UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

and

)ERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

JOINT MEETING

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FRIDAY
NOVEMBER 17, 2000

The Committees met at 8:30 a.m. in the Potomac Ballroom, Quality Suites, 3 Research Court, Rockville, Maryland 20850, Dr. Lynn A. Drake, Acting Chairperson, presiding.

PRESENT:

LYNN A. DRAKE, M.D.	Acting Chairperson
ELIZABETH A. ABEL, M.D.	DODAC Consultant
GLORIA L. ANDERSON, PhD	Consumer Representative
JOSEPH BLOOM, PhD	ACPS Member
JUDY BOEHLERT, PhD	ACPS Member
JOHN DiGIOVANNI, M.D.	DODAC Consultant
ROBERT E. JORDON, M.D.	DODAC Member
LLOYD E. KING, JR., M.C., PhD	DODAC Consultant
KATHLEEN R. LAMBORN, PhD	ACPS Member
HENRY W. LIM, M.D.	DODAC Member
FRED O. MILLER III, M.D.	DODAC Member
JOEL MINDEL, M.D., PhD	DODAC Consultant

PRESENT: (Continued)

NAIR RODRIGUEZ-HORNEDO, PhD	ACPS Member
ROBERT S. STERN, M.D.	DODAC Consultant
MING T. TANG, PhD	DODAC Consultant
JURGEN VENITZ, M.D., PhD	ACPS Member
JAIME HENRIQUEZ	Executive Secretary, DODAC

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(8:32 a.m.)

ACTING CHAIRMAN DRAKE: Good morning. I would like to welcome everyone to the Advisory Committee for the Pharmaceutical Science and -- it's a combined meeting of the Advisory Committee for Pharmaceutical Science and the Dermatologic and Ophthalmic Drugs Advisory Committee.

To that end, I would like to begin by first asking our staff to read the conflict of interest statement. I should introduce Mr. Jaime Henriquez. I'm sorry.

MR. HENRIQUEZ: Thank you. Good morning. 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 for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported

by participants presents no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

Since the issues to be discussed by the committee at this meeting will not have a unique impact on any particular firm or product but rather may have widespread implication with respect to the entire class of products in accordance with 18 U.S.C. 208(b), each participant has been granted a waiver which permits them to participate in today's discussion.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of Parklawn building.

With respect to all other participants, we ask in the interest of fairness that they address any concerns of previous financial involvements with any firms whose products they may wish to comment upon.

ACTING CHAIRMAN DRAKE: Thank you very much.

First of all, I would like to go ahead

then and call the meeting officially to order. I will introduce myself. I am Lynn Drake, Acting Chairman of this joint committee this morning.

I would like to now go around the room and ask each member of the committee to give us your name and your affiliation, since this is a joint committee and we may not all have met before. I would like to start right down there. It's Dr. Bloom. Is that correct?

DR. BLOOM: Yes. Joseph Bloom from the University of Puerto Rico.

ACTING CHAIRMAN DRAKE: Would you mind telling us kind of what you do so that, at least as Chairman, I have in context who I can really rely upon for specific expertise.

DR. BLOOM: I'm Professor at the University of the School of Pharmacy and analytical chemist.

ACTING CHAIRMAN DRAKE: Thank you.

DR. ANDERSON: I'm Gloria Anderson, Morris Brown College in Atlanta. I'm Callaway Professor of Chemistry, and I am a physical organic chemist.

DR. BOEHLERT: I am Judy Boehlert. I have my own pharmaceutical consulting business. I consult in the areas of quality, drug development and regulatory affairs, and I have a PhD in analytical chemistry.

DR. RODRIGUEZ: Nair Rodriguez, University of Michigan. I am Associate Professor at the College of Pharmacy, and my expertise is in material science and solid state.

DR. LAMBORN: Kathleen Lamborn, University of California San Francisco, Professor in the Department of Neurological Surgery, and I also direct the biostatistics corps for the cancer center there. My field is biostatistics.

ACTING CHAIRMAN DRAKE: I'm not sure her mike was on, Ms. Lamborn's mike. Can we check, sir? I'm not sure her mike was on. Could you guys hear her in the audience. I didn't think hers was on. Would you do it again, Dr. Lamborn. I'm sorry, and maybe we can do it with the mike on, because I think our audience would like to know who is on the panel also, please.

DR. LAMBORN: Kathleen Lamborn, Professor in the Department of Neurological Surgery and also director of the Biostatistics corps of the cancer center at the University of California San Francisco, and my field is biostatistics.

DR. TANG: Ming Tang, St. Jude Children's Research Hospital, biostatistics.

DR. MINDEL: Joel Mindel from the Department of Ophthalmology and Pharmacology at Mt. Sinai Medical Center, New York.

MR. HENRIQUEZ: Jaime Henriquez, CDER, FDA.

ACTING CHAIRMAN DRAKE: And I forgot to tell you what I do. I told you my role here today, but I am a dermatologist, and I am on the faculty at Harvard Medical School. This year I happen to be on a paid sabbatical.

DR. ABEL: Elizabeth Abel, clinical professor of dermatology at Stanford and private practice of dermatology.

DR. JORDON: I am Bob Jordan, University of Texas Medical School at Houston where I am

Professor and Chairman of the Department of Dermatology.

DR. VENITZ: Jurgen Venitz, Virginia Commonwealth University, Associate Professor in the Department of Pharmaceutics and clinical pharmacologist.

DR. DiGIOVANNI: I'm John DiGiovanni. I am a dermatologist on the faculty of Brown University in Providence, Rhode Island, and I am the Director of the Division of Dermatopharmacology.

DR. STERN: I am Robert Stern. I am a dermatologist in Boston at the Beth Israel Deaconness Medical Center.

DR. LIM: I am Henry Lim, Chairman of Dermatology at Henry Ford Hospital in Detroit, Michigan.

DR. KING: I am Lloyd King. I am Professor and Chairman of Dermatology at Vanderbilt University and at the Nashville V.A. Medical Center.

DR. MILLER: I am Fred Miller, Chairman of Dermatology at Geisinger Medical Center in Danville, Pennsylvania.

DR. WILKIN: Jonathan Wilkin, Director, Division of Dermatologic and Dental Drug Products, FDA.

DR. HUSSAIN: Ajaz Hussain, Acting Director, Office of Testing and Research, CDER.

DR. SHAH: Vinod Shah, Office of Pharmaceutical Science in FDA.

ACTING CHAIRMAN DRAKE: Thank you very much. I would like to now ask Dr. Wilkin to make an opening comment or two about what we are about here today.

DR. WILKIN: Well, we have quite a few chemists here with us today. So they will resonate with the concept of an elegant synthesis, and my understanding of an elegant synthesis is one that requires the fewest number of steps and gets the highest yield in the end.

There is also the notion in mathematics of elegance, and it would be a mathematical proof that takes the fewest number of logical steps to get to the answer.

I submit that there is also the notion, at

least we should think actively about the notion of regulatory elegance where, when we are working with the industry group, be it innovator or generic, that what we are thinking about is that informational need that represents what is necessary and sufficient so that we are not really asking for anything more, that there is no excessive regulatory burden.

Part of what our role is at the agency and, of course, working with academicians and those in industry, is to continuously think about how we can reduce that regulatory burden in a scientifically sound manner.

I would argue that there are actually three R's of regulatory elegance that we should always be thinking about. The first is reduction, decreasing the number of tests or the extensiveness of the tests required; refinement, optimization of the test design to generate the maximum amount of relevant data for the least cost; and the final is replacement, substitution of a simpler, cheaper, more informative test for a complicated, expensive, less informative test currently used.

I think we have an opportunity in the area of topical drug products to think about a variety of alternative methodologies to the clinical trial which may be a more elegant way of achieving our regulatory informational needs.

We are going to be talking about one of those methods this morning, dermatopharmacokinetics, DPK, but I am happy to tell you that I have really enjoyed working with the OPS group, the different folks who are not thinking only about dermatopharmacokinetics but also other alternative methodologies and working to figure out what exactly the informational base needs to be before such methods are adopted.

We are going to speak to that this morning. Dr. Shah is going to present many of the studies, talk about the kinds of evidence that already exists. In the next presentation I am going to talk about some of the concerns I have with actually the current information base and moving forward without some additional information.

Then Dr. Hussain is going to talk about

the kinds of additional information that we can obtain, and also his endeavors and others' endeavors into additional alternative methodologies.

Thank you.

ACTING CHAIRMAN DRAKE: Thank you, Dr. Wilkin. Some of the committee asked me earlier what is our primary role here today. I think our primary role here today is to be questioners, thoughtful participants.

As you know, some of you have been on some of these committees before. This is almost a continuum of looking at alternative ways to evaluate pharmacological agents. So this is a continuum.

We have had previous hearings on this, and this will be just one more in a series. We will not come to any final closure today on any subject, but what we want to do is truly be advisory.

We want to ask good questions. We want to bring up honest concerns. We want to offer positive suggestions or offer thoughtful critique, when appropriate and when it is helpful.

So that is kind of our goal, is to be an

information body and a thoughtful body, to help the FDA and industry and users and, ultimately, our end users, our patients, to have a better product that is developed in a cheaper and more efficient manner.

Do I have any questions from my committee about how we are going to progress today? Great. With that then, we will -- There will be an open hearing. Just so that everybody knows, we have had four individuals ask to speak, plus we have a written statement that I have been asked to just make a comment or two on that will be submitted for the record.

With that, I believe we will begin. As I understand it, Dr. Shah, you are starting today. It's nice to see you again, sir.

DR. SHAH: Same to you, too. Good morning and thank you for giving me again the opportunity to talk with the joint advisory committee meeting with respect to the pharmaceutical science of as well as the dermatological individuals.

There are quite a few new members and, as you indicated, Chairman -- Chairwoman, that we would

be providing you the information updated to where we are, and try to seek input from you so that we move in the proper direction for finalizing.

So with that view in mind, I will be documenting the dermatopharmacokinetics from the bioequivalence viewpoint. I would like to here indicate I am going to be primarily focusing my presentation on the bioequivalency, and the bioequivalency, I mean comparing the test product and the reference product. The reference product would be the best product, so how I see that the DPK could be useful for achieving this information.

With that, I will also provide the historical background and some of the make-up on the pharmacokinetics or the dermatopharmacokinetics.

In my presentation I will briefly discuss the methods to assess the bioequivalency of the topical drug products, history of the DPK, the draft guidance which you already have in your handouts and also it was issued about in June 1998, and some of the ongoing studies at University of Utah.

I will indicate here that these studies

are the ones which came out as a recommendation from this Joint Advisory Committee Meeting when you met about a year, year and a half ago.

Now what are the different methods to document the bioequivalence? Again, here I am talking about comparing the two products, the test product and the reference product.

The first method commonly used in the dermatological field is the clinical studies, because we make a comparison of the test and the reference product. The clinical studies, at least in my opinion, are comparatively slightly difficult, slightly expensive and at times they are insensitive, because they require large number of subjects in order to achieve the comparison and say whether the two products are equivalent or not.

The other way of comparison is the pharmacodynamic studies. Now this is applicable only to a few types of drug products like the Glucocorticoids where the Glucocorticoids provide a pharmacodynamic form, and you can then make a comparison.

There is some indication that maybe in some of the data there is, like tretinoids, the transepidermal water loss might be used in this area, but it has lots of questions and has not proved responsive.

The other one is the dermatopharmacokinetic or the pharmacokinetic principles applied to the stratum corneum concentrations, and that is the refer to as the dermatopharmacokinetics.

In my opinion, this is one of the methods that we are exploring in products. This is the method on which we have more information gathered together over the last 13 years or so, more or less slowly, and have -- because, as you can see, it is a very logical way of doing it, primarily because we are measuring the drug concentration in the stratum corneum which is very close to the site of action.

In some cases this may not be exactly the site of action, but it is fairly close to the site of action, and I think it is universally applicable.

The fourth method offered to document

bioequivalence is the in vitro drug release, which is something similar to the dissolution of the product, but even though that is universally applicable, we don't think we are ready to move forward only using this method for the bioequivalency process, and we think that this data may provide a signal for the possible inequivalence.

Okay. Let's talk about what is dermatopharmacokinetics. The dermatopharmacokinetics is the pharmacokinetics principles applied to drug concentration measurements in the stratum corneum, and that is what we call dermatopharmacokinetics or briefly abbreviated as the DPK.

In order to achieve this, we use a method what is known as the tape stripping method. So the tape stripping method is a tool to measure the drug concentration in the stratum corneum and to determine the drug uptake and elimination or the disappearance from the stratum corneum.

I would like to indicate here that these principle of the dermatopharmacokinetics has been discussed and talked about for over the last -- more

than 30 years. In fact, in some of the earlier work I do recall that we were measuring the pharmacokinetics or the dermatopharmacokinetics after the drug the drug is already administered.

We measured how rapidly the drug is appearing in the stratum corneum and how it is disappearing from the stratum corneum. Using the pharmacokinetic principles we have tried nearly 30 years ago in some of the earlier work done with Professor Sidney Riegelman and Professor Epstein from University of California San Francisco where I did my post-doctoral work.

So these principles have been studied for a long time, and some of these principles have been presented and discussed at lots of international meetings that I will show you in a minute.

Just to provide the knowledge that this is a method which we thought might be used and be applicable for the topical drugs, we have started out with a research in 1987 at University of Utah. Since then, we have several workshops and presentations, for example, the AAPS/FDA workshops in May 1989 and March

of 1990, December 1991; FDA/Industry conference in March '92; Advisory Committee meetings, first one after the Drug Advisory Committee Meeting which is now a new name. It's the Pharmaceutical Sciences Advisory Committee meeting. It was also discussed at international meetings like Bio-International and in the PPP conferences in Europe; also the EUFEPS Conference, again the Bio-International and several other workshops.

Continuing on that, we have the meetings with the Advisory Committees. Also we had two meetings, a Joint Advisory Committee meeting similar to this, and this is the last Joint Advisory Committee meeting we have.

Since then we had the meetings with the expert members and the special government employees meetings in July 1999. The expert members consisted of the people from the academia, from industry and the general drug industry.

We had two such meetings. We had a symposium just a few weeks ago at the annual AAPS meeting, and again today we are meeting here with the

Joint Advisory Committee on November 17 to discuss the dermatopharmacokinetics.

We have quite a lot of knowledge, and that is what we would like to share it with you to move forward in this area.

As I indicated, the draft guidance was issued in June 1998, and we have requested the comments from the people by August 17, 1998, and the guidance is already on the Internet.

We did receive a few comments, total about 15 comments also, but the comments were not on the DPK. Even so, we have asked the sponsors or the commenters to please provide the data which are in support of the use of the DPK. We did not get any such information.

The comments were clearly divided into two blocks, one supporting it,saying it's a great idea; another group saying, no, it's not a great idea.

So just to produce you with the guidance process: Initially, we need to define the process -- the problem and the issues. That's what we defined by having a lot of discussions and coming up with the

solution, that let's move forward with the DPK.

We get a lot of scientific input, do some research, some workshops, Advisory Committee meetings, and then we have come out with the draft guidance.

After the draft guidance, we received the comments. We reviewed it. We are doing some research. Again we are discussing with the experts and the Advisory Committee meetings and, hopefully, with the input from all this area, we will revise the draft guidance and, hopefully, come up with the final guidance.

So our main concern is what is needed to have a confidence in the DPK? That's what we are looking for, because many times a new technology, a new method comes up, there is always a question as to why we are doing this. Is it going to be useful? So what kind of information do we need so that we get a good confidence in applying this new technique?

In my way of thinking, at least there are these three issues which needs to be addressed very clearly so that we can get a good confidence in the dermatopharmacokinetic application principles, again

primarily for determining the bioequivalency of the two products.

The first important factor is the relevance to the clinical efficacy or the data. Is there any data results that can say that, yes, the DPK and the clinical data could be joined together and they go hand in hand?

The other factor is the ability of the DPK to differentiate between the formulations, such as maybe there are minor changes or the manufacturing changes or any other changes, and can DPK predict the properties of the vehicle, because we all know that for the topical drug products, the vehicles, even though they are inactive, they are primarily also functioning as a source for driving the actual drug substance -- So can we determine the properties of the vehicle by using this method, and also to find out the reliability and the reproducibility of the method?

So let's take one question at a time. The first one is the relevance to the clinical efficacy or the data. Can the DPK differentiate the products with the same concentration of the active drugs but with a

different clinical efficacy?

Now this was the question we were really raising in the last Advisory Committee meeting, Joint Advisory Committee meeting, that we would like to have the data such that maybe there are products which shows the same clinical efficacy, and it should show the same DPK values. And the product that showed differences in the clinical efficacy should show the differences in the DPK.

That was an excellent idea, but the problem comes up is where shall we go and find such products? Well, this is one example where we are talking about the clobetasol propionate.

This is a topical steroid, and two different -- slightly different forms of products that are on the market. One is called the emollient cream, and the other one is called just the plain cream or the Temovate cream and the Temovate emollient.

Here are the two products. One is the innovative product, and this is the generic product. We see that both products have the same clinical efficacy, because they are both based on the data, and

this is the Temovate-E product, which is supposed to be different clinically, because the labeling of these products indicate that these two are not the same.

This is more potent than this one. Now all these products contain exactly the same amount of the active ingredient, which is 0.05+ clobetasol propionate.

So here we can see clearly that the products which has same pharmacodynamic response, same clinical response, same DPK response, the products with different clinical indications having the different DPK response.

Also there was one more challenge which has come up of the same nature that we need to take a look at the products similarly. That was the glucocorticoid but not directly applicable, plus there were some concerns that when we take a look into the DPK, we are really trying to move away maybe to some extent for some of the products like tretinoin where a follicular pathway is supposed to be playing some role.

So we started looking for a product, and

we are fortunate enough to find this product. We have three products here. One is called the Retin-A gel, which is the innovator company; another product which was first based on the clinical data, which is the Tretinoin gel, same concentration made by Spear; and the third product, which is the Avita tretinoin gel, .025 percent, made by Bertek.

Now the clinical findings were the product A is equal to product B. These two products were equivalent, and they were both approved, and they are labeled as interchangeable products. But when the studies were done comparing the product A and product C, the finding was they were clinically different. They were not the same. But the product C was approved primarily because it was effective.

Now these three products contain exactly the same amount of the active drug, all in the form of a gel. So we thought it would be a good idea to take these particular products, these three products, and do DPK dermatopharmacokinetic studies, because the clinical is already established. So let's do that.

So we are doing the research right now at

University of Utah to confirm and validate the clinical findings that A is equal to B, and A is not equal to C. This is then the ongoing study, and I would really indicate here that this was the example which was again discussed at the last Joint Advisory Committee meeting and the strong recommendation had come from this Advisory Committee meeting that the study of this nature needs to be done, and that is the ongoing study right now.

May I have the next slide?

Okay. then coming back to the second question as to whether can the DPK differentiate between the different formulations. Now what do we mean by that?

Well, it should be having the same vehicle but different concentrations of the active. by that, we mean it may be the different concentration/dose response relationship. Very often we know that it cannot be achieved with the clinical findings or the pharmacodynamics findings, but can we see such responses with respect to the DPK?

The second question was can the same

concentration of the active drug but different vehicles could be differentiated by the DPK, which meaning that they are significantly different formulations.

The third question which also comes up is can the DPK predict the properties of a vehicle?

With these questions, the first question was can we see a good dose response relationship or not, and we see here that there is an excellent dose response relationship between the concentration of the tretinoin preparation and the concentration of the amount of the drug in the stratum corneum, and we see there is a nice, clear response.

On this side, what is shown is by the tape stripping method, as you go deeper and deeper inside, the concentration starts falling down, and that is exactly what is being observed here. So again, this shows that we can very easily see a nice dose response relationship with the tretinoin.

Now we have seen this kind of dose response relationship for several other glucocorticoid drug products like betamethasone dipropionate and

quite a few others, this kind of response is seen, but this is just only one example to show that.

Now here is the example of the Temovate preparation which we saw before, that there are two preparations which have almost the same formulation, the brand name and the generic name, and there is a Temovate E which is a slightly different formulation.

We can see that with the differences in the formulation, again it could be easily picked up by the DPK. This is the same slide that I had shown earlier which can differentiate between the clinical efficacy or the clinical settings and the DPK concentration.

So to summarize these concerns, the relevance to the clinical efficacy data, I think it could be done. Ability of the DPK to differentiate the formulations, I think it can be done. And then the question comes up can the DPK predict the properties of the vehicle? I think, yes, that could be done also. We have several example with the glucocorticoids, especially that when the formulation is different in terms of the vehicle like

betamethasone dipropionate, Diprolene and Diprosone creams, which the major difference between the two is the vehicle, that can be easily picked up by the DPK data.

The question comes up with the reliability and the reproducibility of the method. At least in my opinion, we have shown that the method is very reliable and reproducible, because we have in-house a study right now where the same product has been studied by two different investigators, and we come up with the same results, or a same product studied by the same investigator a year later, we come up with the same kinds of results.

So at least in essence, in principle, the reliability and the reproducibility of the method has already been established.

Okay. Then what are the applications of the DPK? Again, my main question again is to take a look into the bioequivalence assessment, comparing the test product and the reference product.

So at least the way I see it is it could be definitely used for the comparison of the two

products, test and the reference product, but there is also a possibility, which I hope that Dr. Wilkin will go into more details about it, that the DPK could also be applied in terms of the bioavailability assessment, especially when you are measuring the bioavailability of the product and the application of line extensions.

That's where the DPK could be useful, during the bioavailability area. But again I want to go back and say that my focus is going to be taking a look into the bioequivalency areas.

Okay. Just to summarize and come back to the conclusion, what do we mean by the bioequivalence and what type of products we are looking at: We are looking at the same percent of the active drug.

We are looking at the same route of administration or the same type of application, the topical application, and we are also looking at the same dosage form category; that is, comparing the cream versus cream, ointment versus ointment, and gel versus gel.

We are not going to use the DPK for the bioequivalency purposes to compare like cream versus

gel or ointment versus gel or anything like that. Our comparison is going to be strictly between the cream versus cream and so on and so forth.

Generally, in our comparisons, as it is required for the generic products in our 21 CFR, that inactive ingredients of the generic product has to be essentially the same, and nearly the same amount. So what we are indicating is generally it should have qualitatively the same ingredients, which we are identifying it as Q1, and also the same amount of ingredients, which is approximately ±5% of the composition.

So we are looking at nearly the same composition, same inactive ingredients for the bioequivalency purposes of making the comparisons.

Sometimes what happens is, even though it may have the same inactive ingredients, same composition, depending upon the rate that people are manufacturing it, the rate is prepared. It may end up in a slightly different finished product.

In order to take care of both types of issues and the scenarios, we have added what we call

as an in vitro release or the drug release from the formulation itself.

So for the bioequivalency comparisons comparing the test and the reference product, we would imagine that the bioequivalence documentation would require the dermatopharmacokinetics. Also the product has to be Q1 and Q2, and we would also add an in vitro drug release, which will take care of the manufacturing variabilities that might be seen with the same formulations.

Now I should indicate that there has been a lot of work done in this area by Professor Flynn and other people who have really clearly indicated that this would be a good approach to do that.

In addition to that, we have the guidance out which is called the SUPAC-SS, which is for the semi-solid preparations, and even in that guidance we are allowing for the site of manufacturing changes and the other changes, the in vitro drug release to be a key factor. If the drug release is the same, then we would imagine that -- We would assume there is no further change in terms of the activity of the

product, and we would be approving that.

So -- Okay, this I just talked about. I didn't know that I had the slide. In vitro release can differentiate between the different formulations, between the two products manufactured differently, and the products containing the different particle size of the active drugs. This has been also used in the SUPAC-SS.

So then what is really needed for us to accept the DPK? Number one, we need to have a validated tape stripping or the skin stripping procedure, validated analytical methodology. We also require a mass balance of the information/study data on that.

The sponsor needs to conduct a pilot study, the pivotal bioequivalency study and the DPK data which should meet the 90 percent confidence interval for the bioequivalency limits of 80-125 for AUC and Cmax. This is exactly the same kind of criteria we have now for all orally administered products.

The advantages of the

dermatopharmacokinetic technique is: It is a noninvasive procedure. It shows a good dose response effect. It can differentiate significantly different formulations. It measures the drug concentration in the vicinity of the action in the skin. It is a sensitive, reliable, reproducible and cost effective measure.

Very recently we heard, just before I came up, a nice presentation from Dr. Wilkin who indicated that we need to be aware of the three R's. At least I think that this does fall into the same category that we can meet all these requirements of the three R's of the regulatory people with this DPK methodology. It is applicable to all topical dermatological drug products.

The only disadvantage I see is it requires the validation of a tape stripping procedure. It's not that easy, but it is not that difficult either. Somebody has to spend some time just like people learning the use and operation of the HPLC or a DC or any other technique. They need to spend some time so that they can do it, and it could be done, but that's

a slight disadvantage. It requires a good sensitive analytical methodology and validation.

Okay. Now what is the skin stripping procedure? This is just in brief. You apply the test and the reference drug products concurrently at the multiple sites. It's on the forearm. I'll show the picture in a minute.

After a certain time interval, you clean the area, and apply the adhesive tape. At least some of the different work that we have been doing in the different laboratories is using either Transpore tape or a Cuderm tape, but people can use any other adhesive tapes, as long as they validate the information. With uniform pressure, remove and discard the first stripping, because we feel that the drug has not been completely penetrated, and what is remaining on the top is removed.

We apply and remove, collect nine successive tape strips at the same spot. Extract the drug, and determine the concentration using the appropriate validated analytical method, and express the results as amount per surface area.

It is important to know that each application site yields a single drug concentration in the stratum corneum, and this is just an example, that the drug uptake, how long it takes for the drug to come up to the maximum concentrations. It could be done -- The samples could be removed at the end of 15 minutes, half an hour, one and three hours, and you can follow the same drug elimination pattern, like making the tape stripping and concentrations at three, four, six, eight and 24 hours.

This slide just shows an example as to how the arms are being used, the left arm and the right arm, for the drug uptake and the drug elimination. Also in order to make sure that we take care of the variability information, it is the same -- applied for the same time duration in both the sites, and this data would provide us the variability between the active procedure of the skin sites, the site of application and all.

Similarly then we have a system where we can do the drug uptake and elimination for the test and the reference product, and that would result into

the bioequivalency study. Only important factor is we have to use the sufficient number of samples.

What we end up is in a profile of this nature, this is the true data from 40 subjects for product A and B. One of them is the generic product. The other one is the reference product, and you see that both of them are almost giving us the same kind of information, how rapidly the drug is penetrating or being absorbed into the stratum corneum, and how it is eliminated after it is absorbed.

So that's in terms of the DPK information. In the draft guidance we had indicated that it should be applicable to all topical products, including the vaginal drug products, retinoids and all the other classes.

We had also indicated that we would like to shift the envelop a bit more and go up to -- Q1 has to be the same, the same inactive ingredients, but Q2 can be ±10%. But there were some comments from some of the folks and the experts that, no, we should not do that; we need to be a little bit more considerative, and in order to achieve that, they said

that, okay, you remove this from the -- that it will not be applicable for the vaginal drug products, and change this Q2 from 10 to 5%.

That's what we intend to do in the revised guidance when it will be coming out, that it will be applicable to all the products, to retinoids and the other products, and not applicable to the vaginal drug products, with the Q1 and Q2 being ±5%, and also we will be adding the in vitro release test.

The reason why we feel that the retinoids should be also included is, as you may recall, just a few minutes ago I showed a slide where we are right now doing the studies using three different tretinoin gels at University of Utah.

Those products were also selected not only from the clinical endpoint but also to take a look into consideration that people feel that those products has a follicular pathway as an important route for the drug to reach its effective concentrations.

If we find that our clinical data and the DPK data are in agreement with one another, then this

would be applicable. That's why we are leaving the retinoids into this. We hope to have the final data completely analyzed of that nature before we come out with the final guidance on that.

So with that, if we take the different classes of the drugs, starting with the antifungals, glucocorticoids, antibiotics, antivirals, the retinoids and the vaginal drug products, using the DPK, I think the vaginal drug products might be at the highest risk, and the antifungals are at the lowest risk; because these are the ones where you measure the concentration in the stratum corneum, and that's the site of action, whereas the others are slightly different. This would be from low risk to high risk, would be the assessment of all these topical drug products.

So in my conclusion, then I would indicate that for the bioequivalence determination, the primary means to document the bioequivalency will be the dermatopharmacokinetic data, and the supportive information will be coming from the in vitro drug release, the particle size distribution of the active

material of the drug substance.

The DPK is a reliable, reproducible and relevant method to document the bioequivalence between the test and the reference products, and again it is applicable to all the drug products, and is also cost effective, because it is less expensive and more reliable compared to the clinical studies.

Again, this is only for the bioequivalency purposes. There are other methods also that could be used, but right now we have more information on the DPK. That's what I mean here by saying that DPK is a reliable method, and some of the other approaches that we are trying to study and look will be discussed later on by Dr. Ajaz Hussain.

So I think this is my last slide. With this, I would like to thank the Committee for listening to me, and will be happy to answer the questions either now or towards the end, as the Chair decides.

ACTING CHAIRMAN DRAKE: Dr. Shah, I think I'll use the Chair's prerogative and save questions until we have heard the three presentations, because

often these questions get answered. But I thank you for an excellent presentation.

I believe now, Dr. Wilkin is coming next.

DR. WILKIN: Dr. Drake, members of the Committee, members of the audience, I would like to talk about the issues and opportunities. I think there is some potential here that certainly needs to be explored, not only for DPK but for other alternative methodologies.

I would like to say, though, at the beginning that I think there are two ways to get to DPK at the moment. One would be from the database or from first principles; that is, logical, inferential kinds of steps.

I would make the argument that we don't really have the logical structure to get to DPK at the moment inferentially, and that the database is -- It's got some important and supportive kinds of information, but it really is not sufficient at the moment.

DPK -- If you really think about it, DPK is intended to pick up the differences in the vehicle

between two topical products where we know that the active is going to be there. It's the same identical active, and it's in the same identical concentration.

So what we are really thinking about is how well does DPK tell us what is going to happen in the clinical setting because of a different vehicle?

So I would say that there is probably insufficient evidence to adopt DPK now, but I think there is hope for the future, and it absolutely must be explored.

There are three parts of validation of any assay technique. The first is: Is it reproducible within a laboratory. I think this probably has already been accomplished for DPK.

The second is: Can it be reproduced among different laboratories, looking at some written recipe? I believe that there is great potential for that. I'm not sure that I have seen the evidence, but I think that is extremely likely that that will occur.

Then the third level of validation is understanding how it relates to the current standard. The current standard is the clinical trial. Is it

really answering the same question that the clinical trial would be answering?

Now this is a graphic from one of Dr. Shah's earlier papers, and he emphasizes what eventually I will be calling the grand analogy, that the plasma concentrations for drugs that are given orally -- that that area under the curve really has a lot of the same logical content as the area under the curve for dermatopharmacokinetics.

So what is dermatopharmacokinetic? Kinetics of drug in the skin, pharmacokinetics applied to the skin.

Now there is a difficulty for me with the word dermatopharmacokinetics, because that means skin. What we are really talking about is stratum corneum. If you look, this is the epidermis up here. It's the baklava type layers on top of the sea of collagen that has the blood vessels and the other ingredients that sits on the butter.

What we are talking about with the stratum corneum is not really the entire stratum corneum in DPK. We are talking about just the upper layers of

the stratum corneum. It is not even all of the stratum corneum.

So I would point out that we are really talking about a very tiny, very superficial portion of the skin, even though we are referring to this as DPK.

So again, perhaps this could be misleading to someone who reads about DPK very superficially, and I have suggested that, you know, some other terms might be identified to really more properly identify next. But that is really a minor, trivial issue compared to the fundamental issue of the analogy between the plasma area under the curve and the stratum corneum area under the curve.

The question is: Is the DPK area under the curve truly analogous to the plasma area under the curve for oral dosage forms?

I've got a catalog of concerns that I have with this grand analogy. The first is that, of course, the stratum corneum is not the same thing as the skin. The skin has a lot of structures in it. It is very heterogeneous.

The stratum corneum is not the sole

pathway to get from the surface down to where the action site is. There is a follicular pathway, and the follicular pathway in the literature has been regarded as quite important for some agents.

The stratum corneum is not a real compartment. Unlike the blood, which is well mixed and which the active is an equilibrium with the active site, the stratum corneum is not well mixed, and the drug that is the -- the active drug that is in the stratum corneum is not an equilibrium with the actual target within the skin.

Then my final concern is that this is all based on this superficial portion of the stratum corneum, and that anatomic area is actually absent in much of the skin diseases, and it really has no cognate in the lip or in the vaginal mucosa. There has been some consideration that DPK would be used to approve products for these sites.

Okay. We will go through that list in just a little bit of detail. For the oral dosage forms, again they get dissolved in the gastrointestinal juices, and that really represents

the vehicle, if you will. There's a lot of homeostasis that keeps that gastric fluid relatively similar.

So in essence, for solid oral dosage forms, the vehicle is pretty much the same for all of those forms, and yet DPK -- that's what we are interested in, is how does the vehicle differ from one topical to another -- The active then migrates through the gut wall. That's the biological limiting membrane area.

To my way of thinking, that corresponds, really, to the stratum corneum. Then once you get beyond the gut wall, for these agents that are circulating in the blood stream, they are intended to have some activity in the heart, the kidneys, the brain and so on.

It is important to have the active in the blood, be able to make it to the target organ, and then it's an equilibrium, and that equilibrium is an important aspect of our modeling and interpretation of what the plasma blood level can actually mean.

So again, the plasma blood level -- this

is well mixed, and there is an equilibrium with the target organ.

Equilibrium is essential to the notion of interpreting plasma AUCs. Plasma levels produced by two generic formulations should be similar at equilibrium, as their plasma level tissue/tissue level ratio will remain constant at equilibrium.

Now let us evaluate what happens in normal healthy skin, which is where DPK is going to be studied. The vehicle will be applied to the surface of the skin. There are two pathways to get the active down to the action area, which might be the viable epidermis or it might be in the superficial dermis.

One pathway is through the stratum corneum. The other pathway is through the follicle, and then again there is really no equilibrium here. There is more of a kinetic flow kind of mathematical model for this.

Again, one of the key questions is that healthy stratum corneum does not exist in most skin disease and, certainly, in the lip and the vaginal

mucosa. So that what will happen is the vehicle will be applied to the remnants of the stratum corneum, and the remnants will be those lower levels.

So that the upper levels tested in DPK will not be there for most of the disease entities in dermatology for which these topical products will be indicated. Next slide.

Okay. So Jamoulle & Schaefer have actually commented on this. When a dermatologic drug is used, it is usually applied to diseased skin, which may not have the same permeability as healthy skin. To simulate diseased skin, the stratum corneum can be removed.

So to recap the concerns about the analogy with the plasma area under the curve, for topically applied products the vehicle is actually the in constant that we really want to know something about, what its attributes are, how it is altering the performance of the topical product, and it is again in constant.

On the other hand, for solid, oral dosage forms, they make it to the gastric juice which is

relatively constant, and so that I see a substantial difference there.

The stratum corneum is the biological membrane that is the penetration barrier that needs to be crossed for topical products. For oral products, it is the GI mucosa. One of two pathways to the target is the stratum corneum. The other is the follicular pathway.

The stratum corneum amounts may not predict the follicular pathway. There is certainly a huge difference in the stratum corneum between healthy and diseased conditions.

The stratum corneum is not well mixed. There is no equilibrium with the target, and it is absent in the lip and in the vaginal mucosa.

I don't think there is a cognate with the topical pathway and getting from the surface, the area of application, to the action site that exists for the organs like the brain and the heart and the kidneys when you are giving a solid, oral dosage form.

Here you have the plasma or the blood. It's the single path to the target. In healthy and in

diseased states, it's generally very much the same with only a few exceptions.

It is well mixed, and there is an equilibrium with the target, very important for interpreting this model.

One of the other difficulties in the dataset for DPK as I have seen it is that it is looking at initial doses, and there is the concern about the metabolic activity and permeability of the skin may be changed under the effect of repeated exposure to the product during a toxicity or clinical study. The longer one is using the product, one can alter enzymes.

Dr. Shah mentioned the enormous history of DPK being discussed, and I did attend one of those workshops, and a document emerged from that workshop, "The Bioequivalence of Topical Dermatological Dosage Forms: Methods of Evaluation of Bioequivalence."

This was one of the key lines that -- It was a consensus document, and I would just remind everyone that what a consensus document is, is that you get lots of people signing off on a document that,

if they were going to be the only signatory, they probably would not have signed off on it.

This was the line that, I think, helped a lot of us who participated in this consensus document. "Before a DPK method is adopted as a basis for bioequivalence, it must be shown that the differences in dermatopharmacokinetics capture or reflect significant clinically important differences in formulations."

Now Dr. Shah has also mentioned that at the October '98 Joint Advisory Committee meeting we talked about what kinds of evidence might be very helpful to meet this informational need.

First of all, I think, if the DPK is going to be accepted for all topical products -- you know, a really wide variety -- that we ought to have evidence from several therapeutic classes that represent different targets within the skin.

The second aspect of this is the evidence should come from blinded, three-arm comparisons where there is a reference product, a product that has been found to be bioequivalent in clinical studies, and a

product that has been found to be bioinequivalent in clinical studies.

If we had data from that kind of comparison, that would truly be supportive for DPK. While I find it difficult to accept DPK on first principles, I think we could get there pragmatically with a database that showed that, in fact, it does do what the intended claim is.

Again, I think DPK cannot be derived from first principles, that it is underdetermined by the current dataset, and my thought is that the really broad applications that are within the current draft guidance, that either the draft guidance could be withdrawn until adequate evidence exists for all of those or, alternatively, based on some new information that is coming in once that information has been evaluated and we have had -- perhaps the Advisory Committee has been involved in looking over the dataset, it might be that the draft guidance, instead of really being withdrawn, would be modified to really match the data. In other words, it might be limited to one particular class of compounds at the very

beginning.

Next slide. So although there are insufficient data to support the regulatory utility o dermatopharmacokinetics at present, I do believe the assay has potential for bioavailability and bioequivalence determinations for topical products that should be investigated.

I also salute Dr. Hussain's efforts to look at other methodologies beyond DPK for this same end.

I do have another difference with Dr. Shah's interpretation. That is, I see the potential regulatory utility of dermatopharmacokinetics exceeding the limitations imposed by qualitative and quantitative similarity between the comparator products.

I actually believe that, if DPK works, it is going to work independently of that attribute. So that it would lessen the burden not only for the generics but also for new drug products.

Thank you.

ACTING CHAIRMAN DRAKE: Thank you, Dr.

Wilkin. As usually, a very excellent presentation and thoroughly understandable. Again, I would beg the indulgence of the Committee to defer the questions until we have our third speaker.

Dr. Hussain, I believe, you are on.

DR. HUSSAIN: Good morning. My presentation will focus on methods for assessing bioequivalence for topical products. The question I am posing here is how should FDA redirect its research program?

In my handout material to the Advisory Committee, I have included a number of slides which deal with some ongoing efforts, such efforts on vaginal products. My intention is not to really discuss those, but have those for the Advisory Committee as an example of what could be done from a reductionist approach. So let me have the next slide.

I would like to start with some distinction between bioavailability and bioequivalence so that we provide a framework for thinking about research approaches for assessing bioequivalence.

Clearly, the factors that affect

bioavailability and bioequivalence are similar, but bioavailability tends to be in an absolute term. What amount of drug gets absorbed, and at what rate does it get absorbed? It is more of an absolute value.

Bioequivalence tends to be a relative comparison. I just want to share some thoughts on that. Factors that affect bioavailability include: Drug attributes. This will include solubility and dissolution rate of the drug in the vehicle itself, size of the drug molecule, the charge on the drug molecule, membrane permeability characteristics, and metabolism characteristics of the drug molecule.

The vehicle, obviously, has a significant impact on bioavailability, and here you could also look at how efficient is the vehicle in dissolving the drug and allowing dissolution to occur, how quickly the vehicle spreads, does it adhere to the skin or to the membrane applied, and also its ability to change the characteristics of the membrane on which it is applied.

Clearly, the membrane attributes are of importance: Status of the barrier function, exudates

and other fluid secretions that may or may not be present, blood flow to the organ or the tissue site of application, its metabolic capacity and so forth.

Also, I think bioavailability clearly is impacted by method of application. For example, if you apply a gel and just simply leave it or you rub it in, and so forth, could have a impact.

If you focus on bioequivalence of a topical product, I think the question we are asking is: Do we see equal rate and extent of exposure at the intended site of action or sites of action?

With respect to understanding the basic absorption processes, I think equivalent rate of membrane penetration and permeation is a must to see equivalent rate and extent of exposure, and rates of membrane penetration and permeation will depend on function of the vehicle and its effect on these processes, as well as how the rate of drug release is effected from the vehicle itself.

Also important in this equation is equivalent application site, formulation contact time and area, and also inherent in that is I think you

would like to see equivalent or better systemic exposure, because systemic exposure is a body burden and not truly a desired exposure pattern.

In order to talk about how should FDA redirect its research program, I would like to share with you some brief information on the current research projects. We are doing some work on DPK, as you heard from Dr. Shah, as well as just a brief mention.

We started a project last year to address issues, concerns that were brought to us by the medical -- or clinical sciences here, and there is a working group called Topical Microbicides Working Group. These product are being developed to prevent STD and AIDS transmission in women.

We had concerns with respect to the deployability or distribution of these formulations in the vaginal cavity. So we started some work, and we are using a sort of reductionist approach, trying to identify the key processes, the critical processes that would affect the way a formulation was spread and for what coverage in the vaginal cavity.

So that is the research as an example of the reductionist approach. As I said, I will not discuss that at length here.

I would like to then share with you some thoughts and proposals of such projects. What body of evidence is needed for regulatory acceptance of DPK is sort of a question? Other tests to complement DPK, is that a way to go, or do we need to go and look at new methods for bioequivalence assessment?

The current activities with respect t dermatopharmacokinetics research: You heard from Dr. Shah, we have a study which is essentially almost complete now with Professor Lynn Pershing at the University of Utah. The key FDA investigators on this have been Surendra Shrivastava and Don Hare.

We are not presenting this dataset here today, because this was done in a blinded fashion, and we will complete the analysis and bring it back to the Advisory Committee when the study is complete, and you already have the information on what that study is.

What we are doing at present in our labs is actually trying to repeat some aspects of the

study. There have been some concerns raised that this method may or may not be reproducible in different labs.

We felt that, if we are able to have some hands-on experience with DPK and actually are able to show that this is a reproducible method, using individuals in our lab who have not worked with this technique before, that would add to a level of confidence with this method.

So you have FDA investigators from the lab as well as from different areas of review sciences who will be doing the study. So they will have their own hands-on experience.

In addition to that, what we are doing is we are exploring the feasibility of other techniques. At present, we are looking at -- we have the capability in-house, and we are looking at using near infrared spectroscopy as a means for quantifying drug levels in stratum corneum.

We are also exploring different methodologies from spectroscopic methods as well as imaging methods to see how one can quantify drug

levels in skin in a noninvasive manner.

I think we will be planning to present some of our thoughts and feasibility data next time when we meet with you. However, I think the question here is: Even if both studies that we are doing are positive, would this evidence be sufficient to introduce DPK in regulatory practice?

I think the answer will be yes or no, depending on -- I think that is the discussion we are having.

Clearly, Dr. Wilkin has pointed out several concerns with respect to this approach. In order to address those concerns, we have to take a look at those concerns and try to elucidate a reasonable process to address those concerns.

Let me start with some of those concerns. Stratum corneum is not skin. I think that is obvious. I think the other is it cannot be derived from first principles.

The way I look at that concern, I think from my perspective, it deals with the issue of generalization. Can we generalize the available data

which may be limited to certain classes of drugs to the rest of the population of formulations out there, and so forth?

Generalization of regulatory finding, if it's empirical, is always a challenge, and we will try to address that. Obviously, clinical relevance is a question.

I just wanted to share my personal opinion with respect to DPK. I think with respect to the technique itself, if we are going to measure bioavailability on a healthy stratum corneum, obviously, that is not going to give us accurate information on bioavailability under disease conditions, as the lips, vaginal, for example, different routes of administration. So that is not the intention.

So the key questions, I think, in my mind are as follows: Can comparable DPK profiles be used to assess bioequivalence between two pharmaceutical equivalent products; and the pharmaceutical equivalence is quite rigid in this particular scenario, not only that products have to be cream

versus cream, but in addition to that, the strict requirement on quantitative and qualitative similarity of excipients.

So if we pose the question now as equal in stratum corneum exposure -- and I'm showing that as a ratio or reference to stratum corneum levels -- is that equivalent to follicular exposure? That means having the same ratio between test and a reference formulation for stratum corneum levels. Would that imply that the follicular or appendagial concentration ratios would be similar?

Secondly, we could ask, equal in stratum corneum, exposure is equal to exposure in disease states. Thirdly, I would like to share some of my thoughts on does Q1 and Q2 criteria ensure equivalent physical attributes of a multi-phasic system?

Dr. Wilkin has alluded to the fact that I think this probably is too restrictive, and I actually would like to see if we can expand and move away from this criteria, not only because I think it is an artificial divide, but there are several management issues that it sort of brings to FDA, and I think if

we can move away from this, that will be a better approach. However, since excipients vehicles are being applied directly to a membrane without dilution, the challenge is how do you address the effect of these vehicles on skin or any of the membrane that they are being applied to?

Let me go on. So let me rephrase the concerns that we have heard into something which we could sort of reduce it to, projects that might be helpful to move forward.

The postulate here is that two topical products applied to skin surface provide equivalent rate and extent of drug exposure in all layers of skin when these products exhibit: (1) equivalent thermodynamic activity of drug in vehicle; the two vehicles have similar interfacial transport kinetics, and I think that is where the concern or the issue between stratum corneum versus follicles come into play.

The effect of excipients on skin permeability has to be similar, and this is where the concern between healthy versus disease conditions come

into play. And then skin contact time and area: here also, I believe, healthy versus disease questions can come into play.

To give you an example, if you are comparing formulations on healthy stratum corneum, the rate at which water evaporates from that is pretty much fairly, I would say, constant among individuals. Constant is the wrong word, but I think -- But now if you are comparing that to a diseased skin where stratum corneum is damaged, you have exudates. You have secretions that come in. Would the two formulations absorb those exudates to the same extent or similarly? So that becomes a question there.

Let me use the follicular -- next one -- transport issue and try to see what sort of -- how do we move forward in this arena.

As I said earlier, equivalent stratum corneum exposure is equal to stratum follicular exposure. That is the question. Clearly, from a basic physical chemistry and diffusion perspective, I think -- and knowledge of the distribution of follicles and their prevalence on skin, we could say

likely -- this is likely when drug is in solution and the formulation is a simple formulation, as the single phase formulation. However, at the same time, you have to look at what does equivalent stratum corneum exposure really mean?

Equivalent stratum corneum exposure implies that you have equivalent thermodynamic activity plus the impact or effect of those excipients on the stratum corneum was similar. So there are two components to that equation.

I think equivalent thermodynamic activity is not really a concern here because of the nature of what we are doing. We are comparing to pharmaceutical equivalent products. But the issue comes on effect of excipients on stratum corneum.

Clearly, there will be a higher potential for seeing differences between stratum corneum and follicular exposure when the drug is either encapsulated in the formulation or is a suspension where particle size differences could contribute, and/or it is a multi-phasic system. You have a cream formulation, and the distribution of drug in the

cream, depending on the droplet size and so forth.

However, I think we could also address that. I was looking at the Physicians Desk Reference, PDR, and you see there is already a product on the market which I believe -- at least my sense is -- was intended to essentially improve or reduce the adverse effects of this drug, Retin-A Micro.

It is an acrylate copolymer porous microspheres. So this product contains microspheres with the drug. However, if you further read in the PDR, it has not been able to claim -- and I will quote from the PDR -- "contribution to decreased irritancy by Microsponge system has not been established."

There is a body of evidence saying that targeting two follicles using encapsulation, liposomes and so forth, have not really been very successful to date.

So there are means for modulating exposure to follicles, and I think that could be used as a challenge to the question that we have set. Let ;me go to the next one.

I think I have tried to sort of put a

cartoon together to explain what that really is. What you see here in this figure is you are looking at a multi-phasic system with different droplet size of particle size.

Based on the anatomy of the follicles, some might get in. Some might not. I think that is what we are talking about in this case. Also, I think there have been numerous reports where -- or tools available now that could modulate or that could change the distribution of drug.

I am talking about techniques such as iontophoresis which can enhance follicular penetration, or you could look at low intensity ultrasound. That could actually shut the follicular penetration down.

So you have tools available that could be used to modulate distribution, and then see whether that could be used as a challenge to the DPK and probably compare that. There are opportunities in that regard. Go on.

At the same time, I think we can bring to bear some mechanistic and other techniques to evaluate

this issue. So there is a possibility of developing a mechanistic evidence base plus distribution and imaging approaches.

I think, just to go down on this side, what I would like to say is supporting evidence can be generated via in vitro experiments using excised human skin. In vitro experiments using excised human skin is a well established technique in industry, and that is quite used with respect to when formulations are being developed.

It has not been accepted in regulatory practice, and I think we have been looking at that as a means of bringing back and looking at some mechanistic analysis. I think one concern is the viability of the skin, and that can be addressed also.

If we use this tool, what can we do? We could look at different anatomical sites. We can obtain skin samples from different sites, and it is possible to maintain viability, if necessary, for, say, about 24 hours.

We could emulate compromised stratum corneum barrier functions, and provide indirect

supporting evidence via transport and skin distribution studies.

We could also get direct supporting evidence via visualization of follicular and nonfollicular transport, and bringing into play techniques such as laser scanning confocal microscopy. That is not the only one. There are other techniques available. Next one.

So I think the question is what body of evidence is needed here? Clearly, we have empirical evidence, and this comes in the form of comparative evaluation between DPK and clinical studies.

I think it is always a challenge when you deal with empirical studies as generalization. Empirical data essentially provides proof of concept for products that are being evaluated. Generalizations beyond that is a challenge.

For generalization, obviously, I think at least my way of thinking is mechanistic and reductionist approach might be a way to do this. Clearly, DPK has been in development for a long period of time. I think I am correct, Dr. Shah mentioned

about ten, twelve years.

It is time to look at other methods, too. In the last ten years, there has been such a dramatic increase in development of new analytical tools and so forth, and we would really like to explore some new methods and new spectroscopic imaging techniques.

We hope to provide to you next time when we meet some assessment of feasibility, but just wanted to let you know that any new method would take a significant amount of time.

DPK at present is the most developed technique in this area, and I think we would like to continue to provide the support for generalization and in the meantime work toward methods other than DPK.

Just wrapping up, one more slide I will show you is the vaginal products. The slides you have, the intention I had was to share with you a reductionist approach that we have initiated for this area.

We are working with Professor Katz and the biomedical engineering school at Duke to do this. The reductionist approach is simply identified as a

processes, understand the mechanistic basis, and then bring them together. So you have slides which essentially show that.

At the same time, toward the end of the slides you will see in vivo analysis that show differences between formulations. Just an example.

I'll stop with that here.

ACTING CHAIRMAN DRAKE: Dr. Hussain, thank you so much. We appreciate all this information that's been put before us.

What I would like to do now is take a few moments before we begin a full scale discussion to make sure if there's any questions. I would ask the Committee to distinguish between discussion and questions that relate to clarification.

So I would now call upon the Committee to see if you have questions for clarification from our three speakers before we begin the discussion. Dr. Abel? I don't think your mike is on.

DR. ABEL: Thank you. I have a question as to the physical mechanics of tape stripping. How is it done to ensure consistency between different

researchers who are doing this?

There is pressure involved. Could someone describe the actual tape stripping technique?

ACTING CHAIRMAN DRAKE: Dr. Shah?

DR. SHAH: Yes. We -- I can describe to you very clearly, and in case if you are not too clarified, we can have Dr. Lynn Pershing, who is here -- she can describe it in farther details, because she is the one who is actually performing it.

What we do is we mark the forearm area with respect to the eight different spots and apply the tape. The tapes also come exactly in the square, in the round size edge so that you can apply it to the spot. Apply the pressure uniformly.

DR. ABEL: How?

DR. SHAH: By rubbing it, using a plastic ruler so that there is no effect on the tape itself, and that's how it is applied. But additional work by Dr. Chris Surber and others has shown that, even though there may be differences in the pressure, it does not make any difference with respect to the amount you are removing it.

We have also made available rollers by which you can apply the rollers and have the uniform pressure, but there is no need to do that. So there are different techniques of doing it, but it has been indicated that it is not really necessary; because the different pressures do not make any difference in terms of the amount removed.

ACTING CHAIRMAN DRAKE: Other questions? Yes? Dr. Lamborn, right?

DR. LAMBORN: Right. I'd like to --

ACTING CHAIRMAN DRAKE: Mike for Dr. Lamborn, please. Thank you.

DR. LAMBORN: I'd like to ask Dr. Wilkin: You had noted that you thought there was potential --

ACTING CHAIRMAN DRAKE: I still don't think we have her mike on. Now let's try it. Do we have all of your attention now? Yes. Now, Dr. Lamborn, would you try one more time? If not, would you just speak real loud?

DR. LAMBORN: I can do that, too. Basically, my question is: You said that you feel there is potential, but that we are not there yet. I

would like your sense of what is it that you would think we would need, and do you think that Dr. Shah's studies that he is describing -- are they addressing that need, should they be positive, or are you saying that you would be looking for something very different from that in terms of what you would want to see in order to be convinced that this methodology was appropriate?

ACTING CHAIRMAN DRAKE: That question was addressed to Dr. Wilkin. Try it again. Can we get Dr. Wilkin's mike on? Speak loudly. You know, usually it's just a matter of pulling it closer to you, but I think that it actually is not working very well.

DR. WILKIN: Well, again I think Dr. Shah and his colleagues and those with whom he has been working, Dr. Pershing and others, have accumulated a lot of supportive evidence. I think they have convincingly demonstrated that you can look at the same vehicle and detect different concentrations. They will lead to different AUCs, if you will, in the superficial stratum corneum.

So I think there is a really good substrate on which the critical test against the gold standard needs to be considered. The gold standard is the clinical study, which is imprecise, admittedly, huge confidence intervals; but the important thing about the clinical study to compare a topical innovator and a topical generic is that, even though the answer is imprecise, it's the right answer to the question.

What we are thinking about with DPK is we are going to have a precise answer, but is it the answer to the right question? The question is does DPK tell us what is going to happen in the clinical setting? Is it a surrogate for that?

So I think it's just -- Basically, my way of thinking is a standard is the clinical study, and DPK needs to be validated against that particular standard. The USP describes how validation can occur for CMC types of methods.

There has been -- I think it was perhaps NIOSH or Environmental Sciences, there was a commission that considered this for nonclinical animal

types of toxicity studies: How does one end up with a "validated" test.

I think that's the right learning piece for me, is that I would really like to see that there is a known product that has a certain efficacy and safety outcome in a clinical trial, there is a separate product that has the same kind of efficacy and safety profile in a clinical trial, and there is a third product that has the same active and the same concentration but, for one reason or another, doesn't have the same efficacy and safety.

To my way of thinking, that kind of three-arm trial done in a blinded manner would at least tell us about that particular active ingredient.

DR. LAMBORN: Well, that is actually my question. As I understand it, that study is ongoing. So my question to you is: If that study, which is ongoing, turns out to be able to distinguish, will that meet the concern that you have or did you envision something broader? Did you have the feeling that there needed to be multiple studies in multiple areas?

Just as we are going to be getting the question as a group, if we feel that this study that is ongoing is sufficient, since you have specifically said you wanted something more, I would like to know if you feel that the study that is ongoing meets your -- what you would hope to see.

DR. WILKIN: Yes. Well, I've seen the protocol, and I would say the protocol looks quite good, but it's always difficult to say before you see the results and the outcome of the study exactly what one would derive from it.

Studies can end up being sufficient and determinative. Studies can end up being -- I mean, the outcome of the study, to my way of thinking, could be that it does work, it doesn't work, or it might and we still don't know. I think it depends on what the dataset look like.

DR. LAMBORN: But it is the type of study that --

DR. WILKIN: It is absolutely the type of study, yes.

DR. LAMBORN: Thank you.

ACTING CHAIRMAN DRAKE: Dr. Stern, and then Dr. Anderson.

DR. STERN: Thank you. I have two questions, and I am not sure whether they are more for Dr. Wilkin or Dr. Shah.

First question is: Does it concern either of you that, when you look at a single preparation at various doses by this method, it looked like the curve showed very great differences in what the method showed; whereas, in clinical experience the differences in clinical response between those different doses is rather modest?

In a certain sense, you are having a very much more sensitive measure of what is getting into the stratum corneum, but compared to at least the clinical impression of the magnitude of difference of clinical response. That's my first.

The second is in a certain sense a related question. My understanding that the period of application before the tape stripping are relatively short, how long you apply it, how many days, how many applications; and I'm sorry, I missed exactly what the

standardization is there; whereas, we are often talking about products that are typically used in the case of some at least for a week or two, and in the case of others sometimes we don't expect to get to a clinical endpoint with acne products for one to two months.

So how much does stratum corneum concentration after one or two days tell us about equivalency at the end of two weeks for a topical steroid and perhaps two months for a retinoid or topical antibiotic?

Those are my two questions.

ACTING CHAIRMAN DRAKE: Gentlemen? Dr. Shah, then Dr. Wilkin. Can we get that second mike working over here now? It's on? Bingo. Thank you, sir.

DR. SHAH: Okay. With respect to your first question as to whether, when we see the different concentrations in the stratum corneum when you are applying the different concentrations clinically: Yes, that's true that the DPK is definitely more sensitive, and it is easy to pick up

the differences than what the clinical is.

Now when we are making the comparison between the two products, the bioequivalency -- that's where again we plan to use the DPK to start with as a considerative approach. We do want to make sure that the products are at least the same type of potency.

That's why we take a look if there is 20 percent difference in the activity, can that be picked up easily by the DPK or not. That's why we are moving toward a more specific, more sensitive analytical method.

ACTING CHAIRMAN DRAKE: Please?

DR. STERN: May I just respond, because --

ACTING CHAIRMAN DRAKE: But discussion, no. If it's a question, yes.

DR. STERN: It's the issue of what it means to be sensitive. The way I think about this is we have whatever we want to call the gold standard on the right side of the equation as the dependent variable, which is clinical response. On the left side of the equation we have DPK.

If there is more variance in DPK than

there is in clinical response, that is not more precision but, in fact, that's a less good predictor of clinical response.

So the idea of sensitivity for things on the left side of the equation that have more variance and are not well correlated with the -- are not good predictors on the right side, to me, does not mean sensitivity.

So that is, I guess, a difference in interpretation.

DR. SHAH: No. It is actually the opposite, and we are trying to --

ACTING CHAIRMAN DRAKE: I'd like to let Dr. Wilkin -- I want to make sure everybody gets to address a question. Dr. Shah, we will come back to you. Yes.

DR. SHAH: Could I respond to the second question, please?

ACTING CHAIRMAN DRAKE: Yes, you may. Please. Then I'll have Dr. Wilkin respond.

DR. SHAH: Second question was with respect to how long do we keep the drug on the stratum

corneum before we take the samples. More or less, that's what it was.

Well, we have seen in the experiments that the drug diffusion through the stratum corneum is very rapid. In fact, within 15 minutes you can see the drug has already gone down into the deeper layers.

So the prime reason why we are trying to take a look and see these samples at earlier time point is really to pick out any differences between the test and the reference product with respect to its ability to penetrate, the rate at which it is going down, the rate at which it is diffusing through the stratum corneum, and then trying to see how long it remains into the stratum corneum, the rate of disappearance.

These factors would really add in our estimation of the rate and extent of variability between the two products.

ACTING CHAIRMAN DRAKE: Dr. Wilkin.

DR. WILKIN: Well, I think Dr. Shah responded to the second, and I will just respond to the first question, and perhaps Dr. Tang may want to

jump in on this, because I think it has to do with the statistical notion of the difference between accuracy and precision.

In essence, we are going to have a DPK output. We are going to compare that with a clinical trial output. The first question is are they -- is the point estimate going to be the same for both? Are they answering the same kind of question?

A different way of looking at it is how closely the actual data points cluster about what the true meaning is. There can be a lot of precision for -- and I think there probably will be a lot of precision for DPK. The question is, is it really accurate? Is it going to give us a precise answer to the right question?

In the end, it may actually -- With the kinds of studies we have been talking about, we may believe that it is going to be an accurate predictor, but then precision may be a problem. It may be overly precise.

It may actually be a less expensive way to develop generic products, but it actually might be a

higher hurdle. You can think of it as a goal post, a couple of feet wide, because it's the dataset.

ACTING CHAIRMAN DRAKE: Dr. Anderson and then somebody else had their hand up. Dr. Lamborn, okay, and Dr. Miller. Okay. But Dr. Anderson first.

DR. ANDERSON: Dr. Wilkin, you listed a number of concerns during your presentation. I would just like to know if there exists a brief analysis of your concerns and a side-by-side response to those, what is being done or what could be done, etcetera, etcetera.

DR. WILKIN: Well, I haven't seen a side-by-side response to those particular concerns, but I think it's because my concerns are based on the -- I see two ways to getting to the acceptance of the DPK methodology, as Dr. Shah has proposed its regulatory utility.

One would be getting there with first principles, and the other would be there on a more pragmatic pathway with substantive data. I don't think that the first principles pathway is going to work. I haven't heard responses actually to each one

of my concerns about getting there with first principles, but I think Dr. Shah and others have focused instead on that second pragmatic pathway of, you know, how do we come up with the correct dataset that they can bring back to the Joint Advisory Committee.

So that's my interpretation, but since I was the one that came up with the list of concerns, I am maybe not the one to really ask about the response to those concerns.

ACTING CHAIRMAN DRAKE: Dr. Shah, did you want a moment to respond to that?

DR. SHAH: Well, as you saw it in my presentation, we have moved away from calling this dermatopharmacokinetics as the skin level concentrations to the stratum corneum concentration. I think this was again brought up at the last meeting, and we have changed that.

So today, like I have referred to as definitely a stratum corneum concentration. We are definitely not taking a look at the vaginal drug products. I clearly indicated that we are moving away

from that.

So, you know, we have taken some of these concerns very clearly to address the issues, because as it comes up -- Our goal is not to keep on saying exactly the same thing, but try to make an improvement and move so that we can move forward with it.

ACTING CHAIRMAN DRAKE: Dr. Lamborn, and then Dr. Miller, and then Dr. -- Well, just let me interrupt. Dr. Tang, is yours in reference to this question? Okay, I'll come to you in a minute then. Okay, Dr. Lamborn.

DR. LAMBORN: I'd like to follow up on the question of potentially over-precision of the DPK, because it is my understanding that, obviously -- that the thought was that, if the DPK was the same, then this would result in clinical equivalence.

The question was then if, in fact, it was different, does that imply that it is going to be meaningful clinical differences? Are you planning with this guidance to say that you must demonstrate DPK equivalence or I know in some instances you provide alternative ways which would say that you may

demonstrate it either by DPK or by demonstrating equivalence in a clinical environment, if you felt that that was an alternative method? What is the intent at this point of the guidance?

DR. SHAH: Right now the intent is it should be documented as bioequivalence using the DPK methodology.

DR. LAMBORN: And the clinical would not be an alternative?

DR. SHAH: That's right.

ACTING CHAIRMAN DRAKE: Dr. Miller.

DR. MILLER: This is for Dr. Shah, just clarification. On the clinical data, Dr. Shah, that you presented on the tretinoin, you said that B equaled A, but C did not; but C was efficacious.

Was it as efficacious as B and A? Then are there preliminary dermatopharmacokinetic studies on C at this point?

DR. SHAH: Okay. That's a very good question, and that question comes back, really, to the heart of the whole discussion which Dr. Wilkin had even pointed out in his slide that he would like to

see this as a three-prong study completely blinded, and that's the way we are doing it.

You are correct in identifying that A and B and the same, clinically exactly the same. They are completely interchangeable. But A and C are clinically different. They are not the same, but the product was approved because it was shown to be superior than the placebo.

So that is the way we are doing it. It is completely blinded, and we are hoping next time when we meet we would be able to present this data, and again going back to what Dr. Lamborn indicated, hopefully, the DPK would be the same for the two products and different for a different product.

Again, we don't know. It's a completely blinded study, and it is ongoing.

DR. MILLER: Then my second question was on the clobetasol studies. The emollient -- The dermatopharmacokinetics, there was less concentration with the emollient product. Is that correct?

DR. SHAH: That is true.

DR. MILLER: And do we have clinical

correlation there? Is the emollient less effective clinically than the others, but had the higher --

DR. SHAH: Yes, that's true, Doctor. The PDR very clearly says that the emollient could be applied up to four weeks, whereas the non-emollient should not be applied for more than two weeks, again indicating that the potency -- how it could be applied. That's an indirect evidence of its activity.

I was very, very much surprised to see that type of DPK data, which again starts supporting some of our thinking process that we have.

ACTING CHAIRMAN DRAKE: Okay. I have Dr. Tang, Mindel, DiGiovanni, and King. Dr. Tang.

DR. TANG: Is this one?

ACTING CHAIRMAN DRAKE: Yes.

DR. TANG: This is regarding to the rationale issue. You have the DPK and the two drugs are reference and the to-be-tested ones. You have to see that clinical efficacy is reflected in the reference gel, for example.

I know you show the equivalence. I know you infer that the new drug is going to be effective.

I think right now what is lacking is from this DPK, how do you infer that this is clinically -- you infer clinical efficacy. This will also depend on, as Dr. Wilkin showed Netter, that not only the type of gel or retinoids and also depends on the type of diseased skin.

I think you ought to factor the type of diseased skin into this study design, because the key thing, I think, is generalizability. How can you generalize this to a future product?

ACTING CHAIRMAN DRAKE: The question -- If I may just add a little point of clarification, and this was brought up at the previous Committee meeting, is the issue of diseased versus healthy skin, a very important point.

I didn't see any data presented today regarding that, and I think the question is do you have data regarding diseased versus healthy skin? I mean, that's at least a part of what you are asking.

DR. TANG: Right. I think you ought to -- I mean, the dermatologists can really say more about it. Maybe you should somehow classify the disease

types, skin types.

ACTING CHAIRMAN DRAKE: Yes. That's kind of getting into discussion, but let me just ask a very -- For those of you who haven't been with me in a committee meeting before, I try to get all the fact on the table. Then it saves a lot of time when we get to discussion, because we've got all the facts there.

So factually, have you done, as suggested in one of the previous committee meetings, studies on diseased versus healthy skin?

DR. SHAH: If you are thinking about having a stratum corneum concentrations on the diseased skin, which is DPK, it's impossible to get the stratum corneum. When there is no skin, how can we get that?

So, but we have some evidences, done by Dr. Lynn Pershing again, which would be supporting the fact that indirectly how it has been measured, but there is no direct measurement of the diseased versus healthy skin.

ACTING CHAIRMAN DRAKE: Dr. Mindel.

DR. MINDEL: I have been on the previous

two committees that looked at this methodology. The new data is the clobetasol data. I had trouble -- a little trouble following that slide.

I want to ask one specific question, but first I would like to know where is that published? Is it in the peer reviewed literature, you know, so it could be referenced, because since it is the only new data since '98, it would have been nice to have been able to look at it prior to seeing a slide that was very small.

One of the questions I have -- I mean, I would like to understand what the ordinates and so forth are, but for the drug that has lower equivalency it says that -- it indicates that the neighboring region has a higher level. At least, that's my interpretation.

I'd like some explanation as to what neighboring region, how it was measured, and what that interpretation means, if there is more drug there than in the other products that have the better bioavailability.

ACTING CHAIRMAN DRAKE: Dr. Shah?

DR. SHAH: It's published in the journal called Skin Pharmacology and Applied Skin Physiology, Volume 12, page 34-45. I think that is in 1999.

ACTING CHAIRMAN DRAKE: Just as an aside, for future reference, when this committee meets in the future, I would respectfully ask that any pertinent publications like that be included in our packet ahead of time, because that would help us all understand it a little better, and I think help us address your questions a little better.

DR. SHAH; Sure. I will definitely try to do that. This reference as well as any of the pertinent papers that might be coming out on this research.

ACTING CHAIRMAN DRAKE: Then just quickly, maybe you could help address Joel's other question.

DR. SHAH: Yes, that's true. What happens is the neighboring area is one centimeter away from the main area where the drug was applied. This being an emollient in nature, the drug spreads out, and as a result in the main area you do not see it, but with the emollient it just goes out, and that's where the

higher concentration was seen.s

So the adjacent area is about a centimeter away from the main application of the area.

ACTING CHAIRMAN DRAKE: Joel? Okay?

DR. MINDEL: Well, I think that raises questions, I think, that are better asked by the dermatologists than by me.

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

DR. DiGIOVANNI: I had two questions, the first one, I believe, for Dr. Shah, and the second one for Dr. Wilkin, and it has to do with the tretinoin research that is apparently ongoing.

I don't believe we are privileged to see the protocol or how that research is being done, but it was implied that, if there was a correlation between the stratum corneum kinetics and clinical efficacy between different tretinoin products, that that would be evidence supporting its predictability.

My concern is that, as the FDA well knows, it is very difficult with different products to do clinical studies -- to compare different clinical

studies and to do clinical studies to show small differences between products.

Are these clinical studies now ongoing together in a blinded fashion? Is the Retin-A gel being compared directly to the tretinoin gel and the Avita gel or is this something that has been extracted from prior studies which have been done at different times in different places and with different parameters?

ACTING CHAIRMAN DRAKE: Dr. Shah?

DR. SHAH: Okay. Just to answer, the clinical studies are not being conducted. Well, now when you say the clinical, you mean the actual on the patients. That information was derived from the submissions.

What is being done right now exactly is the DPK study which will correlate with the clinical studies done earlier. So we are doing a DPK study comparing these three products at the same time on the same subjects, on the same set of subjects.

DR. DiGIOVANNI: My second question is for Dr. Wilkin. That is: If this sort of a study done in

this fashion demonstrates the predictability of stratum corneum kinetics for correlating with efficacy with respect to tretinoin in acne, would you expect that that would hold for other agents which have actions at different end organs? For example, if someone wanted to show effect of minoxidil on hair growth on different preparations, would you think that that would also -- and that all other agents -- that this would support all of those different agents which act at different places?

DR. WILKIN: No. But I can always add a few words to that. No, I showed, you know, the Netter cartoon of the histology of the skin. The skin is composed of a lot of different components. It really is not just Saran wrap covering human beings. It's got a lot of different pieces to it. There are different ways that topical products get to those sites of action.

So I think that the kind of information coming out of the dataset that we are talking about will have a limited but possibly useful utility.

ACTING CHAIRMAN DRAKE: Dr. King?

DR. KING: I guess where I came in on this was we were considering the issue of antifungals plus topical steroids that are potent. So one of the thoughts I came away from that was there's a difference between bioavailability and clinical response. That's a given. Okay?

Then the question I have really is quite simple. If we have such differences in sites, thick skin versus thin skin, face, eyelid, etcetera, and then we have differences in age such as pediatrics and geriatrics, and then we have a difference in gender, how can some testing of forearm with think skin on the normal adult be predictive in a reliable way for the whole body, including stratum corneum anywhere else and dermis in the follicles?

It seems to me a great leap of faith which I would not like to take that parachute.

ACTING CHAIRMAN DRAKE: Okay. Is there a question tagged onto that?

DR. KING: The question is how are they going to get to the issue --

ACTING CHAIRMAN DRAKE: To all these other

things?

DR. KING: Other issues, which is site, age, gender.

ACTING CHAIRMAN DRAKE: Site, age, gender, hydration, hair bearing versus non-hair bearing? I mean, there is a whole plethora of diseased versus nondiseased.

DR. KING: Right. Well, you can add to addendum that. For cosmetics, you have to make sure the irritancy rate is something less, like one percent, because lots of us are atopic, and you put certain kinds of things around the eyes, you are going to get a bad response. So one percent of a huge number is still a huge number.

ACTING CHAIRMAN DRAKE: Okay. We are drifting just a little bit toward discussion, but it's okay just to touch. Dr. Hussain and then Dr. Shah.

DR. HUSSAIN: No, I was trying to respond to that question.

ACTING CHAIRMAN DRAKE: I'm asking you to respond to it, yes. I'm sorry. I was hoping you would respond. I saw your hand.

DR. HUSSAIN: I think the key issue here is, in the sense, when you are comparing two formulations which will be used in different clinical scenarios, situations, sites and so forth, would they provide the same exposure under those conditions?

We have sort of debated this issue quite a bit 30 years ago. The same debate is coming back. We debated this with orals, for example. The science -- The physical sciences and the biopharmaceutical sciences essentially are focused on the drug concentration, dynamic activity.

Once you start with that as a starting point, irrespective of the membrane that you use, whether you don't even use a membrane, I think the comparative effect of the two products will generally be similar.

So in the dermatopharmacokinetics we are essentially, in many ways, looking at somewhat of a worst case scenario where you have an intact stratum corneum. That is the rate limiting step. What that is suggesting is the dynamic activity is essentially the same.