So extrapolating to other disease conditions on the mechanistic basis is feasible, and I think I was alluding to that. You probably develop that mechanistic support through mechanistic studies.

ACTING CHAIRMAN DRAKE: Okay. In the interest of time, I'm going to keep trying to track through the questions. Dr. Lim and then -- I have Dr. Lim, Lamborn and Jordan. Dr. Lim.

DR. LIM: My question is for Dr. Shah. My concern has been voiced, as many of my colleagues. As clinicians we do treat patients with skin diseases in which there is no normal stratum corneum.

I'd like Dr. Shah to expand for us, if this DPK method is to go forward, would this replace clinical trials with this? Then if it does, how does one correlate the efficacy of that medication, the topical treatment, in terms of treating the various skin diseases in which there is no normal stratum corneum?

ACTING CHAIRMAN DRAKE: Dr. Shah?

DR. SHAH: I think this question has been addressed from the earlier discussions we had. It

goes back to the same standard thing, that for all the older products we do the bioequivalency study in healthy subjects, same way we are doing the bioequivalency using the DPK in the most ridiculous area which is the healthy stratum corneum. If it is equivalent, it is assumed that under the diseased stratum corneum it will be the same.

This is the same principle now we are using it for the approval of the topical glucocorticoids. What are we doing? We are measuring the pharmacodynamic response. Where? On the healthy subjects. That has been the situation for the last so many years.

So we are doing it in a similar manner. We are not trying to come up with something new.

ACTING CHAIRMAN DRAKE: Dr. Lamborn, and then Dr. Jordan.

DR. LAMBORN: This goes back to my earlier question. I just would like a clarification. You stated that you propose to substitute the DPK for the clinical, and I know that one of the objects of these is to say that the intent is to reduce the burden on

industry, but now this is not a case of necessarily reducing burden if you require a substitution.

Could you clarify why you wish to make the DPK a requirement rather than an alternative to a clinical demonstration of bioequivalence?

DR. HUSSAIN: I think the understanding here is I think for bioequivalence you have a variety of different methods available to you. DPK will be one of those methods.

DR. LAMBORN: But that's the question I specifically asked earlier, and I was told that it was not going to be an option to do a clinical, that it was going to be only the choice to do a DPK.

So could you clarify that?

DR. HUSSAIN: No. I think, with respect to bioequivalence, you always have different methods available to you, and this or any other method that will come about would be one of those options, and the company might obviously choose to use that or may prefer to use a different method.

DR. LAMBORN: I think that's an important distinction based on the earlier question, which was

if this was overly sensitive to what was felt to be not meaningful clinical differences. So we are now saying that it would be an option and not the only choice.

DR. SHAH: Well, we'll take your point into consideration and discuss it as to which way we are going to be leading into, because normally for the bioequivalency we have a method that we provide. So--

ACTING CHAIRMAN DRAKE: We're going to get into -- I say this. We'll get into this in discussion. I understand your point, and I think it needs to be discussed thoroughly. I think we are getting a sense that some of the questions aren't being addressed as specifically as we might like.

So I would ask -- Dr. Shah, I would ask you and Dr. Hussain, the committee, I think, is expressing through their questions some concerns, legitimately so. The more specific you could be with your answers, I think the more helpful we can be in return.

So if you could help focus the answer specifically, that would be very helpful. Dr. Jordan?

DR. JORDAN: My question is for Dr. Shah as well, and probably concerns the standardization of this test that was to be used, and I will stay away from the diseased skin. I think we will get into that later.

What about different skin types? If we look around the room, there's a variety of different skin types that are represented here, Type 1, Type 2, so on. I've got Type 1 which is the atopic burn-type skin. You certainly have a different texture to your skin than I have.

Have studies been done comparing different skin types and, if a standardized test is applied to those situations, are they equivalent?

DR. SHAH: Studies have been done, and with respect with the bioequivalency the advantage is we do the test in the reference product in the same subject at the same time. So whatever value we get should be the test, and the reference would be the same, and it will take care of the different types of the subjects that are involved.

ACTING CHAIRMAN DRAKE: Dr. Tang?

DR. TANG: Just to make sure, the intent is if you have DPK, it will be considered adequate if it works in a future NDA?

DR. SHAH: Sorry.

ACTING CHAIRMAN DRAKE: Dr. Tang, could you put that in the form of a question for us?

DR. TANG: If you have the DPK data, you can show equivalence. Was that being considered adequate, is an option. Right? You said it's an option. Would it be adequate without a clinical trial?

DR. SHAH: For new drug applications?

DR. TANG: To license the product.

DR. SHAH: No. For new drug or the abbreviated new drug?

ACTING CHAIRMAN DRAKE: Why don't you do for both, for either new drug or --

DR. SHAH: Well, I cannot answer it for the new drug. That will be with Dr. Wilkin to answer that.

ACTING CHAIRMAN DRAKE: Fine. Then answer for your part.

DR. SHAH: My question is, yes, it will be adequate for a generic drug product.

ACTING CHAIRMAN DRAKE: So you think it would be adequate without a clinical trial, is your proposition?

DR. SHAH: Yes.

ACTING CHAIRMAN DRAKE: Okay, thank you. That answers that question. Other questions? Joel?

DR. MINDEL: Along the same lines, bioavailability of oral products can be tested on a batch basis. One of the failings of the present system is that, once a drug product is approved for topical use, the manufacturer can change the ointment and doesn't have to have, as I understand it -- doesn't have to report it and doesn't have to undergo testing again. Is that so?

DR. SHAH? No, that's incorrect.

ACTING CHAIRMAN DRAKE: Would you tell us what is the case?

DR. HUSSAIN: The post-approval changes have to be done and reported in accordance to several guidances, especially for topical products. We have

a guidance called "Scale-up and Post-Approval Changes for Semi-Solids." So changes cannot occur arbitrarily, and each change has to be justified, and there are different ways of justifying, depending on the magnitude of the change.

DR. MINDEL: Well, let me then say I'm glad that is clarified. I don't know what exactly those changes are, but would this test be used on a per batch test, the way -- In other words, the original manufacturer runs another lot. Would it be expected that this is now going to be -- since this is an objective test, that it's going to be used every batch?

DR. HUSSAIN: Bioequivalence methods are generally -- they are not quality control tests. Batch to batch differences or acceptability, you have in-process controls and release testing, which will be chemistry tests that will be done for batch to batch.

For bioequivalence assessment, we generally will take one lot of innovator, compare it to one lot of the test material. That could be a generic material. So --

ACTING CHAIRMAN DRAKE: Does that answer your question? While you are thinking, Dr. Abel has a question.

DR. ABEL: Well, relating to that same issue, we've been advised that that is one of the problems between generics and the reference drug, is the great variability from lot to lot, so that there is more of a standardization and uniform quality control with the reference drug, and the generics can vary quite a bit.

So if you are only testing one lot or batch of a generic, then maybe that is not sufficient data.

DR. DR. HUSSAIN: Quality control aspects of generic and innovator -- they are the same standards. The standards for quality do not change between innovator and generics.

ACTING CHAIRMAN DRAKE: Do you want a follow-up question?

DR. ABEL: I don't know. I don't have that data. Perhaps the FDA could clarify that or pharmacologist.

DR. HUSSAIN: The standards required are the same. So the quality control procedures, the test methods that one would use would be of the same standards, and eventually the products become -- you have pharmacopeias which define common standards also.

DR. ABEL: Well, perhaps one of my colleagues could help me. I think there have been articles written in the dermatologic literature regarding differences in generics and reference drugs.

DR. STERN: But those aren't differences in the same product over time. I agree, there are standards -- you know, the USP standards and other standards are applied, once something is approved.

So what we are all getting to is the difference between the innovator compound and possible generic equivalents, and there is a big literature on that of varying quality. But I think the rules are the same once you are approved, whether it is under an NDA or ANDA, but manufacturing processes, all these kinds of things -- that's all the same for everybody, once you are in the door.

So the variability within a product is

similarly regulated. What we are looking at here is really between products, innovator and another one. But over time, once a product is approved, the variability in what is going on there should be -- The rules are the same. Isn't that correct?

DR. ABEL: Thank you.

ACTING CHAIRMAN DRAKE: I don't have anybody else that I have noted that has a specific question before we begin the discussion. Are there any -- Anybody I have overlooked on questions?

All right. Now we will begin the discussion, and the discussion is wide ranging. I give you leeway to express opinions, ask further questions, and generally just be yourselves. Dr. Stern -- On second thought, Rob, I may just correct that. Just give me a little hand signal. I put you on my list, and I call you in the order that I spot you. So try to make sure that I catch your eye.

I just want to point out, and mindful on the time, we will take a brief recess. I'm going to shorten it to just ten minutes, because we do have to -- I want to make sure we make available to the public

comment at 11:15, and I have the times down, and I will hold the public comment to time, and I want to make sure that we at this table allow the courtesy for everyone at the table to have a comment.

So please try to keep your comments pertinent and concise so that we get the -- the FDA gets the benefit of the whole committee's opinions or comments or concerns.

All right. So I've got Stern, Lim and -- is it Venitz. All right.

DR. STERN: Well, I have a number of concerns. One is: In all of this, as in my question, we are dealing with -- principally with diseased skin. If this discussion was only about the equivalent for stratum corneum active compounds such as emollients, I would say this is terrific, but we are dealing diseased skin where, in fact, the stratum corneum, if present at all, its penetration characteristics vary over time as the disease heals and, further, things that may not affect with a single application the characteristics of the stratum corneum or, in fact, inflammation.

So for example, the analogy -- I was trying to think of an analogy with oral drugs. I think, if there was an oral drug that was used to treat gastritis and was only biologically equivalent if taken with two shots of rye whiskey, with one single application of that, two shots of rye whiskey probably don't change your gastritis very much, and the drug might be biologically equivalently available. But I doubt the FDA would look on that product as a good drug, a biologically equivalent drug for another anti-gastritis product that had systemic effect if you had to keep on taking those two shots of rye whiskey every day.

We, in fact, have various vehicles in terms of inflammatory dermatosis that may, in fact, be irritants, especially in diseased skin. I don't see that single applications and subsequent tape stripping really get to what I would call both the safety aspect and the unintended effects of the incipients on either penetration with long term application or, in fact, the inducing of inflammation and side effects.

So, to me, if you are looking at something

-- If you want to measure something that the clinical effect is likely to be a number of weeks, you want to know what the safety profile, what the unintended effects that might both lead to a side effect, and perhaps also change what's going on.

You know, we've spent what I found an interesting day yesterday talking about a product that my inferences are that its biologic effects when applied topically on normal skin or skin with enhanced stratum corneum are virtually immeasurable. This is Protopic.

My understanding is when they tried it on psoriasis where you have an enhanced stratum corneum, not a heck of a lot happened, and I thought we saw very persuasive evidence that in diseased skin with an altered stratum corneum there were substantial clinical effects.

So I really have real concerns about agents that are utilized for many of our diseases where either the epidermis is not the primary target, a follicle or something else, or in fact, they are used in conditions with an altered stratum corneum.

I guess those are my two biggest concerns. The other one, I must admit, is completely a bias. I see here that we are trying to validate or discuss the validation of a methodology that's been around for a dozen or 15 years which, to me, as has sort of been implied, is really perhaps not where measurement sciences are now.

I think one should look at it in terms of where the science has moved in terms of the ease of measurement, and secondarily, the elegance of measurement.

Why is this important to me? I think, as Dr. Wilkin implied, if we had a noninvasive measure where for drugs that are effective for skin disease where we could measure equivalence in both the entire epidermis and the dermis over time as they are applied noninvasively, that to me would be very persuasive.

Instead, here we are having something that I actually fooled around with for years. Twenty-five years ago, Irv Blank at our institution was very much into stratum corneum and percutaneous penetration, and it didn't seem very elegant when I was less than 30,

and it seems even less elegant with the changes in science when I'm over 50.

So I really have a problem with endorsing something that, if we endorse it, is going to take at least ten or 12 years to replace when all sorts of measurement are moving so rapidly. So I don't want to put yesterday's science in, even if all these other issues are addressed.

Then I just want to make one final comment. I always thought a consensus document was something you had to sign before they would let you go to your airplane.

ACTING CHAIRMAN DRAKE: Dr. Lim?

DR. LIM: This discussion reminds me quite a bit about the discussion that we had many times, actually, with sunscreen. There are very good multiple studies on sunscreen that have been done -- that has been done, using in vitro method as well as in vivo method. I think the conclusion generally is that the in vitro method is helpful, but in order for the medication, in this particular case the agent sunscreen, to be appropriately evaluated, it should be

done in human beings.

The part that I have concern about is that again -- it has been expressed previously in various questions and discussions before -- that we are treating diseased skin. I am not comfortable replacing the clinical trials even for an equivalent product in the diseased skin condition by a one-time in vitro measurement.

ACTING CHAIRMAN DRAKE: Dr. Venitz.

DR. VENITZ: Yes. I would like to comment that in my mind the discussion that we are having or at the heart of the very discussion that we are having is the different perspective that biopharmaceutical scientists and clinical scientists have on how those drugs work, and I find it interesting as a member of the Pharmaceutical Sciences Advisory Committee that I end up sitting with all those clinicians. I think in the final analysis, I am probably going to agree with those clinicians, even though I am representing biopharmaceutical sciences.

In my mind, DPK is really a surrogate of drug release, and it's a sophisticated release test.

We just use human bodies or human skins as opposed to doing it in vitro.

Apparently, there is a very precise way of measuring drug release. The clinical meaning of it, though, is questionable, to say the least. I think I would agree with what Dr. Wilkin was saying. Based on first principle, we won't be able to explain any mechanistic or any mechanism of action for any drug that can be caused by some kind of a DPK profile, because of their different mechanisms of actions, their different targets.

I am also less optimistic than Dr. Hussain that we'll be able to use empirical data to justify the use for every single drug, unless you literally wanted to do some kind of validation for every single active ingredient. Then you are defeating the purpose of the whole thing, which is to relieve the burden, the regulatory burden.

Finally, I do see some use, at least on a, I guess, probationary period, for this three-arm design that Dr. Wilkin favored where at least you have some idea whether you have a suitable test where you

compare not only a bioequivalent but also bioinequivalent product with your test product.

My main concern, though, is that we are measuring something very precisely, but we really don't know what it means for most drugs in clinical use.

ACTING CHAIRMAN DRAKE: Okay. Dr. DiGiovanni, I had you next.

DR. DiGIOVANNI: I have a number of concerns, but I am not going to express them, because they have been -- Most of them have been more eloquently expressed. But one issue I don't think that's been addressed in great detail that I am concerned about is that the equivalent in content is not the equivalent in quality and in product, particularly when one refers to vehicles.

There may be two preparations, one of which is a proprietary preparation. It may be prepared in ways that are not publicly available and has been extensively tested and while another product may have the identical chemical composition, it doesn't have the identical physicochemical properties

and ability to release the drug to wherever it has to go.

I think that that is an issue that has not been at all addressed with respect to stratum corneokinetics and ability of that to predict clinical efficacy.

ACTING CHAIRMAN DRAKE: Do I have other -- I can't believe my committee, all of a sudden, is quiet. I don't have any -- Okay, Dr. Tang.

DR. TANG: I think the key issue we have discussed so far is really whether DPK is generalizable, whether you can generalize these results. I have no doubt that indeed the case is going to be very precise, but how this is linked to the clinical efficacy is unknown.

So I think there must be a finite number of disease types in a skin disease. So the question is whether to decide whether you are going to go with DPK so you can study. It is possible -- It is feasible to study more different types of skin. Then the study has to be the -- The DPK has to be validated for each type.

If you can do that, then there is hope. If you cannot do that, I think it is very hard to make the quantum leap from DPK to a specific disease type.

ACTING CHAIRMAN DRAKE: Dr. Abel?

DR. ABEL: I agree with all of the previous speakers who have expressed the view that the DPK is accurate, but not necessarily relevant in the clinical setting.

A follow-up to the last comment, it would be very interesting to know -- have more information on DPK in different disease states, because not only are there disorders where there's absence of stratum corneum, but on the other side of the pole there is thick, lichenified, chronic eczematous disorders where there is very thick stratum corneum.

So we should look at diseases where there is acute inflammation, acute eczematous dermatitis, for example, and on the other pole, the chronic lichenified, thick, scaly conditions.

ACTING CHAIRMAN DRAKE: Okay. I have Lamborn, Mindel and King so far.

DR. LAMBORN: Actually, I have a question.

The issue of skin types keeps coming up, and not being routinely on the dermatology committee, I would be interested in knowing, for the current bioequivalence methodology which is a clinical one, what adjustment is made in terms of assurance that, in fact, you have bioequivalence on the multiple skin types or how is that beyond simply the same rule of you are looking at it within the same individual?

ACTING CHAIRMAN DRAKE: Okay. Dr. Jordan just commented he had exactly the same question, and Dr. Wilkin, would you like to -- I don't know who is the most appropriate person to take a shot at answering that question.

DR. WILKIN: Well, for the new drugs we are not looking at bioequivalence type questions, but what we do -- What the innovator pharmaceutical companies do in their Phase III clinical trials is they take all comers. We encourage a wide demographic representation.

We clearly want minorities to be part of the Phase III. So for the new drug products, I think we have very good information in terms of the clinical

assessment, the efficacy and safety studies.

I think what the question, though, was, was how does that happen then when generic companies do their clinical trials for topical products? I would have to defer to the Office of Generic Drugs for that.

ACTING CHAIRMAN DRAKE: Okay. Dr. Shah or Dr. Hussain, one of you want to --

DR. SHAH: I would like to keep one thing for the committee members to think about. There is a clear difference between the bioavailability and the bioequivalence.

When we are talking about bioequivalence, we are talking about the same type of formulation, which means it has qualitatively and quantitatively the same ingredients. So some of the discussions which came about the different ingredients going through or affecting it -- It's out. It is not development when we are talking about a bioequivalence.

The only difference comes up in the nature of manufacturing, how they are manufactured, using the

same components. That, we can very easily detect using the in vitro drug release profiles.

So I will appreciate if the committee gets these two points slightly clear and different when we are talking about all these skin types, skin diseases, this, that and all, between the bioavailability and the bioequivalence; because whatever happens with the one formulation, the same thing should be happening with the other formulation when we are taking a look into the same formulations made by two different companies.

DR. LAMBORN: But that does not address my question. My specific question is: In bioequivalence studies, approximately how many individuals would be involved, and what is done to look at the issue about whether there is any difference, depending on skin type?

DR. SHAH: The study will take anywhere between 36 to 48 subjects for the bioequivalency, and I think that randomly picked up the subjects.

DR. HUSSAIN: For clinical trials, for bioequivalence clinical trials -- I think that is the

question here.

DR. LAMBORN: Yes, bioequivalence -- to prove bioequivalence by clinical trials is the question.

DR. HUSSAIN: That's an excellent question, I think. The issue of skin types, disease and so forth, even in big clinical trials, I don't think we cover all bases when we approve safety. It is difficult to do that, I think. But when do bioequivalence based on clinical trials, there is an attempt to try to do that, but how far is successful is difficult to say.

DR. LAMBORN: Because I know historically in bioequivalence one of the issues was that they tended to use -- you know, I'm talking about oral dosages now -- there was a tendency to use all males in a certain category, and I was wondering whether we had the same situation in the clinical trials for -- historically, for clinical trials with bioequivalence for dermatology products, whether there is a tendency to look for consistency and that they went for a certain type.

You are saying it tends to be random?

DR. HUSSAIN: Before answering that, if you permit me, I haven't dealt with that issue. I may wish to consult later on with somebody who has and answer that at that point. So --

ACTING CHAIRMAN DRAKE: We are getting very close to time. So I have Dr. Mindel, Dr. King and Dr. Lim, and I will stop the discussion for a quick break to go to the public comment, and then we will take up some issues. Tom, did you have -- Dr. Wilkin?

DR. WILKIN: Well, actually, I could comment later. I was going to -- because it may not be all wrapped in my response.

The Q1 and Q2 -- Perhaps after the break I could come back to some thinking.

ACTING CHAIRMAN DRAKE: I think this is important while everybody is thinking on it. So go ahead. I might put off these three comments until right after the break and then move to the public.

Is anybody in the public comment section that that would present a problem to, if we move the

public comment five minutes? Okay, then we are in good shape.

Dr. Wilkin, would you go ahead, and then I'll take up these other three right after the break.

DR. WILKIN: Again for those who do not think about Q1 and Q2 all the time, the Q1 is qualitative. It means the list of inactive ingredients is the same for the innovator and the generic product.

Q2 means that there is a quantitative similarity. It doesn't have to be exactly on the money. It can be five percent or at times it's been suggested to have a ten percent excursion, but it's close.

If you think about topical products -- and let's think about at the very beginning the simplest phasic kind of structure. Let's think of a topical product that is a complete solution. It might have an active and multiple inactive ingredients, but they are all in solution, all in one phase.

Q1 and Q2 is enormously powerful in understanding and predicting what the attributes of

that particular product are going to be, because it really does not matter the manufacturing.

A simple example would be a salt solution. If you take your beaker, if you put the salt in first or you put the water in first, it really doesn't matter the order, whether you heat it, cool it, that sort of thing. In the end when it's sitting there at room temperature in solution, how you got to that solution is -- it's manufacturing insensitive. Okay?

Now for the kinds of products that we are talking about, these semi-solid sorts of things, they are not simple solutions. The active agent may be in solution, but typically these are at least two-phase or multi-phasic kinds of structures.

There may be a continuous phase, and that may be where the active is or there may be a discontinuous phase. It might be in both. My thinking there is actually that Q1 and Q2 do not adequately describe the product at the end of manufacturing.

I think of this as the -- I call it the Duncan Hines theorem. If you think about cake mixes,

you know, you can go to the store. You can get your three eggs. You can get your cup of milk and all the sorts of things, and everyone across the country, when they are using that cake mix, they are starting out the same. But some people forget to preheat the oven. Some people move it to the wrong place on the dial. Some people leave it in longer than others.

The quality of the material that comes out -- It still has the same chemicals in it and the same flavor and probably the same calorie content, unfortunately, but at the end of the day it can be -- the physical properties can be very different.

That's the concern about Q1 and Q2 underdetermines the physical attributes of these kinds of products which may be manufactured in somewhat different ways. I mean, I've heard of one example where, instead of using the cooling coils, they didn't have them on. So things cooled to room temperature, and they ended up with a very different feel to the topical product.

So I think there are limits to what Q1 and Q2 can tell us about these products. I just wanted to

add that.

ACTING CHAIRMAN DRAKE: What I am going to do is we are going to take a very quick break. I am going to ask -- What time do you have, Mr. Henriquez? You are going to be our timekeeper. We have about eight minutes past. I would still like to aim toward reconvening at 11:15. So can everybody hurry, to the best of your ability.

(Whereupon, the foregoing matter went off the record at 11:05 a.m. and went back on the record at 11:20 a.m.)

ACTING CHAIRMAN DRAKE: Would everybody please reconvene. I'm reconvening the session effective immediately.

The next person I'm going to call upon right quick is -- and I'm going to ask us to be quick, because we are about out of time here -- Dr. Mindel, you had a quick question, and I've got three quick questions, Mindel, King and Lim. Then we are going to move right into the public comment phase.

DR. MINDEL: My question has to do with the noninvasible aspect of the assay which, when you

start getting down to, I guess, the seventh and eighth strips, can be pretty uncomfortable.

There are some pediatric preparations, dermatologic preparations. How would they be handled with this type of assay?

ACTING CHAIRMAN DRAKE: Do you have a comment, Dr. Hussain?

DR. HUSSAIN: I was hoping Vinod was here to answer.

ACTING CHAIRMAN DRAKE: I'm sorry. He is not here, and I'm pressing on.

DR. HUSSAIN: All right. Well, generally, I think, for bioequivalence we do it in normal, healthy human volunteers. So that would be on healthy human volunteers. So not on pediatric.

ACTING CHAIRMAN DRAKE: Okay, but I think that is a legitimate concern of the committee, is the age. We've heard that before. It's another issue. Dr. King?

DR. KING: This is, hopefully, a short comment. I remain unconvinced that this methodology is useful other than comparing generics versus the

reference drug or those coming off patent. So I am not going to go any further to say my comments. I don't think it's feasible under Dr. Wilkin's first principles at this point.

ACTING CHAIRMAN DRAKE: And Dr. Lim? Dr. Tang, I mean. I'm sorry. Not Lim, Dr. Tang.

DR. LIM: Dr. Lamborn was asking about what is currently being done for the bioequivalency study.

ACTING CHAIRMAN DRAKE: Quickly.

DR. HUSSAIN: Quickly, this would be sort of a crossover, and each subject becomes its own control. But I do wish to request, Madam Chairperson, a five-minute time, if we could answer the question I deferred and have Dale Conner answer that.

ACTING CHAIRMAN DRAKE: I am going to let you have it, but I want to go to the public comment section first, since they have been very indulgent with letting us run late. I do plan to adjourn at 12:30. I have already got committee members who have made plane reservations and what-not based upon that assumption. So I would like my committee to be

thinking about -- although there is no vote, I certainly having some recommendations might be helpful.

I am going to now call upon the first public comment, and we will keep -- I will call time. Dr. Spear for Spear Pharmaceuticals, which is listed here as generic R&D, asked for ten minutes. You shall have ten minutes, and then I'll call time, and I don't mean to be rigid, but we are just about out of time here, and I wanted to make sure everybody gets heard. Thank you, Dr. Spear.

DR. SPEAR: Thank you for the opportunity to speak. Is the mike on?

ACTING CHAIRMAN DRAKE: Yes.

DR. SPEAR: As you can see, I'm a dermatologist, and also I've been involved in the generic industry for the last five years, and I am from Fort Myers, Florida. Now that's not Palm Beach County. So please don't -- you know.

Some of the generic industry claim that the draft guidance must be accepted, because generics cannot be approved in any other way. I am here to

report that clinical studies can show bioequivalence, and we have performed acne studies to prove bioequivalence to our Tretinoin products.

For anti-acne drugs, which act in the pilosebaceous unit, one can never be certain that stripping the stratum corneum layers ever is better than a clinical study.

The gold standard, double-blind placebo controlled acne bioequivalence studies can be done with reasonable cost. Our generics are Q1 and Q2, and additionally, as has been discussed here, we take a lot of time and constraints to make sure that as manufactured they have the same physiochemical parameters or viscosity.

We have filed three acne clinical trials showing bioequivalence to the originator. Here is an example of one of our clinical studies for the highest strength of 0.1 percent. You can see the improvement over 12 weeks in 398 patients.

Another way to look at this is for the 0.1 percent improvement acne at 12 weeks is approximately 71 percent in a 400 patient trial.

We did another trial on 0.025 percent. About 52 to 53 percent improvement. We have also studied the Retin-A gel versus our Tretinoin gel, and around 56 percent improvement.

We received approval of the middle 0.05 percent cream by clinical bracketing of the studies and in vitro release. We also -- Since we showed bioequivalence in the 0.025 percent gel, we asked for a waiver of another acne study with some supporting data.

Now remember, the 0.01 percent gel only differs from the 0.025 by the concentration of active ingredient. In vitro release studies cannot easily be done on gels. So we had a meeting at the Office of Generic Drugs, and I would just like to provide you with this information.

For both the .025 percent and .01 gel strengths, we provided TEWL, which is transepidermal water loss, and that is in vivo. Our data showed equivalence of our products and originator.

Also in the same lab, TEWL showed differences between different formulations with the

same active ingredient.

We also provided in vitro cadaver skin studies and, as has been mentioned in this committee, this is some of the newer technology, and cadaver skin, I think, is actually somewhat better. We showed equivalence of our products and the originator.

Also in vitro cadaver skin can show differences of the products with the same active and different inactives, and you can look at the patent for Avita Gel where they showed these studies.

There is also a clinical correlation. The Avita gel in clinical studies wa not bioequivalent to Retin-A gel and did not get an AB rating.

Even though the data was convincing, the agency felt, regulatory speaking, that they could not accept this. Therefore, we have done another 400 patient acne study on the lowest strength, and results are being tabulated. So far, they show bioequivalence.

Therefore, in total, we have done four acne bioequivalence studies, both of the creams and both the gels. We have set the standard for approval

of tretinoins, and I am saying this can be done. I'm not that big of a company.

Spears' experience with the Office of Generic Drugs has been very positive. OGD staff have been willing to help, accessible, and genuinely motivated to help bring high quality generics to the public.

Let's talk about the controversies. I'm going to go quickly through this, for this has already been discussed well.

One can show equivalence between a proposed generic and the originator by squeezing it out of the tube and comparing the concentration of active ingredient. Then you would say it's equivalent. But there is more to it than that.

Similarly, if you place it on the skin and strip it off and measure the cream on the tape, one can show that it is the same concentration, I have no doubt. But the issue is can you show with tape stripping differences between tretinoin products with the same active and different inactives? I think this is what is going to be discussed.

Also we have talked about the effect of diseased skin. In dermatology we are dealing with diseased skin. Don't forget, we are talking about acne, psoriasis or eczema where the normal stratum corneum is disturbed.

It is a leap of faith to say that how it behaves on the inner arm of normal skin is how it is going to behave in the diseases that we are treating. I'm really concerned that this would be the only method that we can show, and that we would drop away and can't use clinical studies. That is very, very concerning to me, to bring generics to people.

The draft guidance admits that for anti-acne drugs, those targets are deeper. The draft guidance tries to make the case that what is happening here happens in the deeper glands. It is still a leap of faith.

Summary of my position: Acne bioequivalence studies and other clinical trials can be done without excessive expense to the generic industry.

Skin striping may make sense for anti-

virals and anti-fungals. When I made this slide, I didn't think about all the stratum corneum effect on the anti-virals in the vaginals. So I might even move the anti-virals out of there.

Embracing skin stripping as a surrogate for anti-acne and corticosteroid products will always be suspect, since they do not act in the stratum corneum.

Cadaver skin, which is another technology, may be a better DPK marker, and that should be looked at.

There is also a potential negative effect here on this guidance. The intent of this guidance is to bring more generics to the public, but this guidance could backfire and hurt the reputation of generics, which has really been a hard fought and gradually earned reputation.

Brand companies will be easy to go into the dermatologist's office and just slam generics by saying skin stripping is not good science, and products approved in this way are suspect. At the end of the day, we do not want generic drugs' reputation

tarnished.

Thank you very much.

ACTING CHAIRMAN DRAKE: Thank you, Dr. Spear. You know, you're a wonderful human being. You saved me several minutes, and I appreciate your excellent presentation. That was very, very well done. Thank you.

Dr. Pershing, I believe, is next, and I will hold you to the same time commitments. You know you have a good meeting going on when there is this much lively discussion and interest.

DR. PERSHING: Thanks for allowing me to talk today. I want to address some of the issues that have been brought up during this discussion. I'm going to talk about DPK, the skin stripping model, and its uses and bioequivalence and bioavailability.

As was mentioned in the guidance, there's a number of issues that need to be validated with each drug product that you evaluate, and a lot of those issues are illustrated here.

I want to confirm that you can validate this skin stripping method for bioequivalence and

bioavailability assessment. In fact, we've done that for a variety of drugs that cross four different drug classes that represent different dermatological products in about eight different kinds of vehicles.

ACTING CHAIRMAN DRAKE: Dr. Pershing, maybe it would be better, if you could, to use the mike. That one, you're breathing in it. You clip it on so that it doesn't -- Okay.

DR. PERSHING: So these have been answered, and it is not that hard to do. It does take some diligence in doing so.

My point today is about topical drug delivery, and this is the problem I'm not sure everyone understands. Efficacy: Therapeutic efficacy requires -- of a topical drug product -- that the drug leaves the applied vehicle and gets into the skin.

The rate limiting step to getting drug into the skin is that outer layer called SC on this slide, stratum corneum. This dictates how much will eventually get into the other skin layers.

If you don't get drug into this skin layer, you don't get drug past that skin layer.

That's true, whether you have an altered stratum corneum or not. Okay?

One of the issues we talked a lot about this morning is Q1 and Q2, and I want to show you some examples of DPK profiles of two products, in this case a test and a reference, that were Q1 and Q2 similar. So qualitative similarity in the vehicle composition as well as similar concentration of those vehicle components.

If you meet Q1/Q2, you see similar uptake an elimination profiles in the dermatopharmacokinetic profile. That was for an antifungal.

Here is an antiviral. Again, if you meet Q1 and Q2, you will produce a similar dermatopharmacokinetic profile. But here's the case where they are bioequivalent. They meant to be the same, but in fact Q1 and Q2 were both different. You will note that now the test is not bioequivalent to the reference product.

Another example, an antibacterial. This shows bioavailability where you are comparing a solution to a semi-solid. Here you see that the semi-

solid doesn't deliver as much drug into the stratum corneum, and that it is basically displaced in almost an isothermic kind of situation.

So this really, truly is bioavailability differences, and the vehicle composition changes that.

Here is an example of tretinoin in a 0.1 percent cream and two different gels that are .025 percent. Again, you see that there is a difference in the extent, the amount that's delivered, higher concentration in the cream than the gel, and that you see differences in the dermatopharmacokinetic profiles.

Here is another bioavailability difference where we have compared four different imidazole drugs, all in a cream formulation, different concentrations. But you can see, their profiles are actually different.

Finally, the glucocorticosteroids, that if you apply different potency corticosteroids, you can see that the uptake of those drugs into the stratum corneum can be differentiated, both as a basis of the physical properties of the individual corticosteroid,

the concentration and, in this case, they were all cream.

The other issues that has been brought up is about does stratum corneum predict good drug concentrations in deeper skin layers? I spent the first ten years of 1987 to 1997 developing an in vivo human skin model where we take abdominal skin, and we graft it onto acymic mice.

This allows the skin to be living on an alternate skin source -- I mean alternate model source, and we can actually take multiple biopsies or single biopsies after drug treatment.

In doing that, we then took biopsies after a two-hour application of a variety of glucocorticosteroids, and we quantitated the glucocorticosteroid concentration in the different skin layers.

You will note that if you get more into the stratum corneum, you also get more into the epidermis. You also get more into the dermis. So what you get into the stratum corneum is reflected in the deeper skin layers.

Another example with Monistat-Derm, which is miconazole nitrate cream, and you will see that if you look at over multiple time points the concentration of stratum corneum, that as this stays the same dose, so does the epidermis and the dermal concentrations.

So the amount of drug you get into the stratum corneum reflects the concentration in the deeper skin layers.

Do differences in DPK predict differences in the pharmacodynamic activity of that drug? That's what we are really talking about here. Can DPK predict clinical performance? Can DPK predict in vitro bioassay performance?

This is an example of some recent work on betamethasone diproprionate in seven different formulations with and without propylene glycol that cover both ointment, cream and lotion and gel vehicles.

You will note that all the formulations, independent of vehicle composition, reach a steady state within the skin after about two hours, and that

whether you have with propylene glycol or without propylene glycol between the matched vehicle types, you can differentiate how much gets into the skin.

We compared this data in the same subjects in a pharmacodynamic response. Indeed, the more you get into the skin of this particular drug, the more negative your Emax value and, therefore, the more potent your corticosteroid. That's a beautiful correlation coefficient of .82. Therefore, the more you get in the skin, the better response you get.

Here is an example, however, where the two products were not the same, either qualitative or quantitative, and that a fungal. And you see the differences I've showed you before in the dermatopharmacokinetic profiles.

I show you this because, while the DPK methodology differentiated these two products, clinical efficacy, safety and bioassay results did not. Those differences in the DPK profile were such that they were less than the critical value that was required to differentiate them by either bioassay methods or clinical efficacy methods.

Why did that happen? That happened because -- let me see if I have a slide there -- pharmacodynamics is nonlinear. Pharmacokinetics is linear. So you can deliver more and more and more and more drug. At some point you don't see any difference in the clinical efficacy response.

This is typical with dermatological products, because we always deliver more drug than we need to, because it's not going to stay there very long. Okay? That's why we make them at higher concentrations.

Nonetheless, what's very important here is that DPK was able to differentiate these products, and all the other pharmacodynamic models were not. When you are picking a gold standard, you want the very highest ability of your method to discriminate. That's very important. It's a safety net issue for consumers.

I want to show you, you can also do DPK in diseased skin, that if you just account for the differences in the amount of skin you remove from a state like psoriasis where you have a

hyperproliferative stratum corneum, you have a lot more of it.

It is not biochemically the same. But what I want to show you in the next graph is that, if you correct for the amount of skin you remove from those skin sites, you get a similar response.

Here's a study on psoriatic elbows. We don't like to use psoriasis for corticosteroids, but it's a bilateral disease. If you have it one elbow, you are going to have it on the other elbow, and they are going to be very similar.

What we showed clinical efficacy-wise, we followed the target lesion scar with erythema scaling and duration. There was no significant difference between the trade and generic and, in fact, the DPK profile at multiple doses over time showed no difference between the products.

Another example of tinea pedis where again you have a hyperproliferative inflammatory situation, and we compared whether -- this is kind of hard to see probably, but with seven doses that helped forearm skin and diseased skin, when you account for the

amount of skin removed, is the same. Okay?

So in conclusion, the skin stripping methodology does require validation, but you can do it. We have done it with four different drug classes, multiple types of drug within those classes across vehicle types. You can use it for bioequivalence, and you can use it for bioavailability.

Pharmacokinetics does predict PD, that the drug products actually deliver more drug than is necessary to achieve a maximal effect, and that's why you don't always pick the up in a bioassay in a clinical efficacy study; that DPK is actually more discriminating than the pharmacodynamic assays.

The stratum corneum drug concentrations are relevant to deeper skin layers, and DPK predicts the pharmacodynamics.

ACTING CHAIRMAN DRAKE: Thank you very much, Dr. Pershing. May I ask for Dr. -- and I'm not sure I am pronouncing this right. Is it Parab? Did I get that right? Hot dog.

He is a senior principal scientist from Bristol-Myers Squibb, representing PhRMA. Is that

correct? All right. You have asked for ten minutes, which you shall have, starting now.

DR. PARAB: Yes. Thank you very much, the Committee, for giving me a chance to present. I am Prakash Parab from Bristol-Myers Squibb, and I will be presenting PhRMA view on this topical guidance. Next slide, please.

The oral presentation is shown here. There are many issues. First is methodology issue. Stripping technique for DPK has not been validated, and I'll give you these three examples.

There is a question of the target tissue. Inadequate DPK data exist to correlate stratum corneum drug concentrations to concentrations at different tissue types. I will give you two examples.

Lastly, DPK has not been correlated to clinical efficacy and systemic safety for any therapeutic category, class of compounds or formulations. I will give you two examples.

Let us look at the acne study done on Retin-A in human subjects. You see that about 82 percent of the unabsorbed surface drug is recovered in

washings, and only .2 and .80 percent is found in feces and urine after seven days.

This shows that most of the topical product can be recovered in surface washing, and minimum goes into the skin and systemic circulation.

Now let us look at the acne study. This is shown in many meetings, and it was shown as accent today also. The authors applied .025, .05, and .1 percent Retin-A, and they got a very good dose of same concentrations in the stratum corneum, very good dose response. But when we assumed that the authors had applied 5 milligram per centimeter scale of the product, we calculated how much of the applied dose is found in the stratum corneum. We found that about 76 to 86 percent of the drug is found in the stratum corneum.

This brings into question whether this number represents the residual unabsorbed drug on the skin surface and skin furrows rather than drug penetrated into stratum corneum. The dose proportionality described above is shown in many studies. It may simply reflect an increase in

concentration in the applied product is not increased amount absorbed. Just it is an error.

Let us look at a micrograph of the skin, dermis, epidermis and furrows in stratum corneum. Even after 20th stripping you can see these furrows where the unabsorbed drug can be present, and there are upper layers of the stratum corneum which cannot be reached, and these can contaminate the strips. So you may not get actually absorbed drug. You may be contaminated drug you will be seeing in the strips.

Next slide, please. Now this is a titanium dioxide product applied. First strip was taken. You can see all these spots, white spots, all over the place in the first strip.

Now you look at the tenth strip. You see titanium dioxide, the unabsorbed product in the furrows, and the tenth strip is contaminated with the surface product, not the penetrated product.

Now look at the methodology issues, variability, 20 subjects. At subject seven, you can about 175 micrograms. In another subject you get 425 micrograms of the stratum corneum, two fold

difference, a lot of variability.

Let us look at with-subject variability. In the same subject you can have minimum stratum corneum recorded at Site A, and a lot of stratum corneum recorded at Site B. Next slide, please.

So methodology issues: This is most important. A reliable measure to distinguish between residual surface drug and drug that has been penetrated into the stratum corneum has yet to be established.

Clinical mass balance studies have to be done. Using first 10-20 strips has not been validated to represent the stratum corneum. These strips may be contaminated with unabsorbed drug, calling into question relevance of the data.

Even after 40 strips, furrows still contain stratum corneum tissue and unabsorbed drug. Variability in collection of biosample makes it difficult to normalize the data for evaluation of DPK. So we question whether the DPK is precise.

Now let us look at the stratum corneum and target sites, stratum corneum concentration,

follicular concentration for three compounds.

As the stratum corneum concentration increases, follicular concentration decreases. The ratio varies from 2-37. Thus, DPK cannot be used to assess BA/BE for follicular drug delivery system, because there is no correlation.

Let us look at acyclovir data. This was done on a human skin grafted on nude mice after topical and oral administration. If you look at stratum corneum, epidermal and dermal concentration, topical concentrations are 44, 11 and 57-fold higher.

So one can assume that topically acyclovir is more effective, but in real life oral acyclovir is more effective. So again, no correlation between stratum corneum concentration and clinical efficacy.

Next slide. Now this is the Temovate data, Temovate cream and Temovate emollient cream. It shows a DPK difference, but Glaxo reports comparable clinical efficacy between Temovate cream and Temovate-E cream, and there is no difference in vasoconstriction on these two products when tested on 30 subjects. Labeling classified both products as

super high potency, and this is there in the PDR.

The difference in DPK between these products may be due to issues such as: 18-69 percent of the applied dose was recovered in the stratum corneum in this study may represent unabsorbed drug and questions the validity of the study.

Spreading of the emollient cream beyond application site diminishes the amount recovered. So validation is very important.

Let us look at many of the corticosteroid products. Diprosone lotion, Diprolene ointment gave same stratum corneum concentrations, but everyone knows that Diprosone lotion is a weak mid-potent formulation, where Diprolene ointment is a high potency formulation. So again no correlation.

Two to 11 strips had about 40-93 percent of the drug. So again, questions related to the contamination of the strips. Next.

So future: What we request is we should take a staged approach, whichever the method we select. The critical parameters of the method should be identified, evaluated and formally validated.

Proposed surrogate needs to be demonstrated to be relevant to the target site. DPK results must correlate to clinical outcomes. DPK then to be tested in specific therapeutic classes, different target sites, and different delivery systems, and should be blinded, multi-center study, not one center -- multi-center study.

The dose should be two to three milligrams, and data from these studies must include mass balance.

Clinical studies: Again, relationship between stratum corneum concentration and systemic exposure has to be shown. Dr. Rougier showed it in rodents, but we want to see that this exists in human beings for different drugs having different physicochemical properties, again normal versus diseased, different body sites. That has to be evaluated. Next, please.

So in conclusion, DPK is a research tool that has not been validated or shown to be correlated to clinical efficacy and systemic safety.

We in PhRMA wish to participate on any

expert panel or committee for this topic that is established by both Advisory Committees. Thank you very much.

ACTING CHAIRMAN DRAKE: Thank you so much, and again thank you for the extra minutes. A very nice presentation.

I would like to invite Deborah -- is it Miran? -- from the Generic Pharmaceuticals Association to present, and you asked for five minutes.

MS. MIRAN: Thank you very much. I don't have data, and I don't have slides, and I will probably be less than five minutes.

ACTING CHAIRMAN DRAKE: You get better every minute.

MS. MIRAN: The GPhA or the Generic Pharmaceutical Association would like to take this opportunity to make a brief statement, and we thank you for this.

We have supported, and continue to support, the issuance of this guidance as a means to demonstrate bioequivalence in topically applied generic dermatologic drug products.

GPhA well recognizes the role and the purpose of both the innovator discovery based industry and the generic industry, which provides lower cost, quality alternatives. Both segments can and should peacefully coexist, and I wish to reiterate that there is only one standard of quality for review and approval for both generics and innovators.

Regarding DPK, we have been patient, persistent and diligent in facing the issues and answering the scientific questions about the use of DPK as a measure of bioequivalence. This work, as has been mentioned, has effectively been ongoing for more than ten years, and a vast amount of data have been generated by both the industry, the agency, and academic institutions.

These data have been reviewed carefully by experts around the world. These studies have been designed to look at equivalence between test and reference products, correlations between clinical results and DPK results in both bioinequivalent and bioequivalent situations.

Every time the Joint Advisory Committees

have met and concluded that this is a potential or promising assay for BA/BE determinations, the agency, the industry and academia has responded with more studies and more data. These data have been presented to this group, and as today and in the past and as we have heard from Lynn, there is more to come.

In our opinion, these data support the use of this technique as a means to detect differences between "two like products" and to establish equivalence between test and reference products.

Presently, the generic industry continues to only have two choices for developing ANDAs and registering topically delivered generic alternatives. These choices, unfortunately, are (1) not to develop at all, and not to make available the generic alternative or (2) to conduct and extensive and expensive full scale clinical efficacy trial to determine equivalence.

In our opinion, this approach is inconsistent with FDA's whole objective of reduction of regulatory burden and exposure to patients.

FDA and CDER continue to evolve into and

support a risk based approach to assessing regulatory requirements, so long as they are based on sound science.

As we were reminded throughout this week of Advisory Committee meetings, there is never a no-risk environment, but we believe that the DPK and its use in evaluating bioequivalence has reached the minimal risk category, as Dr. Shah stated earlier.

Remember, too, that the statute does not require that generics reestablish efficacy. This has been proven. Waxman-Hatch, by definition, assumes that efficacy and safety will be proven through the link that the bioequivalency study provides.

In conclusion, we believe that DPK is determined by the current evidence and that the draft guidance, after two and a half years in review, should be finalized and implemented. Thank you.

ACTING CHAIRMAN DRAKE: Thank you. Then there is one last public comment from the American Academy of Dermatology, Cheryl Hayden. Oh, there she is behind the post where I couldn't see you. You are so little. There we go. Again, five minutes.

MS. HAYDEN: Oh, I'll be less than that. My name is Cheryl Hayden. I am the Assistant Director of Federal Affairs at the American Academy of Dermatology, and I would like to thank Dr. Drake and the members of the Committee for the ability of the Academy to present the fifth time our reservations with the guidance document for establishing bioavailability and bioequivalence using skin tape stripping.

The Academy has on a number of occasions expressed our reservations with this document. I am just going to briefly summarize Dr. Scher's statement.

Our concerns mainly have to do with the fact that there is no testing done on diseased skin, that patients with eczema, psoriasis, etcetera, will not be done well by this method.

We are also concerned that the method in and of itself has flaws, including the inability to assess whether or not the drug that is in the furrows of the skin has, in fact, been absorbed into or through the stratum corneum.

In addition to diseased skin, we are also

concerned that the guidance document fails to note that it would require testing on skin in the elderly and in children, which also has its own unique qualities.

Finally, we have also anecdotally heard problems from some of our members. This issue has been discussed at our task force, our FDA Therapeutics Task Force. Some members have tried to replicate the process as described in the guidance document and have had some difficulty. So we wanted to bring that to your attention as well. Thank you.

ACTING CHAIRMAN DRAKE: Ms. Hayden, thank you. I want to thank all of those individuals who took their time from their busy schedules to present from the interested public at this meeting. It is very important, and although I have joked about the time, I can't tell you how important your input is, and I would encourage you at any future hearings to please do this.

For those of you who want to be taken most seriously, be sure you try to give us something in writing ahead of time, because that helps the

Committee then have an opportunity to review it before we hear it the first time. It carries much more weight, but I do want to thank you.

At this point, what I would like to do now is open it back up to the Committee. Dr. Stern?

DR. STERN: Just to get things going, because this is my sense of what's happened, I guess I would like to move that the Committee recommend withdrawal of this guidance document with the instruction that in future DPK guidance documents, at least in the next ones that come forward, that they be limited to specific therapeutic classes; because, to me, the utility of this may well vary substantially according to therapeutic class of the topical agent.

A global one is, from my perspective, a long way from ready for prime time. So I think this global guidance document should be withdrawn, and I certainly think looking at it on a therapeutic class basis -- there may be some classes where it's very useful.

ACTING CHAIRMAN DRAKE: Is there a second?

DR. KING: Second.

ACTING CHAIRMAN DRAKE: Okay. The motion has been made and seconded that this guidance document be withdrawn, with the -- and I haven't forgotten you. I'll certainly allow the discussion period.

Let me just restate the motion, please, so I make sure I have it correctly: That the guidance document be withdrawn, with the instruction that, when it is re-presented, that it is done so with therapeutic classification structure in place. Is that an accurate summary? Okay. That's the motion.

Open for discussion, and it's been seconded, and Dr. Hussain.

DR. HUSSAIN: Just a point of clarification, ma'am. I think the purpose of this meeting was not to call for a vote. We requested this meeting primarily to discuss the issues and bring the new members up to date on the topic.

We would like to reconvene the Joint Committee meeting with all the data. We did not present any of the data here, and the purpose of the meeting was not to call for a decision at this point.

ACTING CHAIRMAN DRAKE: Okay. I think

that may have -- Dr. Stern, I don't want to speak for you, but in one of the presentations it talked about perhaps the guidance document -- a recommendation being withdrawn.

I don't know that this is a vote. What I would like to do then, taking your comments into consideration, which I certainly have healthy respect for the purpose of this meeting, but I also have a healthy respect for the sense of the Committee -- would it be reasonable -- Let me just ask, would it be reasonable, instead of this being a motion, to take it as a sense of the Committee, so to provide you with some guidance? Would that be acceptable? John?

DR. WILKIN: Actually --

ACTING CHAIRMAN DRAKE: Dr. Stern says only if we have punch ballots with curlicues or whatever they are called. So --

DR. WILKIN: Okay. Then I guess we figure out whether they are dimpled.

ACTING CHAIRMAN DRAKE: We need to know if they are dimpled or pregnant or whatever, but other than that, we are fine. Yes. Go ahead.

DR. WILKIN: You have to understand what our views were in coming to the group. If we really thought that we were coming to the group where we were going to get an up-down kind of recommendation or any sort of specific recommendation, I really think we probably might have deferred the meeting until we had the additional data that are coming in, that we certainly would have given a lot more data and informational pieces.

You would have had a much thicker guidance -- not guidance, but briefing document, so you could pour over these sorts of things.

Really, the intent today was not for the up-down or for any sort of aspect like that. It was really for those who are conducting these kinds of studies, for those of us who are working together at the FDA to think about the informational needs and how they might be achieved, to get some thinking along those lines.

ACTING CHAIRMAN DRAKE: I understand. Rob?

DR. STERN: Can I then -- Given that, can

I make a suggestion that at 12:25 we take a straw poll to suggest whether, as individuals, we feel this document is what I would call ready for prime time or not ready for prime time, and a second question would be whether we think -- if we don't think it's ready for prime time as it is currently given, whether we think it might be closer to being ready for prime time and application if it were done on a therapeutic class basis rather than as a global document.

So that's really more the issue of how we feel about it and advice and not really voting, but would that be more in the spirit of today?

DR. WILKIN: Actually, to my own personal sense of fairness, it really wouldn't. I mean, to be honest. My sense is that, had we been thinking that there would be a vote or a recommendation or even something informal as a straw vote at the end, that really we would have had a longer meeting.

We would have presented more data. It would have been a much more thorough discussion. My own sense of fairness is that that really doesn't --

DR. STERN: Then I withdraw my motion.

ACTING CHAIRMAN DRAKE: Rob, are you withdrawing your motion then? Withdraw the second? Dr. Mindel?

DR. MINDEL: The other side of this, though, Jonathan -- this is the third time that we have spent considerable time on this subject, and the only new information that was presented was on two slides, one of -- that one of the corticosteroid, and the other was a study in progress.

It seems that some people are beating a dead horse, and I don't -- You know, I think that enough is enough. So I would like to call on the Chairwoman to use her prerogative as a Chairwoman to have a vote.

ACTING CHAIRMAN DRAKE: I would like a little more discussion. I thank you. And I have three lawyers lined up.

DR. DiGIOVANNI: I'm always good for a little discussion. I also had a sense that the politics of this had moved more forward than we had actually been given enough information to deal with.

I think that, when I read this, my sense

was that this was a work that had been presented as President without the vote being counted, and the votes that I recollect from the prior meetings was that there were many questions that hadn't been answered.

Some of them are quite obvious questions: How much of the topical preparations are left in the crevices and clefts? You know, that may be an obvious one. There are others that may be more or less substantial: What are the various endpoints, certainly, as Rob had mentioned?

I think for dermatologists to look at the skin as one homogeneous group, it just doesn't seem to work that way. So without looking at different classes of drugs and addressing them specifically and coming up with some more scientific sense of addressing this, my gestalt was the same as Rob's. This is sort of being shoved down our throats almost further ahead than the information that we have been able to digest.

So I think the sense of the discussion is that there are some very focused questions that should

be addressed before the term paper is submitted next time.

ACTING CHAIRMAN DRAKE: Dr. Hussain?

DR. HUSSAIN: I think I second that, in the sense, if you really look at the advice we sought, I think -- If you look at my slides, the questions I posed to the Committee is how do we redirect our research focus so that when we come back to this Committee with the data, that would essentially address some of those concerns.

I laid out a means of approaching it, and I didn't get any feedback on the questions I sort of posed to the Committee.

ACTING CHAIRMAN DRAKE: I am going to take the prerogative of the Chairman here for just a moment -- or Chairwoman. I think that -- I do feel that -- Here is what I am going to do, as we will not take a vote, but I am going to poll this committee one by one and ask for their opinion, and I am going to ask you to give your opinion in two sentences or less without a long explanation. But you want our opinion, and I think there are some members we haven't heard from,

and I would like to make sure everybody gets included.

I want to just go around the room asking for your gestalt on the subject. John?

DR. WILKIN: One of the aspects that we realized in coming to the group is that there are members here around the table today from the Pharmaceutical Sciences Advisory Committee and from the Dermatologic and Ophthalmic Drugs Advisory Committee who have not heard this DPK presented at a committee discussion before.

So one of the key objectives was to give with this new group -- bring everyone sort of up to speed as to what some of the concerns are, and to describe informationally not the dataset that we have but what is --

ACTING CHAIRMAN DRAKE: Needed.

DR. WILKIN: -- literally in the oven, that is being worked on right now, and it is with the intent that when that dataset arrive that it will come back to the Joint Committee and then that's the day that, you know, gets the kind of discussion that you are describing. But our intent, really, was more

keeping the awareness and sort of giving a brief and a half-day kind of update.

ACTING CHAIRMAN DRAKE: John, I think we really appreciate -- and I want the Committee to correct me if I am wrong, but I am going to try to state for the Committee from what I've heard, that we're going back to the notion that, yes, a noninvasive measure that is cheap, fast and expensive is needed and useful and important, and we commend Dr. Shah, Dr. Hussain and you, Dr. Wilkin, for trying to make this happen.

We have heard this before. I've been on other committees. There isn't anybody at this table, in my opinion, that doesn't think that's an important next step. Am I correct on that?

Secondly, I do not believe that this committee has had the evidence presented today that would allow them to validate this as the way to go forward. There are serious, serious and substantial concerns about what we have heard today, and I think, if you did hold a vote, it would not be to move forward in this direction.

So I think you are hearing serious reservations from this group about what we've heard. Is that also a correct statement?

All right. The third statement that I think I -- and this may be my own personal opinion -- I love the fact that you've had this combined meeting, because it has allowed the pharmacologists to get together with the clinicians and try to share information, which is extraordinarily important, because that's how best decisions are made, is by having a sharing of information.

Without sharing of information, frequently you get bad decisions, and then bad outcomes. So I want to commend the FDA personally for bringing us altogether, because I've had great fun meeting some of our colleagues who actually know more about areas under the curves than I'll ever know. But it's important.

If we don't have that kind of information -- and I hope it's as important to you to learn what we as clinicians face. But I think it's a sense from all groups that we are not at that point yet. Is that

a correct assumption, and do we like this joint meeting? So everybody likes the joint meeting. All right. So that's the third summary.

The fourth summary is I want to make sure, at least from my perspective, that this information sharing in no way implies that we have given the okay or the go-ahead for the forwarding of this document with the kind of information we have.

In other words, I don't want this to be used on a slide in the future to say we met and liked it, because I think you've heard we've met, and we are uncomfortable at this point, and that we need more information. Is that a fair assumption? Okay.

So I think that is my -- As a chairman, that is my prerogative in where we are, and I think that probably I can't -- We've asked this before. I asked it once as a member of this committee when we had this.

To come into a meeting with two things not happening, not having all the studies and information before us is a mistake. I understand some of it is not ready, but there is some stuff that's been done

that was not in our packet.

So I would beg of you to make sure the committee gets all that information ahead of time, not only from the FDA but from all the audience here who has a vested interest in the outcomes. Please give us your work ahead of time, and the back-up documentation, because we may not like wading through all of it, but I'll assure you, you have a conscientious committee here who will wade through it, and we will try to come to some rational recommendations that ultimately benefit the end users, the patients. That's our goal here, as I understand it.

Now then, having said that, I probably talked too much. But I wanted to try to synthesize and condense what we have heard. Now I do want to take this moment to call on two people at this table who I have not heard them open their mouth, and I want to know if you have any additions or comments to what has already been said or what I've said. And Dr. Bloom, you are one.

DR. BLOOM: This is the first I ever heard

of all this information. So it's kind of hard to just suck it in. The other thing, I am concerned of the need for a validation of analytical methodology. Meanwhile, these studies are being performed. So it's kind of like there is no balance.

My concern is you first have to validate an analytical methodology, and then go ahead and do the particular studies. This is a concern of mine, because maybe the data might be influenced just because of that particular aspect. That's one of them.

The other one, I got concerns of maybe information that I don't have, for example, if it is taking into account the possibility that the active ingredients are being intercalated into proteins, although here on the follicles -- So I don't know that information. That might be influencing the bioavailability studies that might be taken into account.

So basically I am trying to get all the information and try to figure out the outcomes. So that's my perspective. There's other aspects about

this skin stripping that needs to be validated, and the pressure that should be applied, the area that should be taken into account, the need to spread the emulsion.

All those little, bitty details may make a big influence in the bioavailability studies and bioequivalence studies in terms of just the concentration to be estimated.

ACTING CHAIRMAN DRAKE: Do you see why I make everybody speak? What you've just said makes so much sense. Thank you.

Dr. Boehlert, would you please contribute?

DR. BOEHLERT: Yes. I am concerned that we are extrapolating a small database, what I've seen from the data presented today, to a larger population. I have listened to the combinations, different skin types, different disease states, and I am not sure we have enough data or I have seen enough data to make that extrapolation. That is always a concern of mine.

The other thing that I would bring up that I think Dr. Wilkin addressed to some extent is that Q1 and Q2, in and of themselves, may not be enough to

distinguish products.

They do not get into the physical state of the active ingredient. Particle size is critical in dermatological products. I have had experience with developing dermatological products and seen them to be very different based on just the physical state of the active ingredient, and that is not addressed in Q1 and Q2. You can have the same ingredients at the same concentration and different particle size.

So there are other issues here that we need to look at.

ACTING CHAIRMAN DRAKE: Thank you very much. Again, validating my notion that everybody needs to comment, because you bring different perspectives to the table that all of us need to hear about.

With that, I am going to just quickly track around the table, asking for any additional comments. Please, I am going to suggest we don't repeat, but that we, in one sentence, summarize.

Right before I start that, Dr. Shah, you have a comment?

DR. SHAH: Yes. I just had a comment on what Judy indicated, and that's true. Q1 and Q2 by itself is not enough, but along with that we also have the physical, chemical characterization of the product.

We also have the in vitro drug release, which is similar to the dissolution that's a part of the requirement, and also the particle size of the active ingredients.

All this put together is going to be the total body of evidence for the bioequivalence.

ACTING CHAIRMAN DRAKE: Okay. Dr. Lamborn?

DR. LAMBORN: I think that I share a number of the concerns that have been expressed before. There were some of the questions that I posed that I think at the next time we come back it would be very helpful if they were clarified, both in terms of the basis currently now in bioequivalence and also the intent of the guidance, and also to reiterate what others have said.

The next time through, it would be very

helpful if we are presenting new data to make sure that we had the background that led us to truly understand what the trials are that are being done, potentially the protocol as a document, not necessarily spend the time during the meeting but prior to it so that we can bring out questions.

ACTING CHAIRMAN DRAKE: I think, instead of presenting that stuff here, in view of limited time, if we have it ahead of time, then you don't have to present the protocol. We will know the protocol, but then we can ask questions. So that's a real strong recommendation you are hearing, particularly from your Chairman.

Dr. Tang?

DR. TANG: For the purpose of showing bioequivalence, my suggestion to the future researchers: You go from -- to the therapeutic area, therapeutic classes where you have -- antifungal, and go to another therapeutic classes. This validation should only be done by therapeutic classes.

ACTING CHAIRMAN DRAKE: By therapeutic. Okay, Dr. Mindel?

DR. MINDEL: I look forward to the fourth presentation of this subject.

ACTING CHAIRMAN DRAKE: That's right. Listen, I have a great graph I want you to put on the agenda. Jaime, I have this wonderful thing I want to talk about to start the meeting about dead horses, and I want to be sure that you remind me, because I want to present it.

It was just presented at the Harvard Business School by a very famous leader, John Kotter, and I'm going to share it with this group about "dead horses" before the next meeting. Okay? Can I have permission to do that? It's fun.

Okay, go ahead. Sorry. All right, Jaime, do you have a comment on all this? Okay. Dr. Abel?

DR. ABEL: I agree with all the comments of the Chairperson, and I think there is a great unmet need for the generic drug industry here, and we need to come up with some methodology.

I do question the methodology here, and I think the major concern is that the bioequivalence does not equal bioavailability in the disease state.

Perhaps we need to investigate other possible technologies. I have no background in the imaging techniques, but maybe there is a completely new methodology or involving MR or imaging that might play a role here.

Thank you very much, and I agree that we need to review all materials ahead of time.

ACTING CHAIRMAN DRAKE: Dr. Jordan, you haven't said very much today. So --

DR. JORDAN: Oh, I said a few things. I'm being very pensive. Actually, I have not heard the prior presentation. So this is my first time, but I get a sense that people are tiring a little of it.

I do think this is very difficult, at least for me, and not having seen any of this ahead of time. To be really sure this is some kind of a standardized procedure that could be used to evaluate these kinds of studies, I think it would have been nice to see some of the studies done on generic versus pediatric, the skin types, to really be sure this is something that could be applied to this kind of methodology.

ACTING CHAIRMAN DRAKE: Dr. DiGiovanni.

DR. DiGIOVANNI: I have no further comment.

ACTING CHAIRMAN DRAKE: Dr. Stern?

DR. STERN: I think this is something that we need to think about as not one methodology fits all, but by therapeutic class. I also think, in addition to thinking about the scientific rationale for the application of this to a given therapeutic class, also think about the extent to which equivalency is clinically important for a therapeutic class.

ACTING CHAIRMAN DRAKE: Dr. Lim?

DR. LIM: I have expressed my concerns before about using a one-time application of in vitro method for an in vivo clinical response, and I have no further comments beyond that.

ACTING CHAIRMAN DRAKE: Dr. King?

DR. KING: This has been a useful, informative meeting. However, I am not convinced that the DPK and related studies should be the only criteria that you evaluate for proof of concept, and

suggest, as Dr. Abel did, we need newer methods and another evaluation before we go forward -- new methods, and this is not going to fly.

ACTING CHAIRMAN DRAKE: Okay, thank you. New methods is not -- Without something different, yes. Okay. Dr. Miller.

DR. MILLER: I think that we should remember that this is just a draft, and you know, it can be changed. I think Jonathan very eloquently in his presentation raised most of the issues that we've discussed, and he did say there are different therapeutic classes.

I think it's apparent now that there is the ongoing study with Tretinoin, and we'll be looking for those data when they are available, and then I think from that, there will have to be more similar studies using different therapeutic classes and different age groups.

So I think that the whole thing has to be extended, and we are still in the very nascent stage of all of this, but I think it is still a draft. Certainly, DPK cannot replace clinical trials at this

time.

ACTING CHAIRMAN DRAKE: Okay. So I want to -- I think one additional comment that comes from your Chairperson then, based upon this final roundtable, is that without the clinical correlation that this will be, in fact, a very difficult option for us to support as a committee, keeping in mind that we are totally and completely advisory. But we all want to head toward the same goal.

Again, I want to commend Dr. Shah, Dr. Hussain, Dr. Wilkin for moving us along. I also want to reiterate, though, that perhaps the next time would be a real good time to have a lot of this data in front of us ahead of time so that we can come to some kind of closure or at least some kind of recommendation.

I get the sense from the committee that we have heard it many times, and it's probably time to -- I mean, this may not be the best way to do it. I don't know. But if we don't have data to support it, I think we should -- I guess what I'm trying to say is I would encourage you to not only look at this.

The concept is so important of having noninvasive measures that I would encourage you to look at any other alternatives and other options that might be called into play at this point, particularly with all the new technologies out there today. I mean, there's so many new technologies.

You might even think about offering an RFP or a solicitation or however you do that -- far be it from me to suggest that, but you know, if you canvas the different universities, different pharmaceutical companies, different generic houses, I suspect there's techniques and tools out there that could be brought into play, and with a little bit of support might be developed.

I'll give you one example at my own institution. I do know that there is a way now of screening genetically some new drug compounds, and that has been patented and licensed now, and several companies have licensed that as a screening tool.

I mean, there's just so many new techniques and tools out there that I would really encourage you to do some kind of very vigorous and

aggressive looking about to see what else is out there, because you are exactly right on the concept.

You are exactly right to try to get something that is not invasive and cheaper and more efficient. So my hat is off to you for working in this very difficult area.

I want to -- Before I shut down, I want to make sure that I thank, particularly, Jaime Henriquez and his staff for another great meeting. You guys do such a good job. Thanks, Jaime.

(Applause.)

ACTING CHAIRMAN DRAKE: I want to thank all of my committee members for coming, as big time in your day and your week. I want to thank our audiovisual folks. As usual, good job, guys. Mikes, good job. And thank you.

Before I close the meeting, are there any additional comments? Yes, Dr. Hussain?

DR. HUSSAIN: Ma'am, I had requested a few minutes to answer Dr. Lamborn's question, but I did not.

ACTING CHAIRMAN DRAKE: Shoot.

DR. HUSSAIN: I requested that Dale Conner do that on my behalf.

ACTING CHAIRMAN DRAKE: You did, and I forgot, and I apologize. Would it be more useful to do it now or would it be more useful to do it the next meeting? May I ask that question?

DR. HUSSAIN: We could close with that comment.

ACTING CHAIRMAN DRAKE: You want to close with this? Please go ahead, and I apologize for forgetting. I usually make notes, and I didn't -- because it was during break, and I didn't make a note.

DR. CONNER: Since I've only had probably 15 or 20 minutes and I wasn't preparing to talk --

ACTING CHAIRMAN DRAKE: That's okay. I'm only going to give you four minutes anyway.

DR. CONNER: Just a few comments, you know, probably not in a very logical order. If I had two or three more minutes to prepare, I might have gotten --

ACTING CHAIRMAN DRAKE: You will have it at the next meeting, for certain, but give us some

closing thoughts. This is important.

DR. CONNER: First off, I think we've addressed the fact of what we're after with bioequivalence in approving a generic product. I've been in many, many, many discussions like this, and some of them with simply internal FDA people, and the discussion always gets to the point where people become confused and mix up BA and BE, and they mix up proving efficacy of a product or a drug substance versus simply formulation comparisons.

What we are really after with generic drugs is doing a formulation comparison, and it's a much, much simpler question than BA or clinical efficacy of the primary product. All we are trying to do is form a bridge between this other formulation and the one where we have already done extensive testing and proved, hopefully to everyone's satisfaction, that it works, and that it's safe within known quantities.

So I mean, that's important to always keep in mind. The bioequivalence testing we do, no matter what it is, is always an artificial situation. You look at any of the generic drugs we do, and I would

a lot earlier the fact that, well, the clinical differences, you know, that I see between these different products aren't all that great; yet you are showing big effects on DPK, and that really says that DPK is probably a little bit -- a lot more discriminating.

Perhaps the danger of this, if we answer all the other questions, is it's going to be overly discriminating. It is going to perhaps knock out products that are fairly close together, because it simply says there's a difference here, but that difference may not mean anything, you know, in clinical settings.

So in effect, we may have something that actually knocks out products that might ordinarily work exactly the same way in the clinical setting. But rom a regulator's standpoint, I'd rather deal with that than with something that underdiscriminates.

Finally, and I'll finish up, the part about the sensitivity of clinical versus the kinetic way of doing things -- You will have to remember that clinical and pharmacodynamics operate on a sigmoidal

dose response curve.

So you can be -- You know, at very low doses you can see next to no effect. You get to a part where you increase dose or exposure. You get to kind of a steep, almost linear portion. Then finally you get up to a part where you have a plateau. Even if you increase the dose by considerable amounts, you don't really see any difference in effect.

Unfortunately, most of these drugs are kind of in the upper part of the dose response curve. So even increasing the dose by significant amounts really doesn't give you that big of -- big or any difference between the products.

One thing, when you look at pharmacodynamics or clinical effects, and to do a very discerning study on those, you really have to make sure you are in that steep part or else the test really has no ability to differentiate between products, even if they are very, very different.

That's something you always have to keep in mind when you look at clinical or pharmacodynamic effects; whereas, kinetics usually in most cases are

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: JOINT MEETING

Before: PHARMACEUTICAL SCIENCE AND DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEES

Date: NOVEMBER 17, 2000

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represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Rebecca Davis