No response.]

DR. BYRN: Let's go on to topic 4. I think, Roger, this was the question I was asking, isn't it, in effect?

DR. WILLIAMS: Well, it seems to me I heard some reluctance on the part of the committee to allow market access.

DR. BYRN: Right.

DR. WILLIAMS: If that's the case, I think you can skip this question.

DR. BYRN: This is a moot point.

Is there anybody that would like to discuss this? I mean my take from this is that it's exactly what we were talking about. If your reference product was broad and your new product was very narrow, it could have a mean a long distance from the mean of the reference product and get approved, and this question would limit that difference. Is that what this was?

DR. WILLIAMS: Yes. Maybe I could revisit this a

little bit, Steve, because I'd like to say to the committee this, that I think their comments were very careful and very conservative and I certainly agree with Bob that we need to look at the protocol and exactly what we intend to do before we make a decision about market access.

But I will say that imbedded in that general guidance that Vinod spoke to is the thought that we might use the criterion to allow market access, say, to avoid a steady state study for a modified release product.

And I guess what I'd like to do is note the committee's conservative and thoughtful approach but also allow that further thinking in the agency might say that under circumstances we could use it.

DR. BYRN: Well, there's always an option, you know, as we've done, to bring issues back to the committee as more data's available and so on.

DR. WILLIAMS: And we could do that, too, certainly.

DR. BYRN: Okay, let's go to 5.

DR. WILLIAMS: Now 5, I think, comes back to--I want to give Bob credit for the question and I'm sure Kathleen was thinking of it, too, and perhaps all the committee is--you know, if we really just study 12 subjects, what are we going to see?

I think the expert panel was a bit more thoughtful

in that when they recommended inclusion of certain numbers of people, like both genders and the elderly, and I've got--Les left me his overheads if the committee would like to see those. So we would be very interested in what the committee feels about that.

DR. BYRN: Kathleen?

DR. LAMBORN: I think that it's very important that if this is to be a useful exercise in any way that we, at minimum, ought to try to get some of the key variables that are expected to frequently be related to subject-by-formulation interaction in terms of patient groups included. And I think to just say that the population is welcome to be broader, if you want to still get things through, the logical thing would still be to use a very homogeneous group.

So I think the idea of in some ways mandating for some subgroups to be included I think makes sense and I like what the expert panel was suggesting.

DR. BYRN: Would the appropriate place for this be in this protocol or would it be in the wording in the guidance?

DR. WILLIAMS: Do we have a slide on this?

DR. BYRN: Okay, let's put up Les's slide, Les's recommendation.

DR. WILLIAMS: Is that Les's slide or our slide?

DR. BYRN: Okay, let's put up the FDA's slide.

DR. WILLIAMS: Oh, yes. This is the wording from our guidance that is fairly general and without specific stipulations. The expert panel in terms of their modified release was a little bit more specific.

So it's a question not only of N, the number, but also the type.

DR. LAMBORN: I guess I'm supporting that we should encourage the expert panel recommendation being a little bit more specific. I'm not sure that the general guidance would produce what you would hope to produce in terms of datasets.

DR. WILLIAMS: I'd just like to make a public health statement. One of the remarkable things about the United States is the diversity of its population and I think if we look around this room we see that diversity. And I think the concept of including as many types of people as we could is a very interesting thing.

And I will also say we don't need 12, 12, 12, 12 to get 60 people. We could have 12 elderly, some of whom are women or something like that. Haven't we talked about that within the internal group, Stella, that you can get much information in a matrix sort of way. I'm not saying it right. I'll leave it to the statisticians to say that.

DR. BYRN: Okay, Judy?

DR. BOEHLERT: I agree that you can probably design studies to get age and gender in there at reasonable levels. How do you deal with the absorption subsets that we heard about this morning? Because that, you don't know going in where that can occur. And then when you're only looking at 12 in a study, you have a good chance of not seeing it because those you don't know going in unless you start screening your study participants for those kinds of factors, like achlorhydrate or transit time or whatever matters.

DR. WILLIAMS: Judy, I can't argue the point. Sometimes we've heard people say before the committee like Gehard Levy that the study should be conducted in the patient population for whom the drug is intended. We didn't quite go that far because that seemed especially burdensome.

I think whatever we do will be a balancing between burden and--you know, realistic things to do versus the most wonderful things to do.

DR. BYRN: Other thoughts of the committee? Yes, go ahead, Sandy. Identify yourself, please.

DR. BOLTON: I'm Sandy Bolton. Many affiliations, so I don't want to get into that.

I want to mention something about the sample size here. If we're dealing with, let's say, modified release products, we're not talking about 12 subjects anymore, I

think in principle, because the variability is generally relatively high.

So considering the possibilities of interaction and so on, I think we would be talking of more than 20 subjects in a replicate design for modified release products, based on the variability of those products. That's not great, you know, but it's better than 12.

So I think that 12 is something we shouldn't be thinking about.

DR. WILLIAMS: I think the agency agrees with that, Steve. I think that number 12, we realized as we put it out it was very small.

DR. BYRN: Roger, I'm not a statistician but you also pointed out that under this scenario there'd be a large number of studies, so there would be variability in that way, although statistically I'm not sure of the relevance of that.

DR. WILLIAMS: I think that's a very good thought, that there may be some kind of meta-analysis that we can do here. Did that scare you, Kathleen? Oh, it scared Walter; I'm sorry.

DR. BYRN: That's why I said I'm not a statistician.

DR. HAUCK: I wouldn't go so far as to call it a formal meta-analysis but we certainly are proposing that we

will do analyses that combine across studies, actually picking up on a proposal that Laszlo Endrenyi had made really that looks at the distribution of estimates across studies and it compares that to what would be expected in the absence of anything going on.

Laszlo has pointed out we have to deal with the within-subject variability and we do that. As we presented in Montreal, you also have to deal with the sample size. And then we also need to correct, assuming no change in this policy, we also need to correct for the studies that didn't pass weren't submitted.

So there's a bias in the data that we'll have to correct for but it's certainly our intention to do all that and to look then at how the estimates we obtain across whatever the studies are compared to chance expectation. That's not a meta-analysis, I don't think, in a formal sense.

DR. LAMBORN: I've been wondering when I was going to get around to putting in my two cents worth, which I've said many times before and Walter just gave me the lead-in.

Just for the record I would like to say that I think it's critical that whatever be done be done to encourage the sponsors to, over this interim period, provide failed studies, as well as successful studies if we're going to be able to truly interpret this data. If the only thing

that's submitted is the ones which worked, we will miss a major piece and a major ability to learn what the whole thing was intended to do.

DR. BYRN: Okay, are there any other comments on item 5?

I think to summarize, there seems to be sentiment for the expert panel recommendation, as well as the committee is obviously interested in having a wide representation of diversity.

Okay, are we ready for question 6?

DR. WILLIAMS: Now this question obviously gets to issues that the committee has brought up several times in the course of discussion this afternoon and to again help the committee, if it does, is a graphic. Everybody knows I like pictures with boxes.

Now let me see if I can walk through this very quickly to see if I can create these areas of focus. And some of this was based on comments that we heard in Montreal, as well as from the expert panel.

I think this is what we're talking about. Somehow we'll start seeing more replicate studies that will generate hypotheses that will be subject to the kind of mechanistic understanding that Larry gave such a good talk on earlier today. And Larry has created these sort of risk factors in terms of patients, excipients, substance and product.

We certainly take PhRMA's point that further modeling and simulations may be needed. We wanted to take into account Larry Gould's suggestions for other criteria and other approaches. There's sort of the concept of an average with scaling criterion which we'd like to explore. So there's that.

Before I leave this box I will just say there is also that thought of finding an observation and then repeating a study somehow to see if it is, in fact, a true observation.

Now over here we get more into the realm of clinical pharmacology studies. I would say here the thought is if we saw a significant subject-by-formulation interaction, at least in terms of a number, could we take that into the clinic somehow and show that it had clinical meaning? I think that's the intent behind that study.

Bob, I would argue that that's a proposal you gave to us a year or two ago at a prior discussion.

There is also a goalpost study and I guess one of my dreams in life would be to take a model drug and see if we could build these individual goalposts to yield the kind of data that I would say we usually never see now.

And then finally there is study population. I think that merits some discussion in terms of the protocol along the lines of what the committee just said to us, and

so we would certainly want to focus on that. I will stop there.

DR. BYRN: Okay, comments from committee on this topic?

DR. BRANCH: It seems to me as a comment that we've really been evolving over the last few years from looking at populations, going down to special groups, starting to look at special situations in those groups, and that's going through things like drug interactions, disease-drug interactions. Now we're talking about formulation in special groups interactions.

I would really endorse this idea that the proof of concept would be done but I would like to introduce the idea that the initial studies have an opportunity for identifying individuals who are apparent outliers. And a huge amount of time and effort can often be saved if that identification process is used to then study the more detailed mechanisms. All the pharmacogenetics is sort of based on that, taking advantage of an opportunity by observation of an outlier.

And it would seem to me that somehow linking the replicate studies to the clinical pharmacology component could be very attractive in terms of developing the mechanistic understandings and the hypotheses.

DR. BYRN: One thing, Roger. I think this is maybe an outline of the sections of the protocol, in a way,

that we've been talking about.

DR. WILLIAMS: Which would become text with--

DR. BYRN: Right, and would be passed through the expert panel, I guess. Is that consistent with your thinking, Robert?

DR. BRANCH: [Nods.]

DR. BYRN: Are there other comments by the committee or thoughts on this matter?

DR. BRANCH: I've got a question. If we go back to the calcium channel blocker, if we've got gender-specific differences and you've got nonequivalence in that group, what actual regulatory decisions are going to be made about that?

DR. WILLIAMS: In what regard?

DR. BRANCH: As I was hearing Larry present that, it seemed to me that here was a situation in which you had a generic that has come on the market at which you can never theoretically get equivalent dosages for both genders, unless you create two different formulations for the two different genders.

So does that mean that the generic can never replace or compete with the incumbent drug? When you have a special subgroup that handles the drug differently, how can the generic market address this? It's really a dosage modification. Going back to Lew's analogy, it's how much of

the yellow or blue packet do you put into your coffee. It's a question of titration.

But from the regulatory point of view it's a question of do you allow it or don't you allow it? So how do you cope with this concept that you will never have an absolute one-to-one equivalent?

DR. WILLIAMS: Bob, that's probably one of the great questions of all time. Put the regulator on the spot.

I'd like to talk about a little bit, recognizing that I don't think I have a solution. If you think about it, the subject-by-formulation interaction for that particular dataset was in the pioneer and theoretically the pioneer was allowed market access based on safety and efficacy data studied in both genders.

So they were allowed to enter the market as being safe and effective with the subject-by-formulation interaction being present, the gender-based subject-by-formulation interaction being present.

Now the reality is we want generics to be the same. So I think what you're asking is would we ask the generic to recreate the subject-by-formulation interaction--the gender-based. I find that hard to ask a generic firm to do but maybe that's what they need to do to be allowed market access.

But I think it's a key question and I would argue

what we would really like to propose perhaps, and this gets back into that replicate study from the pivotal clinical trial to the to-be-marketed dose form because you would be able to detect with a replicate study there if you had a subject-by-formulation interaction. And my guess is in the final analysis a pioneer wouldn't want that.

DR. BYRN: Okay, identify yourself.

MS. LANE: Elizabeth Lane. I'd just like to clarify that I'm familial with those study data and that the results of that study did not meet the average bioequivalence criteria. The study has not been submitted for approval. The product has not been submitted for approval.

DR. WILLIAMS: I can tell you that when I was asked about the dataset and what they should do, I said, "I don't know what to do. What do you want to do?" And he said, "Well, we want to study it only in men."

DR. BYRN: Okay, any more discussion on question 6?

[No response.]

DR. BYRN: Okay, shall we try to go through and summarize where we are, where we think we are with these six questions in mind and just kind of do a review for the committee?

I think we are talking about--maybe we need our

box up there again, Kimberly, just to review this. We're talking about a position that sounds to me to be very close to what the expert panel recommended, with some variations, and that would be that we would, in the affirmative--answer question 1 in the affirmative, the modified question 1 as Kathleen wrote it. That would be answered in the affirmative. Maybe we should put that one up there first. Kimberly, do you have that modified?

So let's just spend a moment. We would have a general consensus that this would be in the affirmative, that it's reasonable and appropriate for the FDA to recommend replicate study designs for some drug products for an interim two-year period under the conditions that we've just discussed, all the conditions.

And if you'll put the box up, this is question 2. Does anybody want to discuss that any further? Are we still okay under the conditions?

[No response.]

DR. BYRN: Now what we discussed, I think, is that modified release dosage forms were in and BCS II, III and IV, there would be wording that would encourage them to be included. And Roger would work on that wording in discussion with the FDA lawyers. Is that okay with everybody?

I think the only deviation really if you think

about from the expert panel is that we have put BCS II, III and IV in, with some wording, but it's not really much of a deviation from the expert panel.

We have a comment from the audience. Yes? Identify yourself, please.

MR. ENDRENYI: Laszlo Endrenyi.

It would seem to me, and I wonder whether the only carrot which is being recommended, namely the voluntary inclusion of highly variable IR drugs, if you really would or would not want to be included.

DR. BYRN: Okay, so we have a question which I think is a good one, which is that it might be appropriate to include a carrot.

Yes, Kathleen?

DR. LAMBORN: Since our later recommendation is that we stay with the average bioavailability and do not change the approval criteria, I'm not sure it becomes a carrot. I think the concept of the carrot was if we were going to do scalability.

DR. BYRN: Okay. So that is actually a moot point; that's correct.

Okay, so under this scenario the modified release would go in, as well as wording for BCS Class II, III and IV.

Okay, and then, as Kathleen said, there is not as

much support for topic 3, with the proviso that we discussed with Roger that if it became apparent that the committee needed further education on this topic, it could be brought back to us.

And question 4 was rendered moot. Is that correct? Yes, Arthur?

DR. GOLDBERG: I have a comment on 3 and the way it's worded. I would prefer saying that we use average bioequivalence unless there are compelling reasons not to.

DR. BYRN: Okay. With that change, Arthur has suggested that we use average bioequivalence unless there are compelling reasons not to, rather than it would be brought back to the committee. Is that okay with everybody?

[No response.]

DR. BYRN: And then topic 5, again we need the expert--do we have a transparency that has the expert panel recommendation of the number of--that's 6. It had a statement right at the bottom. There it is right there.

And then on topic 5 the committee seemed to support this expert panel recommendation on the diversity of subjects.

Yes, Arthur?

DR. GOLDBERG: Being over 60, I want to change that to 70.

DR. BYRN: Okay. That'll be noted in the record, anyway.

And then discussion topic 6, there was general sentiment for that wording that would reflect that methodology. We need the other boxes, Kimberly. The protocol would reflect that series of studies and methodology.

Okay, are there any other comments from the committee?

[No response.]

DR. BYRN: Okay, I think we thank you all very much. I'd like to thank all the speakers, excellent input, and thank the committee very much and we'll assemble tomorrow at 8:30. Then we'll meet later on at 6:30. Check with Kimberly.

[Whereupon, at 4:42 p.m., the meeting was adjourned, to reconvene at 8:30 a.m. on Friday, September 24, 1999.]

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CERTIFICATE

I, **SUSAN A. HARRIS,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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