others doing it. It's imperative that we do it, and it's the only way you're going to ultimately get data and have some consistency and hit every pocket, if we restrict prescriptions to the completion of this material.

DR. BERGFELD: Dr. Moore, then Dr. Greenhill.

DR. MOORE: I just want to voice my concern. Although I certainly have sympathy with the ideas that have been put forth of putting everything together in one package, I think the body of evidence, so to speak, for the psychiatric effects are in no way comparable for what we have for the teratogenic effects. And to bundle those two in the same package I think probably puts us at risk for not having a successful program for the known birth defect risk and maybe puts us at risk for getting the kinds of information that Dr. Mills was talking about that we really need to assess whether or not there even is the risk for suicide or other psychiatric conditions.

DR. BERGFELD: Thank you.

Before you go, Dr. Greenhill, I promised Dr. Winokur.

DR. WINOKUR: Actually to follow up on that question, I think we really need the kind of systematic prospective information that Dr. Mills was referring to before to make further headway on understanding the relationship. So, hopefully a program putting together

such information would be an important step in moving forward.

Just to step back to the original question of is there sufficient concern to justify more risk management, I think even from the perspective of Roche's presentation that this population is one that's fraught with potential for significant psychiatric events, even unrelated to what Accutane may convey, and that clinicians dealing with this population are, by and large, not trained psychiatrically extensively I assume in most cases. And this would be a challenging population for those of us trained in the area. I think having the more structured systematic approach could be very helpful and could be justified on those grounds alone, let alone the additional concerns about the potential for problems associated with Accutane.

The one other element that I would underscore -- and I think it's been mentioned, but I just wanted to highlight it -- is I think paying real attention to what kind of information is provided to patients at the outset. We've talked a lot about the information in the really beautiful program put together in terms of the contraception and avoiding becoming pregnant, and I agree that it would not be appropriate to have a comparable amount of attention at this point to the depression issue.

But I think some clear information about depression, again not necessarily saying that this will be because of being on Accutane, but just because of the circumstances of this phase.

But we've heard again from Dr. Jacobs that this population in particular is likely to conceal or be uncomfortable about revealing symptoms. Again, I'm alerted to the low, in my opinion, scores on the Beck Depression Inventory as perhaps another reflection of that. I think from up front, they need a kind of clear, candid discussion that during the course of treatment, there may be some symptoms that arise and some examples should be given and some specific instruction to communicate about that and what to do about that. And in addition, I assume that the clinicians might also need some help in terms of where to go once that comes up.

As a bridging comment, it strikes me that putting some of this together could be an extraordinary opportunity down the road to think about some other coordinated studies that would address another question that we'll probably get to with question 2, which is what do we do when problems do arise in the context of Accutane treatment and how do we most effectively treat or manage that. It sounds like there's great need for better information to guide the field, and this could be a

wonderful opportunity to start to build towards that.

DR. BERGFELD: Thank you.

Dr. Greenhill?

DR. GREENHILL: Just a couple of small points which I'm sure are obvious. One is that the current consent form that's in the package insert has no information on the psychiatric possible problems that could arise, and in all my experience with consent forms, if there is an associated condition that has been found in the past, it's usually put into the consent process. That's an opportunity to put in the warning signs of depression to remind both the practitioner and the patient what they might be looking for.

The second thing is some of the comments made by Dr. King and Dr. Miller suggest to my mind that there might be prescriber practice parameters. We have them in child psychiatry for administering stimulant medication. I wondered if there are any dermatological practice parameters surrounding Accutane. I'm sure there are but I just would like to know a little bit more about them because they may figure into this whole process that we're thinking about now.

DR. KING: Actually thank you for that opportunity. When we approached the original issue of Accutane monitoring, it had more to do with dermatology had

no issues to monitor relative to the hospital quality assurance program except that we always report and follow up on skin cancer. So, that put us at major risk in terms of legal. So, we looked into Accutane and asked the issues of how many people, were we doing the pregnancy tests and following up.

I'd like to suggest that from my experience with dealing with a lot of smart kids and doctors' sons and daughters at Vanderbilt, if you put something in the PDR that says something about depression or anything else and you don't mention it in the consent form, they come back to you like crazy in these days of the Internet and the Web and so forth. It's not like don't worry about that tiger back there, and oh, by the way, I'm not going to mention it anymore. You cannot not put that there.

So, I agree we should not scare the hell out of folks for various kinds of "you may have this," but something in a consent that says there may be a risk and you should know about this and you should report this, not only can you have pregnancy, if you're a female, but you may have depression and you should report that because there are things we need to know about that and we may help you.

So, that was my integrated approach, saying if you're going to make the change for a new formulary, you're

going to make the change for pregnancy, and you're going to address that issue of depression and get a population from which you can select out for better studies, I think you ought to do it all as a package.

So, relative to the issues in dermatology, the American Academy of Dermatology has a series where they basically describe what are the effective treatments recommended for acne, and it does suggest in many articles, as you've seen quoted here, that there are some problems. So, I think you're worried more about the population not being reached, pediatricians, nurse practitioners, than you are about dermatologists. No one, including me, wants to be sued because we did not talk about the issues.

So, I think there is some misinformation, but mostly lack of information outside dermatology. So, I'd like to see an integrated consent form that addresses this in a proper way, negotiated between Roche and the FDA and perhaps even dermatology and general practitioners.

DR. BERGFELD: I have Dr. Epps and Dr. Levin.

DR. EPPS: Thank you.

In regard to the questions, I certainly agree that we definitely need information on the CME program that has already been suggested and discussed with Dr. King, through our academy, as well as publications, press release. I know the FDA often puts out publications and

suggestions. Professional labeling is certainly indicated. In the brochures from the company, absolutely it should be in everything that they discuss regarding the risk or that there have been reports, whatever language that you'd like to use.

I do have concerns also regarding confidentiality. If you're going to document particular risks or possible indications of depression or psychiatric illness, maybe that shouldn't be on the consent itself or whether there should be yes or no. There may be signs rather than each specific question that certainly psychiatrists could aid in the best screening type questions. We can't get into great detail, but there are certain screening questions that may indicate there may be signs of depression or other problems.

As far as, of course, patients would want to be closely monitored. Perhaps through managing of events, we could emphasize that you need referrals not only for psychology but also for reproductive or contraceptive counseling. Certainly I do not personally manage birth control pills or whatever. I leave that to the gyn and the pediatricians and the family practitioners who do that on a regular basis. There are contraindications for all of those things, and certainly I would not manage someone's psychiatric illness either.

As far as formal studies, yes, yes, yes, and yes. We clearly need data, retrospective and prospective. Perhaps those cases that Dr. Byrne referred to, whether it's dose related, whether it's related to the body mass index, who knows? But we could certainly get as much information as possible, maybe the dosing and advancing of the dosage, or whether it started at a large dose or advanced too quickly. Who knows? But if you get that data and look at it, perhaps we could go forward and make suggestions regarding patients who should or should not be treated that way, different ways the medication could be given to avoid the kind of side effects that people have referred to today.

DR. BERGFELD: Dr. Levin, then Dr. Branch.

MR. LEVIN: I'd just like to add to the mix my belief that Accutane become the third drug for which the FDA mandates a medication guide. It seems to me a very appropriate drug for such a mandate not only in terms of the psychiatric adverse events, but other serious side effects and adverse events. Clearly there's a lot of emphasis which is justified on the issue of preventing pregnancy and birth defects. It's sort overwhelming I think the usual presentation of other information about the drug which is also very important.

A medication guide is a safety net. It

requires that if nothing else happens along the way, at least at the time the drug is dispensed, that the patient would get at the point of dispensing an information sheet or guide similar to what you've heard described today. I think this is, again, a perfect example of a drug which meets the statutory criteria, and we would be well served by moving this to a mandate.

DR. BERGFELD: Thank you.

Dr. Branch?

DR. BRANCH: I come in with a slight tone of dissent. I'm a strong proponent of evidence based medicine. I think that it's extremely difficult to see the signal in the background of the psychiatric illness here. I think the most convincing data is the dechallenge/challenge data that the FDA presented. Having sort of seen the quality or heard about the quality of the various data sources, it seems to me it is likely that there is a small but real temporally related side effect profile in a minority of subjects.

I like the idea of doing future studies that look at the potential for pharmacogenetics to identify predisposed people, but we don't have the science to back that yet.

I'm concerned that we're going to be taking what is a therapeutic opportunity to link dermatologists

and psychiatrists to mandate something that may not be as simple as that.

So, my concern is that the patients are given a current state of knowledge in all its imprecise natures. I am concerned that there is a rush to condemn when we don't actually have the requisite information. I think the future studies could be designed and could really throw light onto both mechanisms, identifying potential people at risk, and being able to come up with strategies of what to do if you see something, but I think we need to be very careful that we tell people what we know and not what we feel.

DR. BERGFELD: Thank you.

Dr. Gloria Anderson.

DR. GLORIA ANDERSON: I wanted to come back to question 1 and express my opinion. First of all, I think I've heard enough to answer yes to this question. I believe that there is, at least in my opinion, sufficient concern to justify more risk management. I'm a physical organic chemist, so I'm not going to try to get into any details. I do teach the doctors.

In the area of education and information, I think that there probably is the need for further effort in that area. However, I would suggest that you might want to, as you do that, look at the effectiveness of what's

already out there. I have a great concern for how effective educational and informational materials in terms of prescription and nonprescription drugs can be.

Intervention I believe certainly is an area in which we ought to be doing something. It seems to me that one of the things I've heard a lot is that we don't know a lot about what's happening with a large number of patients. Therefore, it seems to me like monitoring the patients and managing the events might be something that would give us some of the information that we've said we don't have.

So, my answer to question number 1 is yes, I think we should do that, and I think we should move in these two areas that are listed here.

DR. BERGFELD: Thank you.

Have we heard everyone? Because I'd like to call the question. The first question is, is there sufficient concern to justify more risk management? Is that all right to do? All right.

I'll call the question. All those in favor of yes, please indicate by raising your hand.

(A show of hands.)

DR. BERGFELD: Unanimous.

I think that we've heard detailed discussion on what possible considerations could be made and could be expanded and reviewed, but are there any other comments

regarding this area? Yes, Dr. Rosenberg.

DR. ROSENBERG: I think we ought to separate the suggestions that forms be required for the patients to fill out which might or might not include the psychiatric depression index, as well as pregnancy. That was mentioned.

Then there was also the question of certifying certain physicians to be able to handle this material. These are two very separate issues. I certainly would vote separately on the two of them, and I urge that we not mix them up when we vote.

DR. BERGFELD: I'm not sure that we need to vote on them. You just needed to hear the discussion of what the experts think. Is that correct? Or would you like specific actions?

DR. BULL: Going back to Dr. Levin's comment on the medication guide, you may want to in terms of the part of the question in terms of messages and what form that may deserve. You may want to consider taking a vote on how they're made because I think also it's been discussed about including this information in informed consent. The medication guide, as you heard in Dr. Ostrove's presentation earlier today, is a document that would be required to be dispensed with the drug. That would also be a mechanism of ensuring that the information is provided in

a manner that is clearly understandable.

DR. BERGFELD: If I could take this apart then, it appears to me under "education and information," that Roche has supplied some very good materials. There have been some suggestions made that they should be relooked at, perhaps they could be enhanced and some of the words taken out so it would be more simple, so it would be easier read and interpreted by all, both patients and physicians.

There needs to be continuous activity in education of the provider, which is the physician.

Then we move to the question of professional labeling. I think that you've already taken care of, and I think all of us in our conversations agree that the labeling appears to be appropriate at this time.

The information to the patients then, the patient package insert you state here is optional. Is there an opinion that that should be other than optional?

DR. ROSENBERG: But that's the question. Should we move from optional to the medication guide which is required?

DR. HONIG: Right. The point is that a PPI, a patient package insert, is optional that the patient receives it versus a medication guide where we know the pharmacist is required --

DR. BERGFELD: So, they wouldn't receive both.

They would receive one or the other. Is that correct? Or they could receive both? Dr. Levin?

MR. LEVIN: The medication guide is at the point of dispensing. They could receive a PPI at any point from a prescriber or at the point of dispensing or by going to the PDR or going on the Internet. So, there are a variety of ways.

DR. HONIG: From our perspective, a PPI is part of approved product labeling, and it's virtually identical in appearance to a medication guide. The only difference is that with the medication guide it's required that the pharmacist provide that to the patient filling the prescription.

DR. BERGFELD: Dr. Greenhill?

DR. GREENHILL: I had one question. I understood that the medication guide could be avoided if the prescriber thought it was somehow not indicated. How would the patient know that there was a medication guide that he or she was not being offered?

DR. BERGFELD: Is there a response?

DR. BULL: What I recall of Dr. Ostrove's presentation is that it's required to be distributed at the time that the drug is dispensed by the pharmacist. It goes with the package.

DR. BERGFELD: It could be overridden by the

physician we heard, but the patient could request it and override the physician.

DR. GREENHILL: If the patient knew about it.

DR. BERGFELD: Right.

DR. HONIG: As Dr. Ostrove mentioned, there's a label on the vial saying that a medication guide is available for this product.

DR. MURPHY: I would suggest that you not mix the patient package insert and the medication guide. The patient package insert is part of our labeling that we do things to. There are very specific regulations for the medication guide, as were laid out this morning. It has to be given, except in that circumstance just discussed. There has to be a notification on the bottle that you're supposed to get one, and it has very specific language as to how we're supposed to address, as you heard this morning.

So, I think that what Dr. Bull was trying to get us to focus on was are you saying, when you voted we need to do more, in addition to trying to coalesce some of the activities here and information exchange and education for professionals, when it comes to the patient, do you want a medication guide to be utilized? I would say we're asking you for the psych aspects of this right now.

DR. BERGFELD: I think that's quite clear then.

The rest of it the FDA already is engaged in doing with the company.

So, let's go to the medication guide. May I put the question on the table and see how it falls here? All those that are in favor of a medication guide, specifically as it relates to the issues?

Yes?

DR. MOORE: I'm sorry. What would the guide say?

DR. MURPHY: Basically as Nancy Ostrove went through today, it has to have certain categories. It has to be in language that the lay public can understand, and it has to answer questions like, what do I need to know and what should I do if? It has very specific things that we have to put in it.

DR. BERGFELD: Dr. Levin?

MR. LEVIN: Just one quick comment. The medication guide format is the result of conversations that have been going on since 1995 when the FDA first proposed medication guides for all drugs. That was beaten back by an act of Congress. I won't go through the long history of decades of trying to do this. Although this particular statute is new, the notion of a medication guide and the format that's been developed has been around for a long time.

DR. BERGFELD: Dr. Greenhill.

DR. GREENHILL: Just a point of clarification. Would the medication guide that's being proposed also include the information on pregnancy and danger to the fetus?

DR. MURPHY: We can determine that that is necessary after what we heard from you yesterday, but I think what we're asking you to vote on today is the medication guide as it is relevant to a discussion of psychiatric concerns.

DR. BERGFELD: Dr. Levin?

MR. LEVIN: Just a clarification. Medication guides I did not think were focused to specific risks. Are they? They have to be consistent with the product label. They're supposed to inform the patient. It's sort of a risk-informing process, as well as other things. It says these are the risks of the drugs you're going to take. It may highlight the principal risk. But unless I'm completely confused.

DR. MURPHY: You're correct. I'm trying to focus, because we were mixing the two, that we can put in -- and we had a long discussion yesterday about the risk for pregnancy. Not that we would leave out things that need to be in there, but would you please address whether you think we need a medication guide as is relevant to the

psychiatric risk here.

DR. BERGFELD: Dr. Moore?

DR. MOORE: The question I had earlier wasn't about what should be in there in the format, but how will you describe this risk to the patient?

DR. MURPHY: Believe me, I couldn't do that in one minute right now. I could not tell you that. It takes the experts from the division, the technical experts. It takes a group of people who look at risk communication. There's a process that goes into place. It's not something that we would do very quickly here.

What we're asking for is not what we would say, but do you think we should utilize this mechanism for this specific aspect? Dr. Levin, you're right. We would not just include this. I'm just trying to focus the conversation. Thank you.

DR. BERGFELD: Dr. King?

DR. KING: I'd actually like to come back to what I proposed earlier, like load all the freight on one boat. It seems to me that the purpose of this is actually to inform the patient as a follow-up to the consent form. I agree with Dr. Rosenberg. I don't think that it's practical to list all these things that we'd like to do to follow the potential etiology of psychiatry and all these scales and tests. I just would like to know if my son gets

this medication somewhere, that what he signed in the consent form is the same kind of information he's going to get when he gets the medication. It seems to me that's the follow-up. If you don't get educated at the point of prescribing, you should get educated at least where you pick up the medication. That's why I was saying symmetry relative to telling people you may get depression and you should report it. If you want that answer from me, the answer is yes, but I wouldn't want to say you can't get pregnant unless you're a male. That's okay.

DR. BERGFELD: Dr. Rosenberg, did you have a comment?

DR. ROSENBERG: No.

DR. BERGFELD: We're coming back to the medication guide and specifically whether the importance of the psychiatric events that have been reported to us meet the guidelines to be included. Should we recommend that a medication guide be done with all the other information regarding making it one unit package for us physicians who have great difficulty with these separated pieces?

Dr. Greene?

DR. GREENE: I'd just ask one question. It seems to me that the data linking Accutane with birth defects is far stronger and more compelling than the data linking Accutane and any of the psychiatric symptoms or

diagnoses that we've discussed today. I'd just like to ask why the issue of the medication guide wasn't raised with respect to the congenital malformations as opposed to it now being raised with respect to psychiatric issues.

DR. BULL: I think if you look back to our discussion yesterday, you really have engaged with the recommendation of the registry, the design that was chosen, a much higher level of risk management. What we're talking about now is more of an informational tool and something that makes sure that this message on the possibility, the potential, and that there's reasonable evidence based on what you've heard from the postmarketing analyses to better inform patients about the possibility of mood changes, psychiatric adverse events, depression associated with the use of Accutane and the sufficiency of what threshold do we need to meet in order to sufficiently inform patients.

DR. BERGFELD: I'd like to ask Dr. Kodish his opinion as the ethicist.

DR. KODISH: Good ethics starts with good facts. I think Dr. Greene's assessment of the facts is something that I would concur with. I think we're talking about apples and oranges here in terms of the real risks of the medication. It seems to me that if you've come down on the side of a more forceful regulatory approach with regard to the congenital malformations, the medication guide issue

is somewhat superfluous. I think adding it to the consent form would probably be sufficient.

DR. BERGFELD: Dr. Malone and then Dr. Levin.

DR. MALONE: The evidence for it causing birth defects is very high, but I mentioned I think there is some signal that it may cause depression but it's certainly not clear that it does. So, I think in that circumstance if you want to require patient guides for particularly important issues to avoid patient guide fatigue, I don't know if you'd want to use it for something that was not better demonstrated.

MR. LEVIN: I think Dr. Greene's point is excellent. I would have raised it yesterday except I saw it was on the agenda today, frankly.

I think whatever the issue is with this drug, it is a drug deserving for a number of reasons of a medication guide, and the reason a medication guide is important, no matter what happens in a formal informed consent document -- and we've had some sidebar discussions about whether that's really informed consent or informed decision making. Why it's important is because it's another opportunity to make sure that somebody gets information that they may not have gotten in the previous process. We know from the literature that what goes on between prescriber and patient falls far short of what is

desirable. Therefore, this is a safety net mechanism.

The medication guide needs to be thought of as a safety net. We hope a lot more goes on before that point, but if it doesn't at least the patient gets some information that they can use to protect themselves if they've gotten no other information from anybody else in the process.

DR. BERGFELD: Is there anyone that disagrees with Dr. Levin's presentation? I don't think we have to vote on this. I think you've heard quite clearly where the issue is. I think we'll move on.

I think we've heard quite clearly about the informed consent. It should be consistent with the information given out to the patient and the physician. The areas of interests and hazards should be mentioned.

I think we'll move on to intervention, and I think we've heard about monitoring the patients. There is no one who has spoken who hasn't talked about monitoring the patients and the managing of the events, as best they can, unless there's someone that wants to add something to the discussion. Dr. Anderson?

DR. JENNIFER ANDERSON: I'd just like to be sure that what we're talking about with monitoring of the patients is that what is meant there is a registry for all patients, not just for women.

DR. BERGFELD: Well, we can break that out and discuss that specifically.

DR. JENNIFER ANDERSON: But yesterday we thought we wanted to have a registry for the female patients. Now it's a registry for all patients. It has the big advantage that some of the questions that there's lack of information about with respect to psychiatric problems -- it may be possible to elucidate them given this kind of information that's gathered on everybody.

DR. BERGFELD: So, you're supporting a universal registry.

DR. JENNIFER ANDERSON: Yes.

DR. BERGFELD: Could I get a straw vote on who would support a universal registry just to get a sense of the committee, nonvoting and voting?

(A show of hands.)

DR. BERGFELD: Seven.

And those that would oppose it?

(A show of hands.)

DR. BERGFELD: About even.

DR. ADAMS: With a number of abstentions to lack of understanding of what's being voted on specifically.

DR. BERGFELD: I'm sorry. I didn't see you over there, Dr. Adams. I was wondering about the straw

vote on a universal registry versus just a female registry in the use of Accutane.

DR. ADAMS: A universal registry for males and females that includes some level of psychiatric questioning as well as --

DR. BERGFELD: Well, that's the inference, yes.

DR. ABEL: That's my concern as to a breach of confidentiality if it includes psychiatric data. What is going to be in this registry? That's why I abstained.

DR. BERGFELD: Dr. Mills?

DR. MILLS: I voted against because I don't see exactly what we're getting out of this. Having a registry and knowing that there are so many people with psychiatric diagnosis by a mechanism that isn't clear and how well the diagnosis is made not being clear I don't think is going to be extremely useful information.

DR. BERGFELD: Dr. Holmboe?

DR. HOLMBOE: Yes, I would second that. I'm also concerned that we don't know enough about the relationship here, about what the right instrument would be that we should use, whether it be Beck Depression, Hamilton, how it's going to be collected, et cetera. I think with pregnancy it's much more straightforward, but this is an area that we don't even know what would be the appropriate tool to use at this point.

DR. BERGFELD: Dr. King?

DR. KING: Well, that was my original concept. I think you're taking it beyond what's likely to happen in a dermatologist's office. They're not going to do psychiatric screening. They just want to know what patient prescribed what, and your nurse practitioner, your nurse or whatever is going to give them a universal packet. So, the issue of whether you're pregnant or crazy is not actually the issue. The issue is who got the medicine. So, I think that then becomes a data pool from which you pull out this other information.

So, I agree that you're not going to do all that, but at least out of the population of the prescriptions, then you can go do the studies that Dr. Mills or anybody else would like to do. If you're going to field a team, you've got to know the name of the players, and so the best way to get the players is to have them registered.

DR. BERGFELD: Dr. Murphy?

DR. MURPHY: I think we could define registry here as that the patient would have a unique identifier number. That is one way of identifying a registry irrespective of the rest of those issues.

DR. BERGFELD: Dr. Abel?

DR. ABEL: If that is what the registry is,

then I would agree with that because we talked earlier about further studies being done on a subset or a cohort of patients or those at high risk. And I think it's nice to have all these patient identification numbers, but I think we need to do further in-depth, rigorous research in patients with baseline psychiatric, psychological profiles and then follow it up in a cohort. So, we need more than just a registry.

DR. BERGFELD: Dr. King?

DR. KING: That was my concept. Roche and the FDA can put out a request through the web or whatever for volunteers. You have all the problems of epidemiology but at least you'd have unique identifiers. It's much like going on the web with your American Express. You trust that it's secure and so forth, but I think you have a bigger population to request volunteers from. You can't request volunteers unless you know who the players are, and they have unique, unidentifiable secure numbers or non-identified people. At least you've got a population to look for.

DR. BERGFELD: Yes, Dr. Byrne.

DR. BYRNE: It would actually offer the opportunity randomly choose people and follow them with their unique identifier number. So, you wouldn't necessarily be selecting, as some of the other processes

have, people who voluntarily come forward. This would be a nice way to randomize things.

DR. BERGFELD: Any other comments? Do we need to revisit the straw vote on the universal registry with identifying numbers just as a database for the numbers of patients? Dr. Branch?

DR. BRANCH: I remain concerned from the perspective that the objectives of this really -- the only advantage I can see to a patient going through this is that you're ensuring that they're having to sign an informed consent. I don't see that there's any advantage to the patient. What we voted on yesterday, there was a whole set of safety factors that were being built in.

What we're talking about today is now essentially a male-targeted program because women are already covered. So, we're talking about informing a group of men about a set of information in which there is a tremendous amount of ambiguity and uncertainty.

I think that great care and consideration needs to be given to choosing examples where we're starting to increase the regulatory burden to make sure that the patients are actually being protected by that decision, and I'm unconvinced that we have enough information right now to really protect men going into this because I'm not sure what the issues are. Yes, I think that there is a signal.

Yes, I think there is more to be done, but I have concerns about this.

DR. BERGFELD: Dr. King, did you want to respond?

DR. KING: Let me just finish that. When you buy Windows, you buy it and register it with the expectation it's going to work, but as we all know, if you don't have a product identification number when some glitch shows up, which it always does, you have no recourse.

I'm not suggesting we do anything other than have the possibility of having a recall or some further information or randomized studies. I'm not saying that Roche says or anybody says, FDA, that you're going to have psychiatric illness. I just want to know that they know of the possibility that there are problems, and they should report them.

DR. BERGFELD: Did you want to respond, Dr. Branch? And then Dr. Greene.

DR. BRANCH: The problem with that is what do you do if somebody hasn't registered. Does that mean they don't get the drug? Who is going to enforce this? Who is going to see that the whole process takes place? When you put something in place, it costs. It costs society in the long run. I think there needs to be more than a research outcome of being able to identify a stable of patients to

make a venture like this worthwhile.

DR. ROSENBERG: Could I reply to that?

DR. BERGFELD: Dr. Greene wanted to reply. Then you can.

DR. GREENE: Just one other quick thing. The other thing is I think you have to think of what your outcome measures are going to be. What are you going to look at? People who are depressed, people who are more depressed than before, people who ultimately commit suicide? What are your outcome measures? And even if you do that, how many events are you likely to record? Are you really going to shed any light on the problem? It's just not clear in my mind that you've met any of those criteria.

DR. BERGFELD: Dr. Rosenberg.

DR. ROSENBERG: I was just going to say not to the merits of whether we should do it or not, but in terms of the technical aspects of how it would go. As of now, at least in my experience, the pharmacist won't fill a prescription unless there is a consent thing that the patient has initialed and that I have signed. You can make a photocopy out of the PDR and she initials it and I initial it. Although last time we tried that, it didn't work. They wanted something else for the pharmacist that I told him I'd learn about when I got here.

(Laughter.)

DR. ROSENBERG: But anyway, even now you can't just walk into a drugstore and get this without doing the other, which is I think a good idea. It all relates to that. Am I wrong about that? Maybe it's just our druggist then that wouldn't fill it.

DR. BERGFELD: FDA, do you want to hear anything else about monitoring? I think that we had a split vote.

Dr. Mills?

DR. MILLS: This is a very quick question. If we came up with a registry for men, which just gave us the names and addresses or whatever of everyone who is treated, what can the FDA then legally do with that? Can you take a random sample of those people and ask them to participate in a study? In other words, what kind of power do you have to use that list?

DR. BERGFELD: Someone? Dr. Murphy?

DR. MURPHY: We, first of all, would ask the sponsor, if we've asked them to maintain this registry, to report the registry to us, and we would ask them, if issues came up, how can we look at this information.

So, would we go out and demand? No. Would we go out and demand that they then take that population and randomize them and study them? No. I don't think we can then go out and tell people that they have to participate

in a study. That is not within our jurisdiction.

Again, I don't know why we think this is going to be just for men. I know you're saying we already have women, but I'm just saying that certainly we're going to be looking at both men and women who would be registered. What you want to know is, again, get a denominator and then, depending on how we then wish to look at information from this registry, we would hope that the registry would be involved with the medication guide that would information on it for the patient to call, be it an external source, as we've done in other situations where they would call if they have an exposure, they're pregnant, or they would call if they have a risk factor, in addition to calling their doctor, so that you always have on there to call your doctor, but here's another source too that people could call if they chose. It's up to them to choose to call.

DR. BERGFELD: I'd like to resolve this a little bit. We had a split vote on the last straw vote, and I don't want to make this an official vote. I'd like to call the question again as a straw vote. All those in favor of a universal male and female Accutane registry, if you'd raise your hand.

(A show of hands.)

DR. BERGFELD: Eight.

Those opposed?

(A show of hands.)

DR. BERGFELD: It looks like 12 opposed.

Those abstaining?

(A show of hands.)

DR. BERGFELD: So, abstaining, 1. Oh, you want a question, Dr. Anderson?

DR. GLORIA ANDERSON: I guess I am. I voted for it to begin with, but then after I heard all these explanations, I'm not sure because that wasn't what I had in mind when I read this document. So, now I'm not sure.

DR. BERGFELD: That's all right. You're allowed to abstain.

In regards to intervention, the drug distribution I think we already handled yesterday. I'm not sure that anyone would disagree with how we handled the pregnancy problem, that we would change our perspective.

A prospective controlled trial. Everyone has said that's a need. Unless there's someone disagreeing with that statement, I would say that we have closed the discussion on question 1.

Then moving to question 2 --

DR. GREENE: Can I comment?

DR. BERGFELD: Yes, I'm sorry. Dr. Greene?

DR. GREENE: Personally I couldn't imagine how

a prospective controlled trial would be done to address the psychiatric aspects of this medication. I can't imagine. I'm sitting here trying to think how I would design the trial were I to run it. I couldn't imagine how I'd do it.

DR. BERGFELD: Well, thank you. I think that Dr. Mills proposed another format.

DR. MILLS: That's right. I'd like to clarify that. What I was proposing was not a prospective controlled trial because we couldn't get a control group. So, I was proposing more of a case series or a cohort prospectively evaluated, but not a controlled trial.

DR. BERGFELD: So, the correction there would be a prospective case series trial? Is that correct?

DR. MILLS: Yes.

DR. BERGFELD: Is everyone agreeable to that? Or something else? Dr. Branch?

DR. BRANCH: Can I put up another possibility? It seems to me the strongest stimulus or the strongest signal is the challenge/rechallenge. We've heard that about a third of patients go on to a second course of treatment. It would seem to me that there is a possibility to refine a target group to look at a group of people who have actually experienced some symptoms during the first course of treatment, they still have severe acne, a second course of treatment is being proposed, and to do this under

much, much closer surveillance and be able to measure a much greater number of endpoint measures, and that you would be able to get a comparative group of people who didn't have psychiatric events in the first course of treatment, now going out to the second treatment. It would seem to me that if you really target the people who have the problem, you could really get some insights into it.

DR. BERGFELD: Dr. Greene, did you want to comment?

DR. GREENE: No.

DR. BERGFELD: I think you've heard what kind of study that's needed.

Dr. Abel?

DR. ABEL: Regarding the drug distribution, we've heard of sales on the Internet. Are there any controls to prevent sales of Accutane on the Internet?

DR. BERGFELD: Dr. Bull, Dr. Murphy, Dr. Wilkin?

DR. BULL: I think that that's an area that our compliance group is definitely looking at and is monitoring. So, yes, that is being watched closely and where there are grounds that a case could be built, it certainly is in an area of compliance and enforcement.

DR. BERGFELD: Dr. Ellison?

DR. ELLISON: With respect to the international

sources, over which, unfortunately, there's no jurisdiction from here, we have ourselves tried to shut down the supply of these places, and it has proven to be impossible. We don't have any legal recourse to that either, and they're very difficult to track. So, I think with respect to inside the U.S., I think that's going to be under control very quickly. I think the concern that everybody has is ex-U.S. That's almost impossible to deal with currently.

DR. BERGFELD: Thank you.

Dr. Abel, does that answer your question?

DR. ABEL: Thank you.

DR. BERGFELD: We'll move on to question 2, unless anyone has an objection or would like to discuss something else in question 1. Seeing none, question 2. Would further studies help to clarify the relationship between Accutane use and psychiatric events?

I think that we have heard that answer to be yes.

And if so, what kind of studies? We have defined the study under "intervention" as one. We've also heard comment on basic science studies. I suspect retrospective epidemiological studies are still in order. Are there others that should be added that are not on the list or we have not discussed?

Question. Dr. Adams.

DR. ADAMS: Thank you.

I would like to add a comment regarding basic science studies. I do think there needs to be further clarification or a determination of the role of retinoids in the adult brain, but of perhaps greater importance is the role of retinoids in the adolescent brain. One thing that is widely accepted now among neuroscientists and certainly among neuroteratologists is that the adolescent growth spurt that occurs in the brain represents an additional time of vulnerability. The tissue affinities, et cetera in the adolescent brain may look a little bit different than they do in the adult, mature brain. I think it would be important for these basic science studies to look at those two ages.

Thank you.

DR. BERGFELD: Thank you.

Dr. Lammer, any additions?

DR. LAMMER: No. I agree with that comment completely. It sounds like there's really a dearth of information about the distribution of retinoic acid receptors and related chemicals that might be involved in a pathway with retinoic acid in the adolescent or the adults.

DR. BERGFELD: Thank you.

Dr. Greenhill?

DR. GREENHILL: Are there any suggestions about

how these suggested studies might be implemented in the course of events? Is it something that comes from the agency? Would there be RFPs put out through other agencies to do the work? How is that done?

DR. BULL: FDA, generally speaking, does not fund research. We certainly are currently actively looking at enhancing our science based mechanisms to address questions that are of high regulatory significance, but this is probably going to be an activity that may represent an opportunity to take the question either to the sponsor and their research capabilities or perhaps to the NIH.

DR. MURPHY: I just want to confirm that we can only ask the sponsors to perform the studies. If you look at the history of pediatrics, it's up to them unless you have a specific regulation, which we do now for children. So, we'll ask.

There also is a level which, if we cannot approve the drug because the information they have isn't adequate to ensure the efficacy or the safety, then of course it is prudent for them to go ahead and perform those trials.

DR. BERGFELD: Dr. Tan, do you have any comments to make? We haven't heard from you today.

DR. TAN: I think clearly there is a need for a prospective study. The specifics of the designs need to be

worked out. I think you can do a cohort study or a case-control study, but it's impossible to do a randomized controlled study.

Also, the basic science research is important. I think there has been some research I think in the cancer area where they have used 13-cis-retinoic acid for the neuroblastoma patients. There might be some basic research going on already.

DR. BERGFELD: Any other comments?

(No response.)

DR. BERGFELD: I think that we've completed then questions 1 and 2 to the satisfaction of the FDA. I seem them shaking their heads.

I think we will take a 10-minute break and reassemble here at 3:25 to proceed with the afternoon, which will take up Accutane New Formulation.

(Recess.)

DR. BERGFELD: It has been an intense two days. I think the issues discussed have been exceedingly worthwhile. I think that this very large panel has participated at a very high level, and I thank all of them for their participation.

I've also asked, because we still have a formidable piece of material to review, that both the FDA and Roche shrink their presentations and just get to the

meat of the facts so we can discuss the issues. They have both agreed. So, I thank them.

We're going to first lead off with the Executive Secretary's conflict of interest statement for the panel members.

I will ask the panel members who have any conflict of interest to declare themselves if that is appropriate.

MS. TOPPER: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting when evaluated against the agenda.

With respect to FDA's invited guests, Drs. Jane Adams, Alan Byrne, James Mills, and Edward Lammer have reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Adams would like to disclose that in the past she has participated in two research grants to study

Accutane. One was funded by Roche and the other was funded by NIH/NICHD.

Dr. Byrne would like to disclose that he has published articles on the subject of Roaccutane.

Dr. Mills would like to disclose that he is currently collaborating with Roche on an unrelated research project. He has also written an article and attended a seminar which were unrelated to the particular matters at issue, but sponsored by Roche.

Dr. Lammer would like to disclose that in the past he has served as principal investigator on phase I and phase II longitudinal studies of infants exposed to isotretinoin in utero. The studies, sponsored by Hoffmann-LaRoche, were designed to document the developmental toxicities of isotretinoin following inadvertent human use during pregnancies in North America.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose

products they may wish to comment upon.

Thank you.

DR. BERGFELD: You may breathe now.

(Laughter.)

DR. BERGFELD: We're going to go forward again with the Accutane New Formulation, and Roche is first presenting.

DR. McLANE: My name is Dr. John McLane. I'm going to try to go through this fairly quickly. Since you have a copy of the presentations, I'm just going to do a couple of the first ones and then skip down to the hormonal contraceptive which I believe is labeled slide 24 in your package. After I do that, then I will introduce Dr. David Young. Dr. David Young has been working with us on the pharmacokinetic program, and then I will come back to finish up on the last part. So, I will try to do this as quickly as possible.

Now, as you've heard, Accutane has been on the market successfully for the last 18 years. It has been used at doses from .5 to 2 milligrams per kg. It is the most effective therapy for severe recalcitrant nodular acne.

However, there are drawbacks in our current formulation because of some of the dosing variability that's introduced in the way it is being used. These

drawbacks could lead to decreased efficacy or prolonged therapy.

So, in 1995, we initiated a new formulation based on micronization properties of the isotretinoin. With this new formulation, we're able to get increased bioavailability. The modification of the new formulation results in a dose that could be taken once per day and it could be given either with food or without food. That way it can accommodate the lifestyles of the Accutane patients that are using it. The new formulation addresses the drawbacks of the dosing variability of the current formulation.

There are a number of publications that indicate the efficacy of the current marketed formulation of isotretinoin, and these vary from the doses of .1 all the way up to 2 milligrams. However, our label indicates that it should be used at .5. The minimum dose is .5. The reason for this is because that really is at the low end of the therapeutic range.

Some physicians prescribe Accutane at higher doses than 1. It's used rarely but it is used for patients that have recalcitrant severe acne, for example, acne that's on their backs with nodules that do not clear up. Predominantly the use is of 1 milligram per kg. You'll see this slide later on when we explain some of the dosing

relationships with various doses of Accutane.

Now, the variability that we see with Accutane is due to we know that dosing without food results in a significant reduction in exposure with Accutane. We have a survey in which we know that about one-third of the doctors do not recommend taking Accutane with food. We also know that 21 percent of the patients are instructed to take Accutane only once per day, when they're instructed to take a most common dose, which is around the 1 milligram per kg. We also know that prescribers report that only 33 percent of the patients do not take Accutane consistently with food. We also have reports that 22 percent do not consistently take the second dose when they have the b.i.d. dosing regime. The overall effect then is a significant patient variability in exposure.

Between this once per day and twice per day, with or without food, this creates some of the variability. We also know that the variability that can be affected is due to a dropout of the patients in practice. We know that of the patients that drop out, we have some dose-related effects. Those dose-related effects are the mucocutaneous effects, which 19 percent of the patients that do drop out report that as the reason why. We also have triglycerides, which is also a dose-related effect, and we know that 17 percent of the patients that do drop out, drop out because

of triglyceride elevations. These are the most common single reasons for withdrawing from effective therapy.

This overall compliance or noncompliance would result in some under- or overdosing which overall may affect the efficacy and safety.

The new formulation of isotretinoin addresses these concerns in the variability in this type of dosing. The dosing can be given with or without food, and it is given only once per day. It has fewer and less intense mucocutaneous events, and it has fewer patients with elevated triglycerides.

Overall then you have compliance with the dosing regime and there's more predictable exposure because the way that it is dosed allows a more predictable exposure which can decrease the impact of the individual noncompliance.

What I wanted to just quickly jump into was this and the next slide.

The program that we have, which I will not go into the results because you do have these slides, is that we had a pivotal clinical program in which we had measured efficacy and safety, and within that trial we had looked at parameters which was 90 percent of the patients that cleared, the clearance of the papules and pustules, more particularly the primary criteria was the clearance of the

nodules, how many nodules where clear. We saw that the new formulation was absolutely statistically clinically equivalent to the current marketed formulation.

However, the program had a design where we gave the new formulation in a slightly different format. We gave it in a format in which the patients were given the new formulation only once per day without food, and it was compared directly with the marketed formulation which we know to be an effective dose which was twice per day given at 1 milligram per kg, and they were given with food.

Consequently, we know that the exposure difference between the two formulations and part of the design of this clinical trial then was to identify the minimum effective therapy for isotretinoin. In this equivalency between the new formulation and the current marketed formulation, we were able to identify what was the lower limit, what was the minimum effective therapy for isotretinoin.

From the table that you have in your package, we know that there were some differences between these two formulations. If we went down any further, we would have not reached statistical equivalency. So, consequently, we do know that the new formulation is at this minimum effective dose.

On the safety profile, just to quickly

summarize, the safety profile was really quite comparable with the current marketed formulation. As I pointed out, we had slightly fewer patients and patients that had less intense mucocutaneous events, and we also had patients that had less triglycerides and fewer elevations in their triglycerides.

I'm going to jump on to the other part of the program. David Young will present the food effect on the bioavailability, but I'm going to go ahead and present the hormonal contraceptive interaction.

We had another program within this, and we did this in collaboration with the FDA in order to evaluate the hormonal contraceptives and the potential for any interaction. We wanted to assure that isotretinoin, in either the new formulation or the current marketed formulation, does not alter the clinical pharmacology of hormonal contraceptives.

So, we had two components of the program. We had an in vitro study with hepatocytes and microsomes in which we evaluated five different progesterone components that are found in hormonal contraceptives, and we evaluated them within live human liver cells, hepatocytes, and we evaluated them to both inhibit as well as induce enzymatic enzymes that would be involved with the breakdown of hormonal contraceptives or with the breakdown of

isotretinoin. These studies are in progress. The last of these studies will be presented to the FDA the third quarter of 2001.

We also have a clinical program in which we have two studies. I think it's important to understand the program on this. Let me just step through this quickly.

What we had is that we had a measurement to determine if isotretinoin affects oral contraceptives within patients. We used the contraceptive Ortho-Novum 7/7/7. We looked at pharmacokinetics of ethinyl estradiol and norethindrone. We also measured the pharmacodynamics of markers, luteinizing hormone, follicle-stimulating hormone, and progesterone within the patients. All of the patients being treated were females with severe recalcitrant nodular acne. They are receiving the full course of therapy, the 20 weeks.

The two trials are divided up. One group of patients were receiving Accutane at the 1 milligram per kg. The other was receiving at .4 milligram per kg. The other was the new formulation as a single dose and the current marketed as two divided doses.

The design of the trial is that we have a oral contraceptive stabilization period in which the patients were taking oral contraceptives for at least 1 month in order to reach steady state level. We then on the second

month at two different points during their menstrual cycle, when we know that there are changes within the hormonal levels, we looked at, at day 6 and at day 20, the pharmacokinetics and the pharmacodynamic properties of the ethinyl estradiol as well as the surrogate markers.

We then would take these measurements. These are our baseline levels before we treat with isotretinoin. We started the therapy on isotretinoin. The patients continued and were allowed to reach a steady state level of their isotretinoin in their metabolites.

We were then able to go ahead and -- in their fourth month of oral contraceptives, their second month of therapy on isotretinoin -- measure again the levels of pharmacokinetics and the pharmacodynamics at both day 6 and day 20. We could then do a comparison then between the day 6 and the day 20 for all of these particular markers.

These studies are in progress. So far, there have been no serious or unexpected adverse events. The last patients will be finished in these trials this month, and the reports will be submitted to the FDA in the first quarter of 2000.

I'm going to have Dr. David Young come up to quickly explain the pharmacokinetics.

DR. YOUNG: Thank you.

I'm going to really be talking about the

pharmacokinetics and the dose exposure-response relationship and possible confusion issues with the different formulations we might have.

We did a four-way crossover study with Accutane and Accutane NF, and you have this report. What happens here is that we took 80 milligrams of Accutane, 30 milligrams of Accutane NF under fed and fasted conditions. This really represents the different mean graphs. The top one represents the fed Accutane, and the blue one down here represents the fasted Accutane at 80 milligrams. You can see the very large difference. This is a crossover. So, within-subject variability is very large because of the food effect.

The yellow represents the fed Accutane NF and the red represents the fasted. You can see there's very little variability compared to the large one that exists for Accutane.

The results of that study were there's a 2.5 to 1 ratio between Accutane fed and fasted. There's really inconsistent pharmacokinetics occurring if you have inconsistent eating habits. And the between-subject variability is larger without food than with food.

For Accutane NF, we have a 30 percent difference in exposure. The variability is about 30 percent throughout, within-subject variability, between-

subject variability, as well as the fed/fasted issues, all within approximately 30 percent variability.

What we wanted to next do is we wanted to take this data and try to figure out what's happening in terms of exposure within our patient populations within the efficacy studies as well as with patients that we normally treat. So, what we did is we took the data, using the principles of superpositioning for linear pharmacokinetics, which has been proven with this drug and these products, we simulated the concentrations for different doses under different conditions in order to compare the different doses and conditions.

This is an example. This is the 1 milligram per kilogram divided dose that's the most common. This is what was actually used in the phase III study, for example. This is a simulation of what would have happened. The red one here represents the NF drug, .4 milligram per kilogram single dose. And the blue represents .5 milligram per kilogram divided dose. So, you can see that, in fact, the NF has a very similar exposure to the .5 milligram per kilogram Accutane. NF is red. Blue is Accutane at .5 milligram per kilogram.

If we go back to this table, which Dr. McLane briefly showed, I want to kind of summarize this real quick for you. First of all, what we've done is we've added the

NF study at the bottom, which has 600 subjects, which is much more than any of the publications or even the total publications put together. We looked at 1 milligram per kilogram Accutane under fed conditions, and we looked at .4 milligram per kilogram of NF under fasted conditions. If you look at the other publications, I put the conditions as well as the doses investigated also.

Now, what we have in our NF study is we have a situation where we showed therapeutic or clinical equivalence between the 1 and .4. But we did show also there's a rank order between 1 and .4. 1 seems to be a little bit better than .4, though not statistically.

If you look at the same studies within the publications here, you find that .1 and .2 milligram per kilogram is always worse than everything else, and that's why you see the greater than sign here.

.5 and 1, though, in different publications sometimes it's better, sometimes it's not statistically different. But the general trend of it all is that there's a rank order again. 1 seems to better than .5, sometimes not statistically but it seems to be better.

In terms of 2, this study here, though it's only 14 subjects, that was under fasted conditions, and again 2 was about equal to 1, though in a small number of subjects.

Let's now look at the overall exposure for those doses under those conditions. So, here we have a situation again where we have the .1, .2 under fed conditions. That was some of the studies, and the area under the curve is 1,842/921. But if you remember in that previous slide, we had rank orders between .5 and 1, sometimes statistically equivalent, sometimes just a rank order. They didn't do statistics.

What you can see, though, is if you look at .4, .5, and 1 -- .4 NF under fasted conditions, .5 Accutane under fed, and 1 of Accutane under fed -- the areas under the curves of .4 and .5 are about the same, which we saw that picture before, the red and the blue curves, and you'd expect them to be the same. And they had the same relative relationship to 1 in our clinical studies. Over here .5 relative to 1 was sometimes equal, but generally rank order, 1 was better than .5, sometimes statistically different, sometimes not. The same thing happened with the NF study.

So, we can see from that, well, that makes sense because the area under the curve, the overall exposure to this drug, was about the same for both formulations.

Now let's look at the risk management for the two formulations if we have both on the market. If we have

some confusion and we have both on the market, we have a situation where, in fact, instead of taking Accutane b.i.d., you may take it q.d. Or instead of taking it with food, you take it without food. You could also have the reverse for Accutane NF; instead of taking it once a day, you have b.i.d.

I'm just going to go through a couple of scenarios here so that you can see. We'll go to this one here. This is a situation again where we dosed the normal 1 milligram per kilogram under fed conditions, b.i.d. You get an overall exposure, a daily exposure, of 9,209. NF is down at the bottom; its exposure, 4,161. Again, we saw that these were equivalent therapeutically, but again we saw a rank order in terms of the therapeutic response.

If you take .5 milligram per kilogram under fed conditions of Accutane, though, you get something again around the same area, 4,161 as Accutane NF, and we saw that previous slide too.

But if you take Accutane .5 milligram per kilogram under fasted conditions, your exposure is much less. So, we've got exposure of 1,800 versus the 4,000 range which occurred with .5 milligram of Accutane and .4 of Accutane NF. You can see that variability, and if I had an individual patient who at one time was taking Accutane at .5, and then all of a sudden the next month changed

their eating habits and started taking it .5 under fasted conditions, I could have a completely different exposure one month versus another month, depending on their eating habits.

This is a situation where we actually mix up how we give the dose, q.d. versus b.i.d. The green line here represents the 1 milligram per kilogram b.i.d., and the blue line up here represents 1 milligram per kilogram once a day. So, if it's, for example, a 70 kilogram patient, it would be 70 milligrams. The overall exposure is the same. You can see the curve is very similar. You have little higher peaks than this, but if the patient responds, that's fine.

Now, let's assume that the patient is responding to this 70 milligram once a day dose. Again, let's say they change their eating habits. They go back to school. They go back to college and they start eating differently, as we know they do. What happens then? That exposure of 70 milligrams once a day or 1 milligram per kilogram once a day would drop to this exposure down here. So, we would wonder, in fact, is this exposure where we have efficacy going to result in efficacy down here. Now, if this is efficacious for this individual patient, it may not be efficacious for that specific individual patient down at the bottom here.

So, overall what we found both in terms of NF and Accutane is that Accutane has wide variability in terms of its pharmacokinetics. From day to day, it can change because of the fed/fasted conditions. NF does not have that variability. It always is pretty consistent, which allows us to keep consistent dosing in patients who may not be compliant from one day to another day in terms of their eating habits.

I'll now pass this to Dr. McLane in a hurry here.

DR. McLANE: Let me slow down for one second because you have some questions that you'll be voting on and I want to make sure that we can address those properly.

One of the questions is, are additional dosing studies necessary? Well, we know right now with the new formulation, we are at the minimum therapeutic dose. However, the question is what happens if, for example, you have a confusion on the market and you take the new formulation twice per day rather than once per day? You know from David's presentation that you'll actually have a dose that is still below the therapeutic range that is for the current marketed formulation. So, if you take the new formulation twice per day, you know you're going to be in a range that has already been studied with the marketed formulation.

If you take the new formulation with food or without, it doesn't make a very big difference, a 30 percent difference in the dosing regimen. We know that it's going to be up above.

If you skip a dose on the current marketed formulation, confuse it with the new formulation, for example, you're going to be under-dosed if you take the current marketed formulation without food.

So, the question is taking the new formulation with or without food. We have no problem with that. That's what we want to be able to do. To be able to give it once per day. That's what we want to try to get for a label on this. If you do take it twice per day, you're not going to have an over-exposure with the new formulation.

What we're going to be doing is then how do we differentiate between the products. We want to make sure that we inform prescribers on the differences in dosing between the new formulation versus the current marketed formulation. We'll be able to manage that risk. With the new formulation being available on once per day or, if by mistake, could be taken twice per day. It could be taken with or without food.

We're also going to be able to differentiate it on the market by we're going to have very different packaging. We're going to have individual pouches for

these that are going to contain 30 for their monthly prescription. The packages undergo the child-proof packaging. There will be the informed consent within the box. There will be the survey enrollment form within the box as well.

The capsules are different. We have contrasting color schemes. There will be identification marks and the capsule strengths are 7.5, 15, or 22.5 for the new formulation. We have a distinct brand name for the new formulation that we've submitted to the FDA already. It has not been approved at this point.

The new formulation is as safe and efficacious as Accutane. It can be given with or without food. It can be given once per day. It has fewer and less intense mucocutaneous events, and it has fewer patients with elevated triglycerides.

That means more patients will remain on therapy in order to have better efficacy. It will be much more predictable therapy. This compliance, this predictable exposure from the new formulation decreases the impact of individual noncompliance.

So, are additional studies needed for dosing? No.

Do we have a handle on doing additional studies on this? We don't need to. We know the range of the

efficacy. We know the range of safety of the marketed formulation.

Are we managing the risk for having the two formulations on the market? Yes. We have distinct packaging between the two formulations, and we will make sure that our prescribers know the difference between the two formulations on the dosing requirement.

Thank you.

DR. BERGFELD: Thank you very much. I think we'll hold the questions and discussion to that period of time after the FDA presents.

The FDA will now present, and Dr. Jonathan Wilkin will be the first presenter.

DR. WILKIN: We'll be talking ever so briefly about the new formulation of isotretinoin which is unnamed at present.

I would like to make one clarifying statement at the beginning, that everything we've talked about over the past two days up until this time really are systemic isotretinoin issues, and at some point in the future, the patent will run out and there will be generic competition. So, there will be ANDAs, possibly 505(b)(2)'s. What we are talking about and what we are hearing recommendations from the committee on the psychiatric issue and on the pregnancy aspect, teratogenicity, we will be incorporating into

letters of approval and these sorts of things so that it will apply to other systemic isotretinoin forms in the future.

DR. BERGFELD: Thank you.

DR. WILKIN: The Accutane New Formulation has all of the issues, of course, that we've discussed up until now, but it also has some specific issues that merit some consideration.

The first is dose ranging. Dr. McLane has actually already prepared the way for much of this.

The hormonal contraception and concurrent marketing. They've already introduced the topic.

For those who are coming for the first time today, we are talking about isotretinoin, a drug substance that was approved in May of 1982, and the sponsor has just restated their goal of improving bioavailability and reducing the food effect.

The new formulation does consist of three different size capsules, 7.5, 15, and 22.5 milligrams. The sponsor's recommended dosing, which they studied, was 0.4 milligram per kilo per day for 16 to 20 weeks.

The new formulation development program did not have all of the features of a new molecular entity type of NDA. We already know an awful lot about Accutane, and so the program really was designed to supplement the data that

were already available for the currently marketed product. The application included five pharmacokinetic studies and one multi-center clinical trial.

Isotretinoin background information. We do know something about dose ranging. The sponsor has just discussed this. And we have the Orme data from 1983-1984, which is the only currently published information on the hormonal contraceptive/isotretinoin interaction potential.

The current recommended dosing for the marketed product Accutane is 0.5 to 2 milligrams per kilo given in two divided doses daily for 15 to 20 weeks with food.

Now, this is a somewhat complicated slide, but it gives some of the information that the sponsor gave in tabular form. Basically on the y axis is rate of recurrence, and it goes from 0 to 80. So, if there is a high rate of recurrence, that's the need for retreatment, and subsequently longer exposure over time to isotretinoin. So, the goal is to try to find a dose where the rate of recurrence is going to fall to an acceptable level.

These dots do not represent individual patients. In fact, they represent individual studies. The sponsor has mentioned some of these studies. The break point for the current formulation seems to be at 0.5 milligram per kilo per day for 20 weeks. That would give 70 milligrams per kilo as a total dose. You can see that

above that, the rate falls considerably compared to below that.

Now, at doses below .5 milligram per kilo per day, one can get suppression of the nodulocystic acne during the trial. Unfortunately, there's a high rate of recurrence. I think that's the difficulty. In the present data set that we're thinking about today, recurrence rate really was not examined. It was looking at reduction in the number of lesions during the trial. So, one of our questions is going to be, where in the end is the new formulation going to play out in terms of rate of recurrence?

Again, the goal in dose ranging is to obtain the optimal dose, and the optimal dose consists of two competing goals. The first is minimizing the need for retreatment. So, there needs to be a high enough dose to minimize retreatment. On the other hand, one wants to give only that amount and no more because of the risk of dose-dependent toxicities.

The sponsor has addressed their program for the possible hormonal contraceptive interaction. Again, the only data set that we really have from the literature right now is the 1983 Orme study in which there were 10 women taking 6 different oral contraceptives. They were taking, again, the lowest recommended dose of isotretinoin. 2 of

the women had a decrease in levels of the estrogen and progestational agent while they were on isotretinoin, and 1 of these 2 women had a progesterone spike, which was measured sometime between day 12 and day 15 which might not have captured the greatest spike.

So, the need for isotretinoin hormonal contraceptive studies. The new formulation is projected to be more bioavailable. There may be some concerns there. The currently used hormonal contraceptives today are qualitatively and quantitatively different from the hormonal contraceptives in the Orme study. We now have low estrogen preparations, progestational agent only type preparations. We have the implantables, the injectables, and certainly we have a lot of new progestational agents. So, these are areas for concern and for thinking about.

Also we have the accumulating spontaneous reports of pregnancies coded compliant, and our thought is the original data really isn't sufficient to tell us that there is no interaction.

Dr. Bashaw is the next presenter for the FDA.

DR. BASHAW: Yes. As Dr. Wilkin has given the introduction already, the only study we had information on was from the Orme study and that study was just found, when you really started looking at it, to be a very inadequate study. One of the issues that was raised yesterday, which

Dr. Wilkin did not mention today, was in fact in those 10 women in that trial, 6 different hormonal contraceptives were used. So, in fact, the fact that you had some conflicting results, you really had no certainty at all whether or not there was or was not an interaction.

What we wanted to do is to bring it up to modern-day time and use techniques that were not available at the time of the original study back in the early 1980s. We started the program using both isoenzymes, also looking at hepatocytes to look for metabolic interactions not only with isotretinoin but with the oral contraceptives themselves.

Again, Dr. Young has talked on this to some degree. We have studies going on with recombinant p450 isoenzymes, pooled liver microsomes. We've received some data to date regarding studies with specific substrates, medroxyprogesterone, primarily looking at implantable hormonal contraceptions, and to date we've seen no interaction there. I just received last week, in preparation for this meeting, the draft report for the progesterone study. So, I haven't had time yet to go through that one, although the sponsor showed there was no interaction, but that part is still under review at this time.

Again, what we try to do with our in vivo

studies today is try to make it today's quality. We are looking at both isotretinoin and its metabolites, looking at estrogen, progestin levels, dynamically looking at FSH, LH, progesterone levels, trying to make sure that if there's any kind of interaction, meaning it's an interaction with isotretinoin or on hormonal contraceptives or if it's an interaction with the endogenous hormones themselves, that we get a chance to look at them.

One thing that is a little different, it is a 4-month study, a four-cycle study. Two trials are actually being done: one with Accutane NF and one with current Accutane both at the recommended doses of 1 milligram per kilogram and .4 milligram per kilogram. Again, as shown earlier, we are looking at levels of ethinyl estradiol, norethindrone, FSH, LH, progesterone, looking at both steady state levels. We're getting single-dose Accutane levels and we're also getting steady state Accutane and metabolite levels at the end of this trial, trying to make it as strong of a trial as possible.

You notice there are some numbering differences between this slide and the slide the sponsor presented. That's primarily the way you count the days from menses or after menses. That's why you'll see some differences, day 6 versus day 12. It's just a counting difference. The trials are the same and how the sponsor had their slide

earlier. The idea was we wanted to try to get close to day 12 where you would see a spike of FSH/LH if ovulation was taking place. That's why I've got that presented this way on my slide. Again, though, we tried to make it as strong as possible to look for these kinds of interactions if they existed.

To date, we've only received two interim reports. We received data from 9 subjects on the Accutane NF report, and there is 1 subject in there that does have aberrant data, does have a high progesterone level, higher and into the low normal range. We've asked for some follow-up on that. We've not yet received that data.

With regard to the Accutane study, this was more complete. We have PD and PK data from 22 subjects and we see no evidence of interaction either from a PK or PD standpoint. But as the sponsor reported, they're going to be finishing up those reports and we'll be getting those final reports in the first quarter. So, we should be able to come back with better information shortly.

Again, we're here this afternoon to discuss NF. The sponsor has already told you NF is a micronization process, and so we won't spend any time on this right now.

This is what we tried to show earlier. This is what you see with Accutane fed, current formulation. You get very high peaks.

Here's a comparison of what happens when you get the current formulation with and without food. You can see a dramatic food effect, which does cause, as they mentioned, variability between response and in between subjects when meals are taken, meals are skipped, or you change your pattern of taking it.

This is a table of your Accutane data, looking at the 80 milligram dose, fed and fasted. What you really see here and the importance of this table is right here. We're talking about apparent oral clearance. When you give it with food, you get a clearance of about 8 liters per hour. When you give it fasted, you go to 25. There's no metabolic change. It's the fact that the bioavailability is so much smaller for the fasted dosage form, that what they really have done is decreased the variability in absorption with the new formulation which makes it a more consistent dosage form. This is what you really see with the old one, this tripling of the clearance because of poor bioavailability.

This is combination slide again. You can see again we have the current formulation fed, the current formulation fasted. This is the NF fed. So, you can see it is about half again what you see.

Here you can barely see the red line here. This is NF fasted. So, from a biopharmaceutics standpoint,

we would say there is some food effect with the NF formulation with and without meals. Technically there is a food effect, but relative to the effect that you see with current Accutane, it's an insignificant change. We wouldn't consider it one, but there is some degree of food effect there.

But clearly, it is a more reproducible dosage form. You have less variability, and those all cut back to those issues which have been raised previously regarding dosage form and dosing variability. The fact is that from a biopharmaceutics standpoint, one would judge the micronized formulation as a marked improvement in terms of drug delivery and consistency in drug delivery.

The NF NDA consists of dose proportionality studies. It consists of the food effect studies, and also they have a formulation linkage study. The formulation they used in their clinical safety/clinical efficacy trial differed somewhat from what they're planning on marketing. They did a study to look at the to-be-marketed and the phase III study material.

What you basically saw is they were able to demonstrate that at the 15, 30, and 45 milligram dose levels, that the three capsules were bioequivalent, they were dose proportional. The food effect is there. However, it is much less and much more consistent than you

see with current Accutane and there is no significant difference between the product that is proposed to be marketed and that which was done in their phase III clinical trials.

That basically is a very hurried summary of what they did for the pharmacokinetics of this product. Thank you.

DR. BERGFELD: Thank you.

Dr. Kathryn O'Connell?

DR. O'CONNELL: Good afternoon. I'm Kathryn O'Connell, medical reviewer for this NDA in the Division of Dermatologic and Dental Drug Products.

I had planned today to actually focus on the design features and study results that specifically inform three issues rather than go over anything anyway. I'm going to skip over some of these a little more than I planned to for time.

But the issues were dose ranging, adverse events, specifically the psychiatric adverse events reported in the trial, and then the problem of the switch-over risk that the sponsor has already addressed.

The sponsor has already pointed out, as has Dr. Bashaw, that the isotretinoin exposure in the Accutane arm of this trial, the comparison trial, was significantly higher than in the new formulation arm. So, in my mind if

the trial showed equivalent efficacy, then it would suggest that 1 milligram per kilogram per day of Accutane, which is the mid-range of the currently labeled dose, if you give that with food, which is what's labeled, then it's not the minimum effective dose, otherwise they wouldn't be equivalently efficacious.

Again, the trial was to compare these two doses, which you've already heard about, so we can skip by that.

Now, I don't want to get into a big debate about number 1 because it's a little statistical thing and our statistician is here if you want details in the question period.

But the bottom line is the second bullet, and the bottom line is the therapeutic equivalence in our view was established. It's supported by the percent reduction in nodules. As the sponsor pointed out, it's supported by equivalent global assessments, and it's supported by equivalent short-term need for retreatment in the overall population. And I'm going to just talk a little bit about that on the next slide.

This trial, as Dr. Wilkin just was saying, wasn't really designed to look at relapse rates, which would take a longer time. But in this trial, the sponsor did look at week 36 to see if the patients needed to be

retreated with Accutane. It was done by phone interviews. The phone interview is not the same as a physical exam.

The reason that we were interested in having this looked at in the trial was that the need for retreatment is of particular concern for pediatric patients and for women. For pediatric patients, the reason is that they're still growing, and isotretinoin does affect bone. For women, obviously, if you have to have a second course of therapy, it increases the risk of fetal exposure. In the literature there's some evidence that pediatric aged patients may actually have higher relapse rates after treatment with this medication.

Now, these are the results in the pediatric patients. As you can see, the proportion of patients that had at least 90 percent reduction in nodules was a little higher in the Accutane arm, and the requirement for retreatment was higher in the new formulation arm. But again, in a way we're comparing apples to oranges here because, as the sponsor has already pointed out, the exposure to isotretinoin in the Accutane arm was higher than the dose given in the new formulation arm. So, I don't think this means that there's any inherent efficacy problem with the drug. It's a dose thing.

It's interesting when you look at the women who were using Ortho Tri-Cyclen in the trial, these patients

were not included by the sponsor in the per protocol efficacy analysis. And the numbers are way too small -- you can see down at the bottom what the numbers are -- to draw any statistical analysis from this. But I only point this out because if future trials are done, this is a medication that has an approved indication for acne. So, if future trials are done, I think it's important to keep in mind for the design of those trials because there was a difference. Like I said, the numbers are too small, but the difference was between 84 percent and 57 percent in the proportion of patients who achieved at least a 90 percent reduction in nodules.

Moving on and I basically already said this, that these subset results may suggest that Accutane may have been slightly more efficacious at the dosage tested, but it's at the dosage tested. And the overall trial results, in our opinion, do support therapeutic equivalence.

So, this pretty much will sum up our efficacy conclusions. Since the exposure in the Accutane arm was higher than in the new formulation arm, we think that equivalence in efficacy would suggest that 1 milligram per kilogram per day of current Accutane may be an unnecessarily high dose for many patients.

We think this is important for reasons that

have already been pointed out, that the minimum effective dose would help possibly with managing serious adverse events and even nonserious side effects can lead to discontinuation of very effective treatment for severe scarring acne. So, it's important to minimize, as much as possible, the side effects of Accutane.

Now, Dr. McLane has stated that they believe that the .4 milligram per kilogram per day tested in a trial is close to the minimum effective dose. My feeling from the efficacy data, looking at all of the trials, I think that's probably pretty much right. It's hovering right around there.

But the problem is that even if that's true, we don't really know what range of dosing to recommend to prescribers for patients who require dose escalation. As you know, dermatologists in practice or anybody who prescribes Accutane now, you try to start with the lowest recommended dose and work your way up if patients don't really respond. We're not really sure what to recommend. We don't really know the safety profile for higher doses. You might want to, when you're thinking about this, refer to, I think it's, page 22 in the sponsor's briefing where there are some of the simulations that refer to changes in dosage of going from .4 to .5 or .66, the different peaks that you would achieve. So, that's just something that we

want to think about.

Then on the next slide, I want to just quickly go over adverse events that caught our attention. The only thing that we need to look at here is that the total exposure that we have for a safety profile for the new formulation essentially is the 300 patients in the clinical equivalence study because the short-term pharmacokinetic studies were not very much exposure. We did not see and the sponsor did not see any adverse events that have not previously been observed in a safety database. That's important for currently marketed Accutane.

We don't really need to go over this because it was essentially the same between arms, early terminations.

Now, the reasons for withdrawal from the study for safety reasons. The proportion was the same for both arms. In other words, it was 16 from each arm. But the reasons were not. In the new formulation arm, 4 patients -- the doctors taking care of them made the decision to discontinue them from the trial for psychiatric symptoms. None of them were considered serious by the investigators. There was also an additional patient who was discontinued for a possible pseudotumor cerebri, and that patient also answered yes to all four of the screening questions for the psychiatric symptoms. In the Accutane arm, there were no discontinuations for psychiatric symptoms.

If we go to the next slide, when I looked at this trial, I really don't think that the number of discontinuations is probably a very good comparative measure of safety because it appears that there were some problems with the investigators perhaps understanding what the rules were. It was very variable. Some patients that appeared to have mild psychiatric adverse events were discontinued, whereas other patients who, by the scales, appeared to have a greater adverse event were not. So, I think there were some problems there.

But be that as it may, there's no readily apparent reason for the imbalance between arms because those probably should have been balanced. The trial was very well masked by the sponsor.

So, that was discontinuations for psychiatric adverse events.

Now, if we look at the reported psychiatric adverse events. So, this isn't people that discontinued. This is just how many patients had their doctor write down on a case report form that an adverse event occurred. Again, we have this disproportion. There were 11 such cases in the new formulation arm and 1 in the current Accutane arm. Now, this disproportion is statistically significant and it would be cause for concern if it was real.

On the next slide, it's important to note here that the reported number refers only to patients who verbally complained of symptoms. So, in other words, the patients answered this four-question screening tool about whether they had had any significant depression or insomnia since the last visit that "affected their work or ability to perform normal daily activities." And patients with two or more positive responses went out and filled out the Beck's Depression Inventory again.

So, on the next slide, if you add all those patients up -- so, the patients who verbally reported their symptoms, the patients who Dr. Jacobs and Dr. Nelson did in analysis of these cases in retrospect, if you add those cases that did not have a verbal report but were analyzed by the sponsor's consultants, and then you add in some extra patients that did not have a psychiatric adverse event recorded but did answer yes to the self-injurious behavior question or to two out of the four screening questions or had Beck's Depression scores within a few points indicative of severe depression, it comes out pretty even, not exactly equal but the difference isn't anything that would catch your attention.

Now, do I know that all those patients had psychiatric adverse events? Absolutely not. All I've got is what the investigator checked off on the case report

form, and I don't know if they did or not.

The bottom line is that if they did or they didn't, there's still no readily apparent reason for the disproportion in the reporting of psychiatric adverse events because the bottom line is we could try to retrospectively analyze this as much as we want, but the fact is that in the doctor's office, the people that were taking care of these patients, something happened that the patient complained of the adverse event and they wrote it down. If the other patients didn't complain and they had these scores, I tried to add all that up to try to see if perhaps this was just a chance finding and not anything to worry about.

So, on the next slide, I just want to say what I said this morning, which is that the trial was really not intended or designed to specifically evaluate this question at all. We wanted to monitor the safety of the patients in the trial. And the design and conduct of the trial really preclude I think reliable case ascertainment in retrospect or any estimates of incidence. There was bias against reporting I think because the patients wanted their acne treated. They knew that they were getting a drug that works, and if I was in that situation, I would be afraid that I'd be discontinued if I said I was depressed. I'd probably say I wasn't.

Then, like I said, the recording of events and follow-up was variable.

If you go to the next slide, a chance finding I think is also consistent with the fact that the reported psychiatric adverse events in the new formulation arm -- really the worst case scenario is they weren't greater than the range that we showed you this morning for those studies where psychiatric adverse events were noted in trials.

Also, it's consistent with the fact that there were lower serum levels of the drug in the new formulation arm.

And it's also I think consistent with the fact that the other adverse events that are thought to be dose-related were not more common in the new formulation arm, in fact, were probably less common.

Now, this does require some assumptions, though, because even if the association with psychiatric adverse events is causal -- if -- we don't know what the dose threshold is. So, it could just be that its less than these other events.

It also requires the assumption that there's no pharmacokinetic basis for greater central nervous system accumulation of the new formulation relative to currently marketed Accutane. We have no pharmacokinetic reason to believe that there would be more central nervous system

accumulation, but we don't have any direct levels or anything in the central nervous system.

So, the bottom line here is that causality between psychiatric disease and isotretinoin use has not been established. If there is no causal relationship, then the new formulation cannot be less safe than current Accutane in that regard. If future studies did support a causal relationship, then I think some uncertainty would have to persist simply because we can't explain away the disproportion in the reporting.

Psychiatric adverse events do not occur in isolation. You want to ask yourself what's the big picture here. How did the two formulations compare for other important adverse events?

We can skip mucocutaneous adverse events.

Headache you would think we should look at that because we're talking about the central nervous system. Is there any signal here? I don't really think so. The frequency of headache in the two arms was approximately equal, but the duration was a little bit longer in the new formulation arm. Both cases, characterized as migraine, occurred in the new formulation arm, and there was one possible case of pseudotumor in that arm. The Accutane arm had three discontinuations for headache, and the new formulation arm only had one. So, I'm not really concerned

about this. I think it's probably the same.

Pregnancy is another issue, as the sponsor pointed out yesterday. One patient did become pregnant while taking the new formulation. The stated facts of the case that I've seen don't suggest to me that the patient was noncompliant with her contraceptive measures, which included oral contraceptives. But I don't know that. There's no way to really know that. Everybody I think would agree that 1 pregnancy among 244 female patients in the controlled setting of a trial for a known teratogen is of great concern.

The next slide. We can skip over this essentially. Dr. McLane already covered that.

The risks associated with switch-over. There are two issues here really. That's if one product replaces the other or if both are on the market at the same time, some of these issues would apply either way and some would maybe be exacerbated by having both on the market. I think Dr. McLane covered what would happen if people on the new formulation took it twice a day or whatever. But I think one thing that we need to think about is what happens if the physician calculates the dosage.

In other words, if the patient is just given the right amount for its formulation and they happen to take it twice a day instead of once a day, I think that's

what Dr. McLane was referring to. But what I'm thinking about is, what happens if the physician calculates the dosage based on the old formulation and it's really the new formulation?

So, again, maybe in the discussion, if you look on page 24 of the sponsor's briefing document where there's some data about higher doses of the new formulation, I think up to .66 milligram per kilogram.

The other issue with switch-over has kind of been alluded to. But our feeling is that whatever trade name we settle on, it should ideally retain the 18 years of name recognition that we have for this potent teratogen. It should at the same time clearly distinguish the two products if both are to be marketed. So, it's kind of a catch-22 there how to work that out. So, that's another consideration.

So, we can get to the bottom line here and close. It's our view that there's no apparent pharmacokinetic basis that we can come up with to suspect that the new formulation would be any less safe than current Accutane, and that applies to the issue of a possible interaction with hormonal contraceptives and to the psychiatric adverse events.

But the real question here is given the unknowns and the switch-over risks, basically you want to

ask what does the new formulation offer to patients.

The sponsor's stated goal is that enhanced convenience improves patient compliance and that reduced intra- and inter-patient variability, while retaining the efficacy and safety profiles of currently marketed Accutane is achievable because of the pharmacokinetics with the new formulation.

Our view is that because the food effect with Accutane is so large, the new formulation does reduce variability in serum levels of isotretinoin, but the benefit for patients would be dependent on equivalent or better safety and efficacy since the impact of the convenience factor is likely to be small. The reason I say that is that in my experience in the clinic, it seems to me that taking medicine on an empty stomach is more challenging than taking it on a full stomach. I think that in the case of this age group, which consists of a lot of teenagers, it's probably hard to find one sometimes with an empty stomach, as anybody knows who has one and tries to feed them.

(Laughter.)

DR. O'CONNELL: So, basically this is our take on it. Thank you.

DR. BERGFELD: Thank you very much.

It is now 4:30. We are due to retire at 5:30,

and what I'd like to do is to limit the discussion period to about 20 minutes and then go the questions, which are two. So, right now if there are any of the committee members that would like to discuss any point of the presentation or clarification.

Dr. Rosenberg.

DR. ROSENBERG: Yes. Of course, like most people of my generation in dermatology who remember before there was Accutane, if it weren't for Accutane, we'd still be giving them x-ray. Accutane made all the difference in the world for the practice of dermatology, and we've come to love it, albeit with its problems.

The idea of changing brings up all the anxieties of change, but whether we vote to approve it or not, based on what I saw, I'm not about to start writing the prescription. I don't think 36 weeks is any time to talk about retreatment. And retreatment is not the same as being perfect. I'm very suspicious of something that causes less mucocutaneous dryness. When my patients tell me they're too dry, I tell them that's what they're paying for, that's what they're buying. They're buying this reaming out of the follicles so that after they've put up with it for 20 weeks, they're never going to have acne again at a high percentage.

And if they tell me that they can make their

acne go away at a half dose, I tell them Dr. Cunliffe has written that paper and others have written that paper. You can make acne go away with a half dose, but you don't have the same percentage of permanent cure. It's never going to be a 100 percent permanent cure.

But if you go through the whole rigmarole for 20 weeks and put up with the symptoms, and so forth and so forth -- and, of course, don't get pregnant -- that there's a good likelihood you're never going to have acne again. And that's why we're doing it. That's why we're spending all this money and going through all this.

Statistically it might not be worse, but it certainly wasn't any better. Actually it wasn't as good. As I say, the finding of less scaliness makes me suspicious. And I don't see any reason to change any of my patients to this until we've seen some papers come out that at the end of 2 years how many are going to not be perfect.

DR. BERGFELD: Any other committee members wish to discuss? Dr. Branch?

DR. BRANCH: I'm just curious as to why a trial that obviously took a huge amount of effort to launch was set up with non-dosage equivalence between the two arms when you have pharmacokinetic profiles that look -- you've stabilized your availability within an individual, but the rest of the profile looks pretty much the same to me. So,

I just find that it's hard to be asked to draw a conclusion in terms of efficacy when you've got a dose-ranging study.

DR. BERGFELD: Dr. Abel, then Roche.

DR. ABEL: I think we need to know the minimum effective dose of Accutane.

As far as questions of efficacy, I'm not convinced how much the NF formulation has to offer. There is a convenience factor and certainly there would be more consistency in bioavailability of the drug. I think there are a lot of questions that I have.

DR. BERGFELD: Dr. Miller, Dr. King, Dr. Epps?

DR. EPPS: From the presentations, I have concerns I guess about the psychiatric findings, 11 I believe and 1 in the other, in the Accutane that there are more problems, we'll say, or symptoms in the NF group. Certainly we would need more data in that regard.

The other issue is the convenience. Certainly you can tell people to take it with food or put a sticker on the bottle that says take it with food. There are other medications that we take with food. And if someone isn't compliant enough to take Accutane twice a day, I'm not going to give them Accutane to take once a day.

DR. BERGFELD: Dr. McLane, did you want to address any of the discussants?

DR. McLANE: Yes. Specifically on the

efficacy, I didn't present my table, but it is in the brochure that the people at the table do have on there. On efficacy, we did reach the statistical requirement.

On the retreatment issue, that was actually agreed upon with the FDA on the time frame. It's the time frame that is twice the time frame that we recommend for the initiation of retreatment, and it was felt to be the minimum time in order to have an assessment of the retreatment.

I think those were the main points I wanted to make.

DR. BERGFELD: Dr. Wilkin, did you want to in any way respond?

DR. WILKIN: Yes. That's what Roche proposed. I think somewhat after they proposed that, we noticed in a Roche brochure, Systemic Isotretinoin, Active Ingredient of Roaccutane. It's published by Roche, Basel, Switzerland, 1994. This was actually where I took the diagram that showed the dots that represented the studies. I don't know that we had actually seen this compelling information on the difference between a dose that would reduce the number of nodules and how that might be different from the dose that ultimately would reduce the need for retreatment.

DR. BERGFELD: Dr. King?

DR. KING: I come back to the same issue.

Again being somewhat of the older Windows generation, every time they say new and improved, '95, '98, 2000 window, it oftentimes is not improved. I'm not sure.

Again, I know we've been voted down on the registry, but now there are going to be two different kinds of Accutane from Roche and particularly those competitors. So, how are we going to distinguish which one is there and which one is not?

So, in the State of Tennessee, they had four people prescribing 80 percent of all the chloramphenicol causing all the adverse effects. So, the reverse side of registry is also identifying physicians who are inappropriately prescribing or monitoring it.

So, given a new formulation, I'm not sure how you're going to figure out psychiatric side effects and all that when half the population is missing and you have two or three different combinations. So, I think we're going to be back here about three years from now debating this once again. So, I'd just like to think that the FDA and Roche have a real thing to deal with. I'm not sure. I'm with Dr. Rosenberg that unless you make them peel and all that, it's not been my experience that people stay cleared.

DR. BERGFELD: Dr. Anderson?

DR. JENNIFER ANDERSON: I'm just unsure. Are we going to be voting on approval of this new formulation?

DR. BERGFELD: No. We're going to answer the questions which relate to dose-ranging studies, are they needed.

DR. JENNIFER ANDERSON: But this drug hasn't been approved yet.

DR. BERGFELD: Dr. Wilkin, do you want to respond to that?

DR. WILKIN: Well, we're talking about two pieces: the Accutane that's on the market and the new formulation, which is currently under review and has not yet been approved.

DR. BERGFELD: Dr. Malone?

DR. MALONE: I would just think that you would need more studies because you have two different dosage equivalents and you'd want to compare the same dosages in one study I would think.

DR. BERGFELD: Any other discussants? Yes, Dr. Rosenberg.

DR. ROSENBERG: Could we be told what happened to the young woman who became pregnant?

DR. McLANE: This woman was given basically all of the components of the pregnancy prevention program with the exception of enrollment into the Slone Survey because they do not accept enrollments of clinical trials. The patient had two serum pregnancy tests 1 day before she

started the Accutane and one 10 days before she started the first dose of Accutane.

There's personal information on this. Her father was her gynecologist that referred her for the medication for oral contraceptives.

DR. BERGFELD: Dr. Greene?

DR. GREENE: I'd just point out that from my look at it, 1 in 244 is not statistically significantly different from 3 in 1,000 which is the rate that we heard about all day yesterday.

DR. ELLISON: That's exactly correct. That was the table we put up with the Slone rate, the rate from the pilot study of UHC, and the rate from this clinical trial.

DR. BERGFELD: Any other committee members that wish to clarify something? Dr. Tan?

DR. TAN: Yes. I think it seems to me that the rate for retreatment needs to be considered as one of the endpoints for approving their equivalence.

DR. BERGFELD: Thank you.

Anyone else?

(No response.)

DR. BERGFELD: I'd like to ask Roche, because I asked you to shorten your presentation, if you think that there's something that you need to include at this point or to expand upon, I'd give you the time to do that.

DR. YOUNG: We're talking about really the dose of NF. You have been treating everybody with doses of Accutane. You're comfortable with those doses of Accutane. I think what we're talking about in NF is what is the equivalent dose of NF to the Accutane.

So, if we take a patient and you're normally dosing this patient -- I'll just pick a weird number -- 1.2 milligrams per kilogram b.i.d. in that patient, that would be your normal therapy as a physician. We easily, based on the pharmacokinetics and the linear pharmacokinetics and everything we've seen, can tell you what would be the equivalent exposure of NF for that 1.2. So, I want to make sure everybody understands, given the relationship and all the pharmacokinetics we've done with parents and metabolite, we're able to kind of equate exposures between NF and Accutane. That's just for information purposes.

DR. BERGFELD: Thank you.

DR. ELLISON: Yes. I'd like to add further to that and one other point.

One of the major issues with respect to the current trade formulation is how many people are not getting the advice, at least from their physician, to take it with food. I think you saw that if you were on .5 milligram per kilogram, what the result would be if you didn't take it with food. This may be in not necessarily a

teenage person, but it may be more likely in someone who is in their 20s. The consequence of that will, indeed, be -- I think nobody would deny it -- that there would certainly be a much higher likelihood of relapse and the need for retreatment. That was of concern to us, the survey we did showing this very large group of patients that weren't getting these instructions on the script.

The second is that if you're going to do this kind of study and you're going to look for one dose versus the other, we thought that we would take the minimum effective dose because of the point that we can model up to equivalent higher doses and to an exposure level where you know you've got the same exposure as that other dose in the trade formulation. So, at least you know you're in those exposure bounds. The efficacy of that may not necessarily translate or may not be entirely known. That was a decision we made because the idea of going down would have been much more problematic. We wouldn't know if your safety would have improved. So, that's why we chose that dose, knowing that you could go up on a modeling basis.

I guess our whole issue around this formulation again, I think the idea of convenience is less important to us than that concern that we have about variability with food, particularly in populations that for them it may be more difficult to take this with food.

Thank you.

DR. BERGFELD: Thank you.

Dr. Rosenberg, then Dr. Abel.

DR. ROSENBERG: My problem is I took from reading the material that at comparable blood levels, there was a suggestion of less mucocutaneous side effect. I just don't think that mucocutaneous side effect is a side effect. I think it's the effect of dedifferentiating epidermal cells. I just wonder if we are really getting, at comparable blood levels, the same efficacy that we're used to.

DR. McLANE: Well, I had pointed out the mucocutaneous side effects for one of the main reasons. It is one of the criteria that has been shown to have a dose relationship. In fact, what I have in the document that you have -- but we had additional information within the NDA -- 99 percent of the patients all had chapped lips on both formulations. So, the mucocutaneous events that I was referring to were the quality of life issues of a bleeding nose or having to not wear their contact lenses in which we had a difference between the patients.

DR. BERGFELD: Thank you.

I have Dr. Abel and then Dr. Malone.

DR. ABEL: The point about taking Accutane with food seems to be a simple physician education issue that

could be addressed with publication of studies showing effects of food and efficacy with and without taking it with food.

Second, if in the Roche trials the lower level of efficacy dose was selected, well, then wouldn't there be greater concern if you go up from there regarding side effects, adverse effects, psychiatric, other?

DR. BERGFELD: Dr. Ellison, are you going to respond?

DR. ELLISON: Yes, just very briefly. I think the concerns would be what we don't know. What we do know is we can model this up so that you can anticipate the same exposures at a given dose calculation of trade, which is what David was talking about. So, the concern would be that drug given from the new formulation or some very subtle differences in the kinetic curve would cause more side effects than not, but overall your AUC, you can calculate what that exposure would be. This is particularly important with respect to the decreased inter- and intra-patient variability with this formulation. So, you can really model the boundary conditions, if you will, for adverse events.

DR. BERGFELD: Thank you.

Dr. Malone and then Dr. Winokur.

DR. MALONE: Because there are so many safety

concerns about the medicine, I would think you would want to compare the same dose of the two drugs rather than relying upon models if you're trying to look at a new formulation.

DR. BERGFELD: Thank you.

DR. WINOKUR: Just an observation or maybe a question. All of the compliance literature that I am familiar with always makes a big point of fewer numbers of doses is always associated with better compliance. Now, this population may be so motivated that it's a different story than any clinical population that I'm familiar with, but I just wanted to not lose sight of that aspect.

DR. BERGFELD: Could I ask Roche if you have any compliance information?

DR. McLANE: We did not measure compliance directly on this trial, but we did measure it by the number of packages of medications that we received back and the number of capsules in these packages. It was quite comparable between the two formulations. It was over 85 percent compliance on the patients that completed the therapy.

However, we do know from our prescriber survey that 22 percent of the patients that are prescribed to get it twice per day don't take it that way. They take it once per day. We know that there's that wide number of patients

that when they're prescribed to take it with food don't. What happens then is that you really do get this under-dosing. When you looked at some of the curves that David had presented, you do see this under-dosing of the patients. That means that their treatments might be longer.

And what happens if you do that with the new formulation, you wouldn't get that type of effect. You would have much more predictable exposure and so your 20 weeks period of treatment would be efficacious.

One of the things that we had in your package is that over 80 percent of our patients had an excellent response when we looked at this criteria, an excellent or cleared response. So, with this new formulation, we are efficacious and we're getting a significant amount of clearance. We're going down to two nodules or lesions in these patients. So, it is efficacious. But with this more predictability, you really get the benefit.

DR. BERGFELD: Thank you.

I think at this point we've moved past our 20 minutes, unless there's a question that must be asked or a clarification that must happen.

Seeing none, I think we'll move ahead with the questions. Dr. Bull?

DR. BULL: FDA questions to the committee.

Again, given the data presented, does the committee feel that further dose-ranging studies are needed for isotretinoin? If so, please discuss possible study designs.

Question 2. Does the committee believe that there may be possible consequences associated with the simultaneous marketing of Accutane and the new formulation for both prescribers and patients? If yes, please comment on appropriate strategies to alleviate them.

DR. BERGFELD: Thank you.

I'm going to set the first question back on the table and ask for comments and even a motion, if that's in your mind. Given the data presented, does the committee feel further dose-ranging studies are needed for Accutane?

Dr. Wilkin?

DR. WILKIN: Actually it's a clarification. The question has been changed from Accutane to isotretinoin so that it's inclusive.

DR. BERGFELD: Thank you.

Anyone?

(No response.)

DR. BERGFELD: Let me put a motion on the table then. All those in -- Dr. Abel?

DR. ABEL: I just had a question. Wasn't it stated that we don't know the minimum effective dose of

Accutane?

DR. BERGFELD: Dr. McLane?

DR. McLANE: Yes. What we observed in this trial is that we do know the minimum effective therapeutic range for isotretinoin. This is the range at the .5 milligram. It's also the range that was shown on the table that Dr. Wilkin presented, and that is the range that the new formulation falls in. In fact, we're slightly above the .5 milligram per kg. So, we are at the minimum therapeutic range for dosing of isotretinoin, and we know it for the new formulation and we know it for the current marketed formulation.

DR. BERGFELD: Does that clarify the position on dose ranging for you?

DR. ABEL: So, it is known then.

DR. BERGFELD: Yes.

DR. ABEL: All right. Thank you.

DR. BERGFELD: Dr. Wilkin, then Dr. Greenhill.

DR. WILKIN: Yes. If I could just ask Dr. McLane for a clarification. The table that I showed wasn't clear in the booklet that I abstracted that from. Is that all the same formulation, all of those studies? And is that the current formulation?

DR. McLANE: To tell the truth, I'm not familiar with that book. It was published in Basel. It

was never circulated in the United States. I do know that it was based on some earlier studies that were conducted in France where they actually have different dosing regimes and some of the dosing that is available throughout the world.

I believe it's based on some of the published material in which dosing has been looked at in retrospective studies where patients have been evaluated for how much accumulated dose they had received during therapy and, consequently then, what was their efficacious range and the need for retreatment based on the retrospective analysis of these patients or patient databases.

DR. BERGFELD: So, the bottom line is it's not applicable to this discussion?

DR. McLANE: No. Exactly.

DR. BERGFELD: Dr. Greenhill.

DR. GREENHILL: In the past, there had been some question about one of the proofs for the presence of a causal relationship between any of the isotretinoins and psychiatric symptoms. I have wondered if part of this question might address the possibility of looking for a study of the kind that had been suggested of following patients for a period of time, perhaps following them on different doses and extending the dose-ranging study so

that it would be possible to address maybe two questions. One is the different dosage levels provide not only successful, immediate treatment but prevent relapse, and secondly, are the higher dosage levels associated, within a period of follow-up, with any psychiatric symptoms at all because prospectively you might have a better chance.

Adverse events are theoretically effects of medication just as the disappearance of acne. And there might be a dose relationship, there might not be. I think it might be useful to try to address this. We're not going to ever be able to rule out the possibility of a type 2 error, but at least any more information we can get would be helpful in addressing it. So, I wondered if this question is the place where such a suggestion might be raised.

DR. BERGFELD: Well, I want to ask the FDA specifically. The question deals with the efficacy or does it deal with the efficacy and the adverse events, or all of it?

DR. WILKIN: Again, the dose ranging is really the minimum effective dose that gives you the least amount of side effects.

DR. BERGFELD: So, the answer to you, Dr. Greenhill, is that there needs to be another study that was proposed to look at those specific adverse events.

Dr. Branch?

DR. BRANCH: It seems to me that there are two new factors that are coming on the table. One is that the endpoint is changing. It's going from early nodule reduction, which is what this clinical trial did, and the focus is now going on recurrence after a full course of treatment.

The other is there has been no discussion on the dose relationship of the adverse event profile. Yet, there is a body of data from the past. Would it be reasonable that before another study is proposed, there's actually a look at the data that's available to look at those two particular aspects? Because it may be that you've already got your answer.

DR. BERGFELD: Dr. Wilkin, Dr. Bull, do you want to respond to that? Dr. Murphy? Dr. O'Connell?

DR. O'CONNELL: Can I just ask for a clarification? Which two aspects specifically?

DR. BRANCH: The need for recurrence or at least the need for a further course of treatment due to recurrence, which seems now to be a key endpoint measure, and the second is there really has been very little discussion on evidence for a dose-response relationship in the adverse event profile, apart from chapped lips.

DR. BERGFELD: Any FDA response?

DR. WILKIN: I think we're always happy to look at data that has already been collected that can answer a question rather than setting out to just simply reproduce that. If the sponsor has that, we certainly would look at it.

DR. BERGFELD: Dr. Rosenberg?

DR. ROSENBERG: I really didn't hear what the final outcome was of that young woman who became pregnant? Did she have a baby at term or what?

DR. McLANE: She had a termination.

DR. ROSENBERG: She had a termination.

DR. McLANE: Yes.

Could I answer just quickly on the question on the trial design and mucocutaneous events?

DR. BERGFELD: Sure.

DR. McLANE: There are some mucocutaneous events and the triglycerides is one that you can measure. The triglycerides is a measurement that, because of a systemic effect and there's a mechanism that has been proposed that is a dose relationship. So, the triglyceride level is a very good marker for a dose response for the adverse event profile. With that, we do see the differences in elevations.

If I could have the slide on the triglycerides, the one that's in my presentation. Within there, you do