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UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG EVALUATION

AND RESEARCH

- - - - -

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

AND DERMATOLOGIC AND OPHTHALMIC DRUGS

ADVISORY COMMITTEE

- - - - -

JOINT MEETING

- - - - -

FRIDAY

OCTOBER 23, 1998

- - - - -

The Committees met in the First Floor Conference Room, 5630 Fishers Lane, Rockville, Maryland, at 8:00 a.m., Robert Taylor, ACPS Chairman, presiding.

PRESENT:

- Robert Taylor, M.D., Ph.D.
- Joseph McGuire, M.D.
- Kathleen Lamborn, Ph.D.
- John DiGiovanna, M.D.
- Robert Branch, M.D., FRCP
- Arthur Goldberg, Ph.D.
- Eduardo Tschen, M.D.
- O. Fred Miller, M.D.
- Stephen Byrn, M.D.
- Gayle Brazeau, Ph.D.
- S. James Kilpatrick, Ph.D.

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PRESENT: (con't.)

Jacqueline Goldberg
Desmar Walker, M.D.
Michael Mayersohn, Ph.D.
Joel Mindel, M.D.
James Stewart, Ph.D.
Philip Lavin, M.D.
Eva F. Simmons-O'Brien, M.D.

ALSO PRESENT:

Roger Williams, M.D.
Vinod Shah, Ph.D.
Martin Okun, M.D.
Hans Schaefer, Ph.D.
Surendra Shrivastava, Ph.D.
Mary Fanning, M.D.
Lynn Pershing, Ph.D.
Jonathan Wilkin, M.D.
Howard Maibach, M.D.
Kimberly Topper, ACPS Executive Secretary

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

8:05 a.m.

1
2
3 DOCTOR TAYLOR: I would like to call the
4 meeting to order. This is the Joint Meeting of the
5 Advisory Committee for Pharmaceutical Science and the
6 Dermatologic and Ophthalmic Drugs Advisory Committee.
7 Before we introduce our committee by committee, I'd
8 like to have Kimberly Topper give us some
9 administrative guidance.

10 MS. TOPPER: The following announcement
11 deals with the issue of conflict of interest with
12 regard to this meeting and is made as part of the
13 record to support even the appearance of such at this
14 meeting. Based on the submitted agenda for the
15 meeting and all financial interests reported by the
16 Committee participants, it has been determined that
17 since the issues to be discussed by the Committee will
18 not have a unique impact on any particular firm or
19 product, but rather may have widespread implications
20 to all similar products in accordance with 18 USC
21 208B, general matters waivers have been granted to the
22 members and consultants participating in today's
23 meeting. A copy of these waiver statements may be
24 obtained by submitting a written request to FDA's
25 Freedom of Information Office, Room 12A30 of the

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1 Parklawn Building.

2 -- the discussions involving the other
3 products or -- not already on the agenda for --
4 financial interest, the participants are aware of the
5 need to exclude themselves from such involvement and
6 their exclusion will be noted for the record. With
7 respect to all other participants, we ask, in the
8 interest of fairness, that they address any current or
9 previous financial involvement with any firm whose
10 products they may wish to comment upon.

11 Thank you.

12 DOCTOR TAYLOR: I am Doctor Robert Taylor.
13 I am Professor of Medicine and Pharmacology at Howard
14 University and chair the Pharmacology Department there
15 and I will serve as the Chair for today's meeting.

16 What I'd like to do at this point is to
17 have the committee members introduce themselves.
18 We'll start to my far left.

19 DOCTOR LAVIN: Philip Lavin, Boston
20 Biostatistics Research Foundation.

21 DOCTOR OKUN: I'm Martin Okun. I'm a
22 medical officer at -- Products.

23 DOCTOR WILKIN: Jonathan Wilkin, Division
24 of -- Products, FDA.

25 DOCTOR STEWART: Jim Stewart, College of

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1 Pharmacy, University of Georgia.

2 DOCTOR MINDEL: Joel Mindel, Departments
3 of Ophthalmology and Pharmacology, Mt. Sinai Medical
4 Center, New York.

5 DOCTOR SIMMONS-O'BRIEN: Eva Simmons-
6 O'Brien, Departments of Dermatology and Internal
7 Medicine, Johns Hopkins School of Medicine, Baltimore,
8 Maryland.

9 DOCTOR MAYERSOHN: Good morning. Michael
10 Mayersohn, College of Pharmacy at the University of
11 Arizona in Tucson.

12 MS. GOLDBERG: Jackie Goldberg, consumer
13 representative, Dermatologic --

14 DOCTOR BRAZEAU: Gayle Brazeau, Department
15 of Pharmaceutics, University of Florida, College of
16 Pharmacy.

17 DOCTOR MCGUIRE: Joe McGuire, Pathology
18 and Pediatrics, Stanford. I'm a member of the
19 Dermatologic and Ophthalmic --

20 DOCTOR LAMBORN: Kathleen Lamborn --
21 University of California.

22 DOCTOR DIGIOVANNA: John DiGiovanna,
23 Director of Division of Dermato-Pharmacology at --
24 University School of Medicine and Adjunct Investigator
25 at NIH and I'm a special government employee for the

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1 Dermatologic Drugs Advisory Committee.

2 DOCTOR BRANCH: Bob Branch, from the
3 University of Pittsburgh, Center of Pharmacology.

4 DOCTOR GOLDBERG: Arthur Goldberg,
5 independent consultant, San Francisco.

6 DOCTOR TSCHEN: Eduardo Tschen, Department
7 of Dermatology, University of New Mexico.

8 DOCTOR MILLER: Fred Miller,
9 Dermatological and Ophthalmic Drugs Advisory
10 Committee, Dermatology Gysinger Medical Center,
11 Pennsylvania.

12 DOCTOR BYRN: Steve Byrn, head of
13 Industrial Pharmacy, School of Pharmacy, Purdue,
14 Pharmaceutical Sciences Advisory Committee.

15 DOCTOR WILLIAMS: Roger Williams, Center
16 for Drug Evaluation Research, Office of Pharmaceutical
17 Science.

18 DOCTOR SHAH: Vinod Shah, Pharmaceutical
19 Science at Duke.

20 DOCTOR TAYLOR: Okay. Thank you. What
21 we'd like to do today is to move through the agenda.
22 I'd like to stay on time. I know that there are a
23 number of issues that you'd like to hear the committee
24 discuss. We will hopefully have a good discussion of
25 those issues. But I'd like to implore those

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1 individuals that are making presentations to be
2 succinct and make their points on schedule.

3 We move immediately to comments by Doctor
4 Roger Williams on the Science/Technical and Regulatory
5 Strategies. Doctor Williams.

6 DOCTOR WILLIAMS: Speaking on behalf of
7 the Center for Drug Evaluation Research, I'd like to
8 welcome members of both Advisory Committees to a day
9 of discussion that I think promises to be both
10 interesting and exciting. Before I get too far into
11 it, I will thank all the members for helping us with
12 I think some challenging science and technical issues,
13 and I would also like to note that there are a lot of
14 FDA staff who've worked hard to come before you with
15 the presentations. I thank them. And I also thank a
16 very distinguished panel of experts and public
17 speakers who will be with us today to talk about this
18 important topic.

19 At the risk of boring the committee from
20 yesterday, the Advisory Committee for Pharmaceutical
21 Science, I'm going to review very quickly some of the
22 overheads that I showed yesterday to see if I can set
23 the stage for the discussion.

24 First of all, my section of the Center,
25 the Office of Pharmaceutical Science, is working on a

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1 series of guidances that will elaborate on and
2 otherwise elucidate the 1977 regulations that require
3 documentation of bioavailability from pioneer
4 manufacturers and bioequivalence from generic
5 manufacturers and also bioequivalence for all
6 manufacturers in the presence of certain post-approval
7 changes.

8 For the particular topic today, we're
9 going to be focusing on drugs that are administered
10 topically. We have two other main guidances: the
11 focus on drugs administered orally, drugs administered
12 nasally, and drugs administered via oral inhalation.
13 About 90 percent or more of the drugs that my center,
14 the Center for Drug Evaluation and Research, approves
15 are in this category.

16 These are a complex series of drugs and
17 dosage forms that have a key feature which makes
18 bioavailability and bioequivalence difficult. Namely,
19 they do not produce relevant measures in the blood on
20 which we can rely for the determination of
21 bioavailability and bioequivalence. I'll say a few
22 more words about that in just a minute.

23 Following me will be Doctor Shah who will
24 introduce the specific elements of this guidance, but
25 I would say a lot of our discussion today will be

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1 focusing on that particular topic,
2 dermatopharmacokinetics as a modality to measure
3 bioavailability and bioequivalence. Let's go on.

4 To remind the new committee members who've
5 joined us today, for a generic product we have a very
6 well evolved system of drug evaluation that was put
7 in place in 1984 by the Hatch-Waxman Amendments to the
8 Food, Drug and Cosmetic Act. It requires a
9 documentation of pharmaceutical equivalence relative
10 to a listed drug. Pharmaceutical equivalence focuses
11 on these four factors, and they will not be discussed
12 today. For the most part when we're dealing with
13 topical products, we are dealing with well-
14 characterized active ingredients, active moieties, and
15 we do not see that the CMC aspect of that is a focus
16 for the discussion today nor, in fact, a particular
17 science and technical issue insofar as topical
18 products are concerned.

19 We're going to be focusing particularly on
20 the documentation of bioequivalence and, as you can
21 see from this particular overhead, we have several
22 instruments available to us via the 1977 regulations
23 that allow documentation of both bioavailability and
24 bioequivalence. I've already alluded to the
25 measurement of the active moiety ingredients and

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1 biologic fluids. We can also use pharmacodynamic
2 comparisons, clinical comparisons, in vitro
3 comparisons, and other comparisons, as well.

4 I would say, as I said before, our
5 principal discussion today will be focusing on
6 something that I will call other
7 dermatopharmacokinetics. If a generic firm can
8 document this and this as well, then we can declare
9 that they are therapeutically equivalent and
10 interchangeable with the listed drug under all labeled
11 conditions of use. Let's go on.

12 These are our statutory definitions of
13 bioavailability and bioequivalence. I won't go into
14 them in detail, but they focus on the rate and extent
15 of absorption of the drug substance from the drug
16 product to the site of action and, as we heard in our
17 discussions yesterday, it's difficult to measure rate
18 and, for that reason, we've moved where we can to
19 systemic exposure measures and it's also difficult to
20 measure drug concentration at the site of action. But
21 our assumption is that systemic exposure measures are
22 the same and that they reflect the concentration of
23 the drug at the site of action. We are willing to
24 rely on systemic measures to document bioavailability
25 and bioequivalence for most drugs products.

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1 I will be showing the committee shortly
2 something that I've shown many times. It relates to
3 the three questions of interest. What is the
4 question? What are we willing to rely on? And how
5 confident do we need to be on the answer? The
6 questions, I would say, today relate somehow to
7 bioavailability and bioequivalence and, from a product
8 quality standpoint, we focus on the release of the
9 active moiety, the active drug substance from the drug
10 product.

11 Yesterday, we heard a very good point from
12 one of our public speakers that contrasts the interest
13 of the clinician versus the interest of the product
14 quality expert and, hopefully, there is not a
15 divergence between those two views but there is a
16 convergence to come to a good understanding of what
17 you need to show in terms of release of the drug
18 substance from the drug product to assure the
19 clinician of therapeutic equivalence and sameness
20 relative to bioequivalence.

21 This is probably one of the most key
22 slides that I want to show, and I showed it yesterday,
23 as well, but basically in the realm of product
24 quality we focus here on the drug product and its
25 active moiety or moieties. For bioavailability and

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1 bioequivalence we focus on release of that drug
2 substance from the drug product which creates an
3 exposure that can be reflected in terms of dose and it
4 can also create a systemic exposure which I've been
5 speaking about that can be reflected in terms of
6 measures or parameters of pharmacokinetics related to
7 concentration time curves.

8 In turn, we have the assumption, the
9 willingness to rely on these systemic exposure
10 measures that they will reflect efficacy and safety
11 end points that we care about for the treatment of
12 patients. I would regard the key question today, are
13 we willing for a topically applied product to
14 substitute systemic exposure for a stratum corneum
15 exposure metric or measure? That will be a key
16 discussion that you hear throughout the course of the
17 morning and in the deliberations later on in the day.

18 And then I think my final overhead just
19 reminds you of our questions. What do we want to
20 know? We want to focus on bioavailability and
21 bioequivalence. What are we willing to rely on? What
22 assumptions are we willing to make in terms of
23 surrogacy? Are we willing to rely on this exposure
24 metric in the stratum corneum? And then how sure do
25 we want to be? I would say this is not a principal

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1 discussion for today nor is this, although it
2 obviously relates to our criteria for comparisons,
3 confidence intervals, and bioequivalence that we
4 talked about so much yesterday in the context of
5 individual bioequivalence.

6 So I would say our main question for today
7 as we talk about dermatopharmacokinetics is our
8 willingness to rely on it to assure bioavailability
9 and bioequivalence. Thank you very much and, Doctor
10 Taylor, I'll take questions if there are any.

11 DOCTOR TAYLOR: Are there questions from
12 the committee?

13 DOCTOR DiGIOVANNA: Doctor Williams, you
14 showed pharmaceutical equivalence. It noted the same
15 active ingredient, but one of the unusual things that
16 happens with the skin is that sometimes the inactive
17 ingredients greatly affect what happens to the active
18 ingredients with respect to absorption. So, for
19 example, with certain steroids, the vehicle becomes
20 paramount as far as how much of that is going to be
21 delivered. Are those considered with respect to other
22 drugs, for example, the nonactive ingredients, when
23 they become actually the determinates of activity,
24 are those considered?

25 DOCTOR WILLIAMS: From a -- standpoint, I

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1 would say no. We have a clear definition of the
2 active moiety, the active ingredient in a drug
3 product. But I think, Doctor DiGiovanna, we're very
4 willing to take into account what you just said.
5 Therefore, a locally applied drug product, the
6 inactive ingredients can contribute to the overall
7 clinical effect.

8 DOCTOR TAYLOR: Any other questions for
9 Doctor Williams? If not, then we'll go directly
10 through the agenda. The next speaker is Doctor Vinod
11 Shah who will discuss the draft guidance.

12 DOCTOR SHAH: Good morning, and I'll be
13 making the presentation with respect to the draft
14 guidance and also the public comments. Everyone has
15 seen the copy of the draft guidance which is primarily
16 focusing on the topical dermatological drug products
17 and bioavailability/bioequivalence -- associated
18 studies.

19 I'll first briefly discuss the key points
20 which are in the draft guidance and then follow up
21 with some of the discussions on the public comments
22 and then what we have done since the public comments
23 and the draft guidance and then bring it back to the
24 floor.

25 We are all talking here about the topical

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1 dermatological drug product and the symptoms of the
2 processes which take place are topical drug products
3 involve the -- response whose onset, duration and
4 magnitude depends on the related efficiency of the
5 three sequential processes. Namely, the release of
6 the drug from the dosage form, penetration of the drug
7 through the skin area, the stratum corneum, and
8 generation of the desired pharmacological effect.

9 Just a few minutes ago we heard about the
10 possibility of some of the inactive ingredients that
11 might be affecting the drug penetration, and I think
12 we can discuss how those things could be really
13 addressed in terms of these dermatological --

14 This is just the overhead after draft copy
15 of the guidance which came out in June 1998 and the
16 main competence of the guidance included reflections
17 on the introduction about the guidance, the background
18 information, inactive ingredients, and that's where we
19 discuss some of the issues which are related to the
20 inactive ingredients, the bioavailability and the
21 bioequivalence approaches that are four approaches
22 that have been identified and one of the most
23 important ones we are looking here at this time is the
24 dermatopharmacokinetic approach and we are also
25 talking briefly on the pharmacodynamics and the in vitro

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1 release primarily for use as a bioavailable for the --
2 That will be discussed in the afternoon. And there
3 are three other sections which talks about the in
4 vitro release extension of the methodology, systemic
5 exposure studies, and the CMC, the chemistry
6 manufacturing controls.

7 We would like really to focus today, as
8 Doctor Williams indicated, on the
9 dermatopharmacokinetic approach for the
10 bioavailability/bioequivalency measures and in vitro
11 release aspect for the lower drugs.

12 This draft guidance was issued on June 18,
13 1998 and in the draft guidance we had the preamble
14 which indicated that "FDA welcomes the submission of
15 data that supports or refutes the use of the
16 dermatopharmacokinetic approach." Also, we had
17 requested that relevant clinical data,
18 dermatopharmacokinetic data, in vitro release data for
19 -- evaluation of bioavailability/bioequivalence
20 approaches in the guidance be provided.

21 So we had been out in the forefront
22 indicating this is what we are intending to do and we
23 went out to the public to all the industry people, all
24 the scientists, indicating please send us the data,
25 provide us the data in this area if you have it in

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1 your files so that we can take a look at it and
2 evaluate it before we finalize the guidance. We also
3 indicated in the guidance that our intentions were to
4 take -- and discuss it with the issues we identified
5 earlier in presence of the Joint Advisory Committee
6 meeting, the Pharmaceutical Sciences Advisory
7 Committee and the Dermatological Advisory Committee,
8 and that's why we are here today to seek your advice
9 and input on some of these issues.

10 We saw this information on a previous
11 presentation from Doctor Williams, but here it is
12 presented slightly differently, as to what is a
13 pharmaceutical equivalent and what is a
14 bioequivalence, how do we determine that, and once
15 these two factors are put together, we come up with
16 the therapeutic equivalence. Here we are talking
17 about the same active ingredient in the same strength
18 and the same dosage form and route of administration.
19 I would like to discuss here the same type of the
20 dosage form because what we are talking here is
21 comparing a cream versus cream product or an ointment
22 versus an ointment product.

23 We are not here to discuss the cross
24 comparisons such as the discussion between an oral
25 administration and a topical product or a cream

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1 product versus an ointment product. We are really
2 looking at the same type of a dosage form and same
3 types of administration.

4 In terms of the in vivo measurement, we
5 think we can achieve the bioequivalency using the
6 principles and the approaches of
7 dermatopharmacokinetics, we have some products for
8 which we are using the pharmacodynamic measures. In
9 cases where these two approaches are not feasible, the
10 other approach is the clinical comparisons which is
11 now being done in several cases. And the last
12 alterative is the in vitro comparisons, but we do not
13 use that by itself for waiving the bioequivalency of
14 the product.

15 When these two factors are met together,
16 then we come to the therapeutic equivalence and that
17 is the prime goal, reasons for the generic conditions.
18 If all these reasons are okay, if they are equivalent,
19 we can switch the product.

20 To summarize it again, we are talking
21 about the same percent of an active drug, same route
22 of administration, same dosage form category, cream
23 versus cream, ointment versus ointment, and gel versus
24 gel. In addition to that, the requirement now is once
25 the -- product is out, they have to identify on the

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1 label what it contains in terms of the inactive
2 ingredients and those are the inactive ingredients
3 which we call in the guidance and we just identified
4 as Q1. Qualitatively, they must contain the same
5 inactive ingredients and then we also have a class
6 where quantitatively also it should contain the same
7 proportion of the same amount or nearly the same
8 amount.

9 In today's technology, the generic
10 manufacturers, they go out and they do what is known
11 is reverse -- to identify and quantitate all the
12 inactive ingredients which is in the -- and by that
13 way, they know the amount and then they try to make
14 the product which is almost a copy of the generic
15 product. I'm sorry. Copy of the -- product. And
16 that's what we mean by here saying that the product
17 contains nearly qualitatively the same ingredients and
18 quantitatively almost the same types of composition.
19 With these factors, we can really confirm that the
20 innovative product and the generic product have nearly
21 the same inactive ingredients and that would really
22 address some of the questions that Doctor DiGiovanna
23 had presented earlier.

24 Next slide please. Now, let's go into
25 what is dermatopharmacokinetics, at least the way we

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1 see it is the dermatopharmacokinetic approaches
2 encompasses the drug concentration measurement with
3 respect to the time and provides the information on
4 drug uptake, apparent study -- levels and drug
5 elimination from the stratum corneum based on a
6 stratum corneum concentration -- profile.

7 Next slide please. For the bioequivalency
8 determination, the dermatopharmacokinetic approach we
9 feel is generally applicable to all topical
10 dermatological drug products. Again, I would like to
11 distinguish here between the dermatological drug
12 products and the TDS or the transdermal drug products,
13 transdermal drug products in the form of batches.
14 Even though they're applied on the skin, they are
15 primarily meant for the systemic activity and that is
16 not considered in today's presentation. We think that
17 the DPK principles can be primarily the means to
18 document the bioavailability and the bioequivalence
19 and, once we have documented the bioequivalency using
20 the DPK approach, the supporting information could be
21 generated from the in vitro release data and the
22 particle size distribution of the active ingredient.
23 Those are the factors which I have identified as
24 supporting information would be adding more strength
25 to the TPK principles when we evaluate that in terms

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1 of the bioequivalency.

2 Next slide please. The guidance makes the
3 reference to the bioavailability and the
4 bioequivalence and here what I am trying to identify
5 is the bioavailability information is coming from the
6 reference product approved based on the safety and the
7 efficacy data whereas the bioequivalency is for the
8 generic products or any time a firm needs to make a
9 comparison to the product which was already studied
10 and found to be acceptable such as even in the cases
11 of the IND when the firm wants to change the
12 composition or the process or something of that nature
13 or with the NDAs or with the ANDAs and also in the
14 case of the post-approval changes whenever a
15 bioavailability study needs to be compared with the
16 initial or the pre-approved product. Then it would be
17 the bioequivalency determination.

18 May I have the next slide please. As we
19 said earlier, the draft guidance was issued on June 18
20 and we had the comment period for 60 days which was
21 from June 18th through August 17th. Now, as a result
22 of the publication in *The Federal Register* and the
23 draft guidance, we had received five requests for the
24 extension of the comment period, but we had denied the
25 extension of the comment period. Then we had also

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1 received 15 comments from different sources, and I
2 would like to summarize what type of comments we had
3 received.

4 May I have the next slide. Again, as I
5 said earlier, our prime goal and the focus is on the
6 DPK approach and the bioequivalency determination of
7 that. Keeping the main aim in mind, we have divided
8 the comments we have received into the following four
9 sections. Those comments which supported the use and
10 application of the DPK, those comments which partially
11 supported that saying that yes, it could be useful for
12 only this type of drug or it can not be useful for
13 this type of drug and could be used for all the other
14 drugs or there were some comments which said they're
15 premature. By premature, I mean they said that yes,
16 it looks promising but we need to get some
17 information, some more data, before we can fully
18 launch on that.

19 Then we had some comments which did not
20 support the use and application of the DPK for the
21 bioequivalency and there was one commenter who did not
22 address any comment with respect to the bioequivalency
23 using the DPK approach. The numbers I have provided
24 here in each column are the same number that all the
25 experts on the planning committee and the advisory

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1 committee members have received, and it corresponds to
2 those appropriate numbers.

3 Totally, we had seven comments out of 15
4 which supported the use and application of the DPK for
5 bioequivalence. There was one comment which was we
6 can not make a clear cut determination whether it is
7 saying partially support is premature or it does not
8 support. When we read the whole package, in some
9 cases we think yes, they're supporting it. In some
10 cases, we say they're not supporting it and that's the
11 comment I have put here in circle and identified in
12 two columns so there are four or four and a half or
13 five, however you want to take it, said that it's
14 premature and it's only a partial support and two or
15 two and a half comments indicated the negative. There
16 was one comment which had no comment with respect to
17 this particular use.

18 Next slide please. The second issue that
19 we want to review is the use of the in vitro release
20 for the low extent. Again, we followed the same logic
21 as to how many were acceptable and not acceptable. In
22 this case, there was a clear cut distinction and there
23 were several comments which did not address this
24 issue. So of the total 15 again, we had two comments
25 which accepted and said this is a very good approach

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1 to do that. There were three comments which were
2 negative and 10 comments did not address this
3 particular issue.

4 Next slide please. So how do we address
5 all these comments which are going on and talking
6 about the transdermals and oral drugs and the skin
7 stripping comparisons and everything? We felt that it
8 would be best to take all the comments together and
9 see how we can address it with respect to our key
10 issues, the key issue being the DPK and how are those
11 comments.

12 All those comments when put together could
13 be rationalized into three different sections. The
14 first section being the rationale itself which talks
15 about coordination of the clinical data with the
16 dermatopharmacokinetic data and use of the healthy
17 skin versus the -- skin. As we know, the drug is
18 applied on the -- skin and the stratum corneum
19 stripping studies are done on the healthy skin. Well,
20 is there any correlation or what is the rationale?
21 How can we justify use of the healthy skin rather than
22 using the -- skin? About the regional variability
23 with the drug penetration. By that, I mean the
24 different area for the stratum corneum or having the
25 disimpermiabilities. If you apply it on the arm or

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1 the sole or the chest or the different parts of the
2 body, the drug penetration properties are different.
3 So how do we address those types of issues when we are
4 coming back to the issue of the bioequivalence?

5 The third point was what is the
6 relationship of the stratum corneum levels target site
7 with respect to the target site such as a predominance
8 -- or something below the second corneum levels? Is
9 there any relationship between these two levels that
10 we identified? And also the last question that came
11 up was what is the relativity of
12 dermatopharmacokinetic approach for the bioequivalence
13 determination? Knowing all these factors, can we
14 still use the dermatopharmacokinetic approach for the
15 bioequivalency determinations. So these were the four
16 major points which came out as a rationale from all
17 the different comments which we had received.

18 The second point was the methodology. How
19 do we do the validation? They said yes, it's a good
20 approach but there is some difference in terms of how
21 the validation will be performed, what number of tape
22 strips should they be using, what kind of availability
23 is used, different application sites, what kind of
24 dose response we give, and if there is a difference in
25 terms of the number of the tape strippings or the type

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1 of the tape strip being used, how can we validate all
2 those things?

3 Well, these are all the methodological
4 issues which will be addressed again in terms of the
5 validations. Once these two major issues are taken
6 care of, then the question comes up with respect to
7 the study design and the metrics. The pilot study,
8 the pivotal study and the statistics.

9 Today's presentations from all our experts
10 and the other members will be focusing initially to
11 start with on the rationale itself, what kind of
12 clinical data we have on the approved products that
13 could be correlated, is the DPK approach more
14 sensitive in terms of the consumer safety aspects
15 compared to the clinical studies, how can we handle
16 this, and what would be the rationale for having the
17 DPK for the bioequivalency determinations? Those
18 things will be addressed by some of the other
19 speakers. I'll identify those in a minute.

20 With respect to the validation, also I
21 think we'll be taking care of those issues in the
22 presentations as to how we will make sure that the
23 person, the individuals who are doing the studies is
24 doing a good validated procedure and then we will move
25 on with respect to the pilot and the pivotal studies.

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1 Next slide. In order to get some more
2 information with respect to the different products
3 which are already on the market to get some more
4 support with respect to the dermatopharmacokinetic
5 approach after the guidance, the draft guidance was
6 published in June. We launched some of the studies
7 which are identified here today. One is to take the
8 products which are equivalent, which are proved to be
9 equivalent using potent corticosteroid and a
10 pharmacodynamic measure because right now the current
11 guidance for the gluco-corticosteroid is to use the
12 pharmacodynamic measure and we took those two
13 products, potent corticosteroid to a -- the two
14 products, innovative product and the generic product
15 which are identical from all respects. We did the DPK
16 and we will show you the data that the products are
17 bioequivalent. From the DPK also you can come up with
18 the same conclusions.

19 Then we move down to the second set of
20 similar products which are again indicating to be
21 clinically different which are formulation why they
22 are different and dermatopharmacokinetic was also
23 there completely different. Again, the example is the
24 clobetasol where it is a comparison between the
25 Temovate and the Temovate E. These two products are

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1 made by the same manufacturer, Glaxo Wellcome, but
2 both have completely different labeling indicating
3 that those two products are not interchangeable, those
4 two products are different, and we will show you the
5 data how different they are.

6 Then following that, we will have taken an
7 example of a product which was approved clinically, an
8 antifungal product, and we will also show the
9 dermatopharmacokinetic data how sensitive the product
10 is, how sensitive the -- is. I would like to bring
11 here one more attention to the Advisory Committee
12 members that we had requested in the preamble and all
13 this time the forms for the sponsors to provide us the
14 information about DPK is the same for two products but
15 the products are clinically different or the DPK is
16 not predictive of the clinical efficacy data. In
17 spite of so many requests, we have not heard, we have
18 not received any information which would be supporting
19 these two documents, these two statements.

20 I just would like to bring it again to the
21 attention that we are trying to do the best to get as
22 much information as possible on the DPK before we
23 launch on this. May I have the next slide please.

24 So this slide sets the stage and also
25 indicates the different presentations, the order of

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1 the presentations that will be moving forward. After
2 my presentation will be the presentation by Doctor
3 Gordon Flynn who will be making the presentation on
4 the scientific basis of dermatopharmacokinetics.
5 Following we will have the dermatopharmacokinetic and
6 the clinical data on the formulation differences, the
7 clobetasol stories, with Doctor Martin Okun from --
8 providing the clinical information and Professor Hans
9 Schaefer providing the dermatopharmacokinetic
10 approaches and those data. Then we will discuss
11 briefly the procedures and the validation aspects
12 which was again one of the major -- presented from the
13 comments by Doctor Surendra Shrivastava from the
14 Division of Bioequivalence. Following that we will be
15 discussing the antifungal studies by Doctor Mary
16 Fanning and Lynn Pershing and we will be also then
17 discussing some of the perspectives of the
18 dermatopharmacokinetic aspects by Doctor Jonathan
19 Wilkin and we'll follow again with respect to the two
20 important issues which was the standard approaches
21 again by Professor Hans Schaefer and correlations on
22 the clinical relevance by Doctor Howard Maibach. Then
23 it will be followed by the committee discussions. So
24 I'll be happy to answer any questions on these general
25 comments if anybody has them, Doctor Taylor.

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1 DOCTOR TAYLOR: Thank you very much. Are
2 there questions by the committee members at this time
3 for Doctor Shah?

4 DOCTOR MINDEL: Joel Mindel. When you
5 gave the responses and categorized them, did you also
6 categorize them by whether they came from generic
7 companies versus makers of brand name and were there
8 any generic that argued against? What was that
9 correlation?

10 DOCTOR SHAH: Well, to be honest, no. We
11 put all the comments together and when we started
12 looking at it, we just added the numbers and took a
13 look at it rather than initially taking a look as to
14 from where the responses came. But yes, we do have
15 the names of the companies who came, from where it
16 came. Some of the responses are from the individuals
17 themselves and some are from the pharmaceutical
18 company. So it's all put together in these types of
19 responses.

20 DOCTOR MINDEL: Was there a correlation,
21 in your opinion, between the nature of the response
22 and the stationary head?

23 DOCTOR SHAH: Yes. I can not deny that.
24 There is a correlation on that and you can even
25 imagine the answers.

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1 DOCTOR TAYLOR: When you identify
2 yourself, if you'll also identify the company.

3 DOCTOR MAYERSOHN: Michael Mayersohn,
4 Pharmaceutical Sciences. The requests that you've
5 made on numerous occasions for additional data, do you
6 think there are no data and that's why they didn't
7 come forth or is there another explanation?

8 DOCTOR SHAH: No. I think there are no
9 data probably and some of the comments, if I put it in
10 a slightly different perspective, Doctor Mayersohn, it
11 says that when people are making cross comparisons or
12 any other area of comparison, they're saying that oh,
13 I gave this product orally and the concentration in
14 the stratum corneum is X nanogram. I gave this
15 product topically and the concentration is higher for
16 the same activity. Why? Well, you are doing the
17 cross comparisons apples and oranges rather than
18 comparing apples and apples and, therefore, I have not
19 seen any data from anywhere, even in the literature,
20 where the same product is given, same dosage from two
21 different cases, and there is a comparison of the
22 stratum corneum levels.

23 DOCTOR MAYERSOHN: So there's no general
24 experience to your knowledge.

25 DOCTOR SHAH: No.

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1 DOCTOR TAYLOR: If there are no other
2 questions, we'll move on to the next presentation.
3 Thank you very much. The next presentation will be
4 given by Doctor Gordon Flynn, discussing the
5 scientific basis for dermatopharmacokinetics. Doctor
6 Flynn.

7 DOCTOR SHAH: Unfortunately, Doctor
8 Taylor, I don't see Doctor Flynn here. I had talked
9 to him two days ago and he said yes, he will be here.
10 But I do not see him.

11 DOCTOR TAYLOR: We can move on and get his
12 presentation when he arrives.

13 DOCTOR SHAH: Okay.

14 DOCTOR TAYLOR: We'll move on to the DPK
15 and clinical studies and formulation differences and
16 Doctor Martin Okun will discuss the clinical studies.

17 DOCTOR OKUN: Good morning. In a few
18 minutes, Doctor Schaefer is going to present some
19 dermatopharmacokinetic data relating to penetration of
20 three different clobetasol propionate cream
21 formulations into the stratum corneum. An innovator,
22 Temovate, generic and innovator Temovate E. My
23 purpose here is to present some of the chemical,
24 pharmacological and clinical data relating to these
25 three different clobetasol propionate cream

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1 formulations.

2 The innovator and generic have an AB
3 rating. They are regarded as therapeutically
4 equivalent. The innovator emollient cream has a BX
5 rating because the data is insufficient to determine
6 if it is therapeutically equivalent to the Temovate
7 cream.

8 This overhead shows a comparison of the
9 composition of the three different clobetasol
10 propionate cream formulations. All three have the
11 same active ingredient, clobetasol propionate, at the
12 same concentration. Across the three formulations,
13 they share qualitatively several of the inactive
14 ingredients but quantitatively the inactive
15 ingredients vary across the three. In addition, one
16 of the noteworthy Q1 differences between the Temovate
17 E and the other two is the presence of dimethicone 360
18 which is functioning as an emollient in that
19 preparation.

20 The next overhead. This overhead shows a
21 comparison of the labeling features of these three
22 formulations. As you can see, all three are
23 classified as super high potent topical
24 corticosteroids in that their classification is based
25 on their equal performance in a multi-point --

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1 vasoconstriction assay. They all have the same
2 indication as a primary indication, treatment of
3 inflammatory and paretic manifestations of
4 corticosteroid responsive dermatoses. They have the
5 same duration of use, the same maximum permitted use.

6 In addition, Temovate E has another
7 indication, treatment of moderate to severe plaque
8 type psoriasis for up to four consecutive weeks. The
9 basis of this other indication is a supplementary
10 clinical efficacy study.

11 Next overhead. None of these three have
12 been compared with each other in a head to head
13 clinical efficacy study. We do have in the published
14 literature one comparison between the Temovate and the
15 Temovate E on the basis of clinical safety.
16 Specifically, it's a crossover study of HPA axis
17 suppression induced by one week's treatment with
18 Temovate or Temovate E and a two week wash out and
19 then another one week's treatment. Of course, among
20 the 12 patients enrolled in this study, Temovate
21 cream, the innovator, was slightly more likely to
22 cause some evidence of HPA axis suppression than the
23 Temovate emollient.

24 The number of patients in the study was
25 relatively small and it's unclear if it was of

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1 adequate size to detect the difference. The
2 difference we see here is not statistically
3 significant. The authors concluded from this studies
4 that the Temovate E is not more potent than the
5 Temovate cream. Again, there is no published study or
6 available data of comparing their clinical efficacy,
7 just the safety.

8 So in conclusion, Temovate and the generic
9 are regarded as therapeutically equivalent and there
10 is insufficient data to generalize any conclusions
11 comparing Temovate and Temovate E.

12 DOCTOR KILPATRICK: My name is Kilpatrick.
13 I'm from Kodak. I want to apologize for coming late.
14 Martin, what was the power of that study? You said
15 there was no statistical difference. Maybe a
16 difference --

17 DOCTOR OKUN: Well, they had 12 patients.

18 DOCTOR KILPATRICK: What's the power? The
19 power is negative.

20 DOCTOR OKUN: There was no power
21 calculated. My comment reflects my -- that it would
22 be dangerous to draw any far reaching conclusions
23 based on what is a comparatively small population
24 size.

25 DOCTOR DiGIOVANNA: John DiGiovanna.

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1 Marty, how was that study done? Was it done on same
2 patients, different patients? People apply creams in
3 very different fashions and very different amounts and
4 applying them to different lesions, for example,
5 different ceriatic lesions, you might get a tremendous
6 amount of absorption through one type of lesion and a
7 different amount at a different time through a less
8 inflammatory lesion. So what sort of control did they
9 do?

10 DOCTOR OKUN: This was a cross over study,
11 so the same 12 patients were used for both parts,
12 exposed both to the Temovate and Temovate E. These
13 were patients, six of whom had psoriasis, six had
14 eczema, 30 percent of their body surface area was
15 involved to get enrollment and 1.5 grains of each
16 cream was applied twice daily for a week to involve
17 the areas. So a lot of those concerns were addressed
18 by authors.

19 DOCTOR WILLIAMS: A question. Martin, did
20 I read that data right to say that most suppression
21 was observed when they didn't have any active adhesion
22 at all where you said no cream?

23 DOCTOR OKUN: No. Actually -- that's
24 right. Five out of the 12 patients did not have
25 suppression with either cream. That's correct.

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1 DOCTOR WILLIAMS: But HPA axis suppression
2 is not universally observed necessarily from use of
3 these topical corticosteroids.

4 DOCTOR OKUN: That's correct.

5 DOCTOR LAVIN: Philip Lavin. I'd like to
6 make the comment that in a study like that, as a
7 statistician, I have real trouble being able to make
8 any conclusions at all with a trial that size and for
9 an issue as important as the one you're trying to
10 address, you're going to be looking at at least a
11 minimum of 100 patients treated with all three
12 compounds in a way with adequate wash out to be able
13 to make any kind of conclusions at all. So I'm left
14 here and that really hasn't done anything for me to
15 give me any insights at all.

16 DOCTOR WILLIAMS: Again, I don't want to
17 belabor the point, Martin, but I've always had these
18 same reservations about this test we do. But it does
19 seem like in seven instances there's no active model.
20 I want to keep coming back to that, Martin, because it
21 really questions the whole study.

22 DOCTOR OKUN: I'm sorry. Perhaps I didn't
23 explain this clearly. All subjects are getting,
24 during the course of the study, both Temovate and
25 Temovate E. None of the subjects are exposed to just

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1 vehicle. So among the 12 subjects that were over the
2 course of a month exposed to both active treatments,
3 the majority did not have H P axis suppression with
4 either active treatment. Among those who did have
5 suppression with at least one of the active
6 treatments, the Temovate was slightly more likely to
7 cause HPA axis suppression than the Temovate
8 emollient. There was no vehicle control in this
9 study.

10 DOCTOR TAYLOR: What I'd like to do is to
11 move on with our agenda. We'll have an opportunity to
12 come back and make additional comments at the end of
13 the session.

14 The next presenter is Doctor Hans Schaefer
15 and he will discuss the DPK applications.

16 DOCTOR SCHAEFER: Good morning, everybody.
17 Since our friend, Gordon Flynn, is not in, I'll just
18 start by making some general comments. I think
19 everybody in the room will agree that next to a
20 clinical study, it's the drug concentration at the
21 target site which is relevant for investigations on
22 bioequivalence and bioavailability. Drug
23 concentration at the target site. So what is
24 happening when you apply in vivo a drug topically to
25 the skin? There is like you have surplus on the skin

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1 which then enters into the horny layer which creates
2 a reservoir -- and we will have to come back on this
3 term of reservoir -- from where to which the drug is
4 liberated and from where the drug then diffuses on to
5 the target tissues, that is epidermis, dermis, the
6 capillary network or other targets in the skin.

7 Now, in an idea case, in an ideal world,
8 you would want to apply radio labelled drug in its
9 original formulation to normal skin and to diseased
10 skin. After a defined time, of course, you would like
11 to remove the horny layer, the reservoir, then take
12 biopsies and then analyze what is in the biopsies in
13 terms of quantities of drug versus layers. Now,
14 that's what we did in the '70s in Berlin and I'll show
15 you just a very few examples. Next slide please.

16 We are talking about this process.
17 Reservoir. From there the drug goes into the skin and
18 from the skin it's leaving, elimination being uptake
19 by the blood vessels. Next slide.

20 And what we would like to do is to remove
21 the access, to remove the horny layer by stripping
22 with adhesive tape, to take bunch biopsies, then to
23 section these bunch biopsies, -- it to the surface and
24 to determine the radio activity in these slices. Next
25 slide please.

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1 We did this with a corticosteroid
2 triamcinolone acetonide in a number of cases. We
3 won't go into the details because these are very
4 complicated studies. Next slide. It's only to show
5 you that we did this on normal and on diseased skin.

6 Now the outcome. Quantification of the
7 drug of radio activity in the horny layer and
8 subsequent concentrations in the deeper layers of the
9 skin. That's what you see. This is unaffected skin
10 of a psoriatic patient. Next slide please.

11 Please pay attention to the correlations
12 between the two curves. Psoriasis patient.
13 Triamcinolone acetonide. Same preparation. Next
14 slide please. And diseased skin. The caveat being
15 stripping is much more difficult. Dermatologists
16 know that. It's more tedious, more difficult. It can
17 not be standardized due to the dynamics of the
18 disease, due to the dynamics of the lesions. However,
19 in some cases we could do that and that's what we see.
20 In other words, if you recall the former slides, there
21 is always a clear cut correlation between what is in
22 the horny layer, upper layers to deeper layers, versus
23 what is in the epidermis and the dermis. Next slide.
24 Same again. Only take a very few
25 strippings and again, here is a severe lesion and very

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1 high concentrations of the drug in the epiderm
2 subsequent to high concentrations in the horny layer
3 reservoir. Now, in variably, in autoradiography you
4 see the dark reservoir in the horny layer on the upper
5 side. There you see the reservoir and invariably you
6 see concentrations in the follicle duct, too.
7 Nevertheless, we have always found the same
8 correlations between concentrations in the horny layer
9 and concentrations in the skin, be it normal skin, be
10 it diseased skin.

11 Next slide please. There's another
12 example. This is -- and again, in the autoradiograph
13 you see the reservoir in the horny layer and you see
14 some drug in the follicles. Next slide.

15 Coming back to this. Now the question,
16 can we conclude from the reservoir from what we see by
17 taking away this amount which you saw in the horny
18 layer on what happened subsequently in the skin? Next
19 slide please.

20 In the past, we did already an
21 investigation with two corticosteroid hydrocortisone
22 preparations in order to establish whether there is a
23 correlation between in vitro liberation, the release
24 in vitro from the formulation, dermatopharmacokinetics
25 that is vasoconstriction, the classic test for

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1 efficacy of corticosteroids on normal skin, and skin
2 concentrations on normal skin and, in fact, we found
3 clear cut correlations.

4 Next slide. Coming from there, we asked
5 again the question. Can DPK, as assessed by tape
6 stripping, detect pharmacokinetic differences between
7 two preparations of the same drug compound in a
8 similar formulation before it becomes clinically
9 relevant because, as I understand, that is the key
10 question.

11 Next please. We started a collaborative
12 effort, FDA, myself and a team in Berlin, Professor
13 Sterry and his collaborators, Doctor Weigmann who's
14 here in the room and Doctor Lademann and a resident
15 student, plus a team of chemists in order to do the
16 following. To take again these three preparations
17 which I have been talking about and to apply them in
18 a controlled fashion -- and I'll show you how -- and
19 then to do the stripping technique and to verify where
20 we can see differences and how we can assess them.

21 Next slide please. So first of all, an
22 HPLC technique for a corticosteroid in the tape
23 strippings and the strips had to be established which
24 is not easy, I have to say. Next slide please. Then
25 without going into details, it's -- are being applied

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1 to the forearm in the -- fashion. Next please. All
2 three preparations. That is Temovate cream, USP and
3 Temovate E on different volunteers. You see the
4 randomizing process.

5 Next slide please. And that's what the
6 people did in Berlin. Skin surface. They applied to
7 the corticosteroid to the red area and within the red
8 area they took tape strippings in order to stay within
9 the area where the drug had been applied. Okay. Next
10 please. Now they have come off the study. Here are
11 the results. After 30 minutes, there is no
12 statistical difference between red and blue and
13 there's a clear cut difference between red and green.
14 That is, clobetasol propionate cream USP is equivalent
15 within the statistical areas to the Temovate cream
16 whereas Temovate emollient is distinctly different.

17 Next slide please. Here is what happens
18 over time. The green and the blue are within the
19 statistics similar whereas the red is clearly
20 different. However, we had a surprise. The Berlin
21 team had a surprise. They called and asked me
22 urgently to come to Berlin because they couldn't
23 explain why the first point was so low because, you
24 see, it's only half of what it should be. Now,
25 Professor Sterry came up with the idea. He said,

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1 Okay, let's look at vasoconstriction, and that's what
2 he did. Next slide please.

3 And now to the dermatological eye, you see
4 immediately here the vasoconstriction is clearly
5 refined to the application area. The next slide shows
6 the forearm of the same volunteer. Right is the
7 cream, left is the emollient. What do you see left is
8 a follicular, very follicular blanching, and what you
9 see, too, it's a bit difficult to see there, it creeps
10 sideways. So what this team did, they investigated of
11 how much of a corticosteroid in this case they found
12 next to the application site. Left and right.
13 Assuming that some creeping had taken place.

14 The next slide shows clearly yes, this has
15 happened. Whereas the red untreated skin, very little
16 concentrations found in the stripping next to the
17 application area. The blue Temovate cream, very
18 little in the adjacent area. The Temovate emollient
19 cream clearly creeping. It crept to the adjacent
20 area. And that is the explanation why they didn't
21 find the amount in the very center where they
22 stripped. It just had almost immediately crept
23 sideways.

24 Next please. So when I come back to the
25 question, the initial question, can we possibly find

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1 identities when they are identical and can we
2 distinguish differences when there are differences in
3 terms of the formulation. Dino, could you please take
4 the formulation slide back. This one and the one with
5 the formulation. Then to me, both questions in this
6 case answered with yes. We could as well show that
7 the two cream formulations were identical and I can
8 not see any reason how to assume that there would be
9 a clinical difference between the two of them despite
10 their identical kinetics. Whereas with the Temovate
11 E I suppose -- and I think it's up to the pharmacy
12 scientists in the room to address this. It's the --
13 derivative which makes the preparation creep which
14 makes it different and, as you see, without us knowing
15 it, we had seen it immediately. It was immediately
16 detected. So in other words, in our hands, this
17 approach is very sensitive and it's very reliable.

18 I will come back on other aspects of this
19 technique later in my second talk. Thank you for
20 your attention.

21 DOCTOR TAYLOR: Thank you. Doctor
22 Schaefer's presentation is open for discussion.

23 DOCTOR MCGUIRE: Doctor Schaefer, the
24 autoradiogram showed a lot of silver down in the
25 follicles and around the air bubble.

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1 DOCTOR SCHAEFER: Yes.

2 DOCTOR McGUIRE: You can't quantitate from
3 one slide, but it looked like there was as much silver
4 down in the follicle as --

5 DOCTOR SCHAEFER: Correct, but this is the
6 drawback of autoradiography that it only finds bound
7 material. It doesn't detect moving molecules because
8 in the process of diffusion, it just don't show up.
9 So autoradiography can be never be taken even for a
10 semi-quantitative analysis of what is going on in the
11 skin. It can show where something had been but it
12 doesn't show where it has been, so we never rely on
13 autoradiography to say anything. The only thing I'm
14 saying is that despite the fact that there is material
15 in the follicles, the method clearly distinguishes
16 between different formulations.

17 I have to assume that since there is a
18 barrier in the atral -- that the same repetition
19 process between formulation liberation to the
20 reservoir and then diffusion from the reservoir into
21 the tissue takes place in the follicle as well and to
22 the same extent. And that's why I assume that we find
23 what we find, that there is equivalence.

24 DOCTOR BYRN: Is the follicle a faster
25 route for the drug to reach lower levels of the skin

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1 than through the normal skin if we just talk about
2 rates of drug penetration?

3 DOCTOR SCHAEFER: In this specific case,
4 I have to be very cautious for a very clear cut
5 reason. In diseased skin, to my mind though nobody
6 has shown that, the follicle route plays no role. It
7 will only play a role in normal skin, and we have done
8 a lot of work on this and published on this, how this
9 occurs and to what extent it occurs. Yes, in fact, at
10 the very onset, it can be prominent and then it levels
11 out.

12 DOCTOR TAYLOR: Doctor McGuire.

13 DOCTOR MINDEL: One more question. I just
14 want to make sure that I understand what you were
15 telling me which is that the total pharmacologic
16 effect of Temovate E, if you take the target area plus
17 the creep area, is if you integrate those two areas,
18 you get the same as you do for Temovate in the target
19 area.

20 DOCTOR SCHAEFER: No, I'm not saying that.
21 Just the opposite. I'm saying restricted to psoriatic
22 plaque. When you will do the same, you will see less
23 efficacy of the Temovate E because part of it has
24 crept sideways to the normal skin, not involved skin,
25 unless you assume that there is an interaction between

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1 normal and diseased skin in the healing process, which
2 I don't think.

3 DOCTOR MINDEL: That's not what I'm
4 getting at. I thought I understood you to say that
5 Temovate E was roughly equivalent to the Temovate if
6 you add the pharmacologic effect of the target to the
7 pharmacologic effect in the crept area. So you don't
8 have that creeping phenomena.

9 DOCTOR SCHAEFER: I can not say anything
10 to this, Joe, because we haven't investigated it.
11 This is very recent. It was a big surprise, this
12 phenomenon, because it hasn't been described in the
13 literature.

14 DOCTOR MINDEL: Do you think that the
15 irregularity at the vasoconstriction with the Temovate
16 E to the -- do you think that's follicular?

17 DOCTOR SCHAEFER: It looks like but what
18 Vinod has said, what Roger has said, as soon as you
19 add an enhancer, as soon as you add something which
20 influences the horny layer and its properties, then
21 this seemingly inactive ingredient of the -- is not
22 inactive. In my book, salicylic acid is inactive.
23 Urea is inactive. Propylene glycol 12 percent is
24 inactive because it changes the properties of the
25 horny layer of the reservoir such that the reservoir

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1 is different. So coming back to this is you can not
2 compare a given formulation with another one without
3 salicylic acid. You can not compare one with or
4 without urea and ask then for being equivalent.
5 However, you will detect the differences. You are
6 blinded and you have one with and one without, what
7 I'm saying is you will see that.

8 DOCTOR MINDEL: Joe Mindel. The first
9 step in the technique is to irrigate the skin, isn't
10 it? Is that correct, to irrigate the --

11 DOCTOR SCHAEFER: What do you understand
12 by irrigating?

13 DOCTOR MINDEL: To take some moisture and
14 dampen --

15 DOCTOR SCHAEFER: No, no. You apply the
16 corticosteroid under induced conditions as the patient
17 would apply it together with massage, of course, na
18 and this is important to know because massaging means
19 that you break the emulsion. The cream is no more a
20 cream. It falls apart. This is part of the
21 repetition process between the vehicle or the
22 ingredients of the vehicle and the active which leaves
23 the vehicle and enters into the reservoir.

24 DOCTOR MINDEL: I'm talking about when you
25 do the assay. When you're about to do the stripping,

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1 what is the first thing that you do?

2 DOCTOR SCHAEFER: We take -- and Y the
3 surplus of. Dry cotton. And then take two strips,
4 measure them but don't include them into the
5 calculation, knowing that the two strips, the track of
6 the two strips is not yet normal. The two strips
7 contain -- one or two, we can discuss about it but it
8 doesn't make a big difference. We put them aside.
9 They are measured. They're quantified. But they are
10 not included in the calculation, the subsequent
11 calculation, a comparison because these two strips
12 introduce a big factor for variability. That's the
13 only reason. And then we strip, in most cases, 15 to
14 20 times, take every single strip and put it into
15 efficacy and --

16 DOCTOR MINDEL: I have to apologize then
17 because my memory of this, I thought my reading was
18 that there was an initial moisture that was placed on
19 it.

20 DOCTOR SCHAEFER: You are not wrong.
21 There are instances with sunscreens where they are
22 very lipophilic where we recommend in this case for
23 toxicology purposes to do a mild washing because the
24 very little felicity disturbs the track of the tapes
25 and makes things subsequently very difficult. But

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1 this is a separate case. Perhaps that's what you had
2 in mind.

3 DOCTOR TAYLOR: Doctor Simmons-O'Brien.

4 DOCTOR SIMMONS-O'BRIEN: I'm from -- The
5 clinical photograph that you showed us, am I correct
6 in assuming that that was a person who had not ever
7 had any type of skin lesions, that was normal skin?

8 DOCTOR SCHAEFER: Correct.

9 DOCTOR SIMMONS-O'BRIEN: Then I guess I
10 have a question as to I understand what you saw and I
11 accept that, but then I guess what our concerns would
12 be is if a person actually had diseased skin and the
13 Temovate E was applied. Would they, in fact, not be
14 getting the amount of treatment that one would assume
15 they would be because it would leach from the diseased
16 area to the non-diseased area?

17 DOCTOR SCHAEFER: That's what I'm
18 assuming. Yes.

19 DOCTOR SIMMONS-O'BRIEN: Okay. But I
20 don't know that we can assume that when we're looking
21 at psoriasis and we're looking at variable thickness
22 of plaques. I think you would have to look at
23 psoriatic lesions on the same arm of that particular
24 individual, then make some determination that you're
25 dealing with similar lesions and maybe you can do that

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1 histologically and then put the applications of the
2 medicine on and see. I mean that would be a concern
3 that maybe you're not, but I don't know that you can
4 extrapolate that that would be the equivalent for
5 diseased skin.

6 DOCTOR SCHAEFER: But look, please let us
7 keep in mind that in dermatology we are in the
8 exceptional situation that in certain very, very
9 limited cases we can do pharmacokinetics on the target
10 site, on the disease target site. You hardly ever can
11 do that in normal systemic pharmacokinetics. You
12 wouldn't apply a drug under fever. You wouldn't do
13 that. So in other words, we shouldn't get confused by
14 what I said. I showed the correlation diseased skin
15 and horny layer. But this is not the point. The
16 point is can we conclude from normal skin
17 pharmacokinetics, dermatopharmacokinetics, as done by
18 stripping technique? Can we conclude on identity or
19 differences. Whether then they have an effect on the
20 diseased skin is a different question. If someone
21 comes up, same preparation, USP and salicylic acid,
22 exactly the case up, and I would say you will see that
23 in dermatopharmacokinetics but you can not no more
24 define by the equivalency. You are not allowed to.
25 It's this way around. You can clearly state when you

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1 can not do it and you can not do it when you leave the
2 simple formulations, when you come into to enter into
3 silicic acid into liposomes, into enhancers, all
4 things like this. Then, as Vinod said, you can not
5 compare pears to apples and we have to do a separate
6 assay. But however, in the case that they are
7 parallel, then you can show parallelism.

8 DOCTOR TAYLOR: Doctor DiGiovanna first.

9 DOCTOR DiGIOVANNA: Professor Schaefer,
10 you have an enormous amount of experience in this area
11 and I was impressed with the ability of what I would
12 consider a relatively small change in the vehicle, the
13 addition of, I guess, dimethicone to create such a
14 profound change in the distribution of the
15 corticosteroid. My question for you is are you aware
16 of any preparation of any active agent where a small
17 change in the composition changes the relative
18 penetration through the stratum corneum versus the
19 hair follicle versus the eccrine gland versus any
20 other mechanism that may exist?

21 DOCTOR SCHAEFER: Second part of your
22 question as to the follicle, I have to say I don't
23 know. I haven't found any publications and in our
24 place it simply hasn't been done. We have not
25 correlated stripping to follicle -- I should be clear

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1 about that.

2 The first part of your question, fine
3 differences and I would say if there are fine
4 differences in crystal size of a crystalline material,
5 in polymorphism or things like this, I'm quite
6 confident that you will see them. Let's say the other
7 way around. Someone would by mistake put 10 percent
8 propylene glycol into the preparation instead of five
9 percent, all the rest being equal, I would say yes,
10 you would see that.

11 DOCTOR TAYLOR: Doctor Walker.

12 DOCTOR WALKER: Desmar Walker -- Sciences.
13 I wanted to go back to your first question about the
14 hair follicle.

15 DOCTOR SCHAEFER: Professor McGuire.

16 DOCTOR WALKER: Yes. And Doctor Simmons-
17 O'Brien's comments on diseased versus normal skin. I
18 think if there's a difference in the distribution of
19 hair follicles between diseased and normal skin and we
20 can obviously see that there's uptake in the
21 follicles, I think it's important that those
22 differences that both diseased and normal skin be
23 looked at. I don't think that you can just
24 extrapolate and say that because you see something on
25 normal skin that your analysis based upon your skin is

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1 going to hold for diseased skin.

2 DOCTOR SCHAEFER: As long as we accept
3 that vasoconstriction is representative for the
4 therapeutic power of corticosteroids and we can show
5 on normal skin, vasoconstriction is done on normal
6 skin, never on diseased skin, as long as we can show
7 on normal skin there's a clear cut correlation between
8 vasoconstriction and DPK, then we have to accept that
9 this is relevant and representative for diseased skin
10 under different status because there is no such single
11 simple diseased skin. Psoriatic has 90 pictures and
12 other diseases have many varying pictures, different
13 areas. But I will come back to this point in my
14 second talk where I show other examples of normal
15 versus diseased skin and correlations between
16 different areas and different formulations and
17 different compounds and different concentrations.

18 DOCTOR TAYLOR: Doctor Branch.

19 DOCTOR BRANCH: Addressing that particular
20 issue, diseased versus normal. The point I think I
21 would like you to address in a more general way, it
22 seems to me that you have a more sensitive technique
23 looking for equivalence than the currently available
24 techniques. So one of the key questions in terms of
25 applying this in terms of new product formation is

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1 does this sensitivity increase or decrease as you go
2 from normal skin to disease phase? Does the ability
3 to discriminate two products change as you go from
4 normal skin to diseased skin? Is it the most
5 sensitive in the normal skin?

6 DOCTOR SCHAEFER: It loses sensitivity by
7 the very reason that when you do tape stripping after
8 we find this to eczemic skin, there are skin diseases
9 without eczema where there is no problem in respect to
10 this technique. As long as the horny layer and
11 epidermis is normal, you can do it. On eczemic skin,
12 you can not strip under normal and validated
13 conditions because sometimes large -- come off, small
14 -- come off, and anyway, the reservoir is different.
15 There is some creeping below the -- and very close to
16 the skin surface so the whole process becomes highly
17 variable and that's why I do not recommend at all to
18 ever apply this technique routinely to diseased skin.
19 And by the way, not to in vitro skin either by the
20 very same reason that it is after 24 hours of exposure
21 in the -- or another diffusion cell, the horny layer
22 doesn't come off any more in a regular fashion. It
23 comes off in an irregular fashion. So there are the
24 limitations.

25 DOCTOR BRANCH: So in terms of applying

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1 this to a policy, if you study normal people only,
2 you've got a high level of discrimination and you're
3 going to have a level of competence going from the
4 normal situation to the diseased situation that truly
5 is equivalent but from the point of view of people who
6 don't make the differences are found, it doesn't
7 necessarily mean that the product that is different is
8 going to be effective.

9 DOCTOR SCHAEFER: That's the risk we are
10 running.

11 DOCTOR BRANCH: There's trade off that
12 we're actually --

13 DOCTOR SCHAEFER: Absolutely. What I'm
14 saying to my students is in clinical assays you can't
15 differentiate between one, three, or 10, 300 and 100.
16 In pharmacodynamics, you can differentiate between
17 one, two, three, four, five. In pharmacokinetics, you
18 can differentiate between 1.1, .2, .3, .4, .5.
19 There's clear cut increase in sensitivity. Yes.
20 That's the trade off.

21 DOCTOR MAYERSOHN: Michael Mayersohn,
22 Pharmaceutical Sciences. I don't want to get into a
23 semantic argument. My understanding of the use of the
24 word active ingredient is something that's
25 pharmacologically accurate. The fact that a

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1 formulation component is pharmacologically inaccurate
2 doesn't mean it won't affect the release properties--
3 Correct?

4 DOCTOR SCHAEFER: Correct. -- of the
5 slide cycle. I'm working now in a cosmetic company
6 and for the cosmetic company urea is an active
7 ingredient.

8 DOCTOR MAYERSOHN: I understand. In these
9 arenas, the components other than the steroid -- I got
10 the impression that you were suggesting that when
11 there are formulation differences and the so-called
12 inactive ingredients affect formulation conformance,
13 that they can not be compared. Is that correct?

14 DOCTOR SCHAEFER: That's correct.

15 DOCTOR MAYERSOHN: Why do you say that
16 because if I have an enhancer which doesn't damage the
17 skin, for example, and I want to promote absorption,
18 I would certainly add it to the formulation. The
19 advantage to me would be that my product might perform
20 better.

21 DOCTOR SCHAEFER: Then you necessarily
22 have to compare two formulations when you're talking
23 about equivalence with the same enhancer.

24 DOCTOR MAYERSOHN: I'm not sure that
25 that's correct because whenever you have --

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1 DOCTOR SCHAEFER: That's what people from
2 FDA say.

3 DOCTOR MAYERSOHN: I know. When you
4 compare oral formulations, for example, that allow the
5 addition of so-called inactive ingredients that might
6 enhance disintegration or dissolution which is not
7 reproduced in a competitive product, it is still valid
8 to do a bioequivalent study, is it not? I don't see
9 the difference.

10 DOCTOR SCHAEFER: Okay. I admit that,
11 provided that you accept that then you will see
12 differences and you will have to say how much
13 difference do I meet and still state that it is
14 equivalent because I predict one product with
15 salicylic acid versus without salicylic acid one
16 percent and you will see a distinct difference. So
17 the difference, how much to admit?

18 DOCTOR MAYERSOHN: So the issue is how we
19 quantitate the difference and because we are unable to
20 distinguish that difference, you are saying you must
21 keep everything the same. Is that fair?

22 DOCTOR SCHAEFER: No. That's not my
23 business. That's up to these gentlemen.

24 DOCTOR MAYERSOHN: Would you comment.

25 DOCTOR SHAH: What we are indicating,

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1 Doctor Mayersohn, is the generic product must contain
2 the same inactive ingredients. That's in the law and
3 that's what we are comparing here. Since it's on the
4 label, the mere fact is people have -- that it may
5 contain an inactive ingredient like urea or propylene
6 glycol in different amounts, different concentrations,
7 may influence the drug activity in this particular
8 case. That's not the case with the respective oral
9 products. We don't know that. Let's put it that way.
10 We don't know that.

11 DOCTOR MAYERSOHN: I think we can argue
12 pretty effectively that there are so called inactive
13 ingredients in solid dosage forms that certainly
14 enhance the in vivo performance of the dosage. Are we
15 not saying the same thing here? Am I missing
16 something?

17 DOCTOR SHAH: No, you are not missing.
18 You are right on the target. But with respect to
19 when we did the bioavailability studies, sometimes we
20 see the differences and we don't -- they're not
21 equivalent if they are different comparing the two
22 products. Here we are doing the same thing. We are
23 comparing the two products. We are hoping that they
24 are nearly the same composition. If they are
25 different by thermal weight and thermal -- we don't

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1 say that they are the same.

2 DOCTOR MAYERSOHN: Okay, but I think this
3 comes back to our inability to distinguish --

4 DOCTOR TAYLOR: Doctor DiGiovanna.

5 DOCTOR DiGIOVANNA: I wanted to make a
6 point with reference to that and then ask a question.
7 I think that the inactive ingredients that are of
8 concern to me are active ingredients. Vaseline is
9 active on scaly skin. It's not an inactive
10 ingredient. It's changing the reservoir and if you
11 have diseased skin, it's often associated with
12 hydroproliferation, loss of scale, and that leads into
13 the question for Doctor Schaefer. This technique on
14 normal skin assumes a reservoir of stratum corneum and
15 a mechanism of penetration dependent upon that
16 reservoir. When one is treating psoriasis or eczema,
17 not only is that reservoir in the barrier disturbed
18 and penetration enhanced but that barrier is being
19 actively lost. Isn't that implying that there's
20 really a very different mechanism of drug delivery to
21 an abbreviated of stratum corneum type of epidermis?

22 DOCTOR SCHAEFER: Right, but only in one
23 sense. That is invariably the delivery will go up,
24 not down, and it will be more variable, not less
25 variable. It will be more efficient. The difference

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1 will become smaller between two formulations, not
2 larger. It's the obvious consequence from this. So
3 in other words, the question of whether clinically
4 relevant differences can be seen by this technique or
5 whether there are relevant differences which would
6 escape, then the answer is due to the sensitivity of
7 the technique, they won't escape. You would see them
8 before. Coming back always to the same question to
9 define identity. Differences, you will see them
10 anywhere. In preparations with and without vaseline,
11 you will see that.

12 DOCTOR TAYLOR: I think the whole
13 discussion boils down to Doctor Williams' three
14 questions. What do you want to know and what
15 assumptions are you willing to make? It sounds like
16 there are a lot of assumptions that you have to make
17 when you compare studies of normal skin and apply them
18 to decision making diseased skin. I think those three
19 questions really gets us into the meat of that
20 discussion in a serious way.

21 There was one other comment, Doctor Lavin.

22 DOCTOR LAVIN: Phil Lavin, SGE. one of
23 the other things that I found interesting here is that
24 even in healthy skin the vulnerability of this
25 methodology to the different types of vehicles that

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1 you have, and I find that interesting that you
2 introduce such a variability. Each new vehicle that
3 comes out, each new variation or combination on the
4 theme will make the statistics that much more
5 difficult. How wide will the confidence intervals
6 have to be in order to preclude parity and will the
7 trials that we have to come up with in the sample size
8 calculations be so adversely affected? So it's almost
9 as if you'd have a very excellent methodology here and
10 yet to reign it in, sample size will have to be
11 brought in to nail down the sources of variation.

12 DOCTOR SCHAEFER: I understand. So I just
13 gave you an idea. In a good lab, a trained lab, the
14 variation is ± 10 percent. In a less trained lab, it's
15 ± 30 percent. You know about variability of clinical
16 studies. Specifically in dermatology. So it's
17 relatively precise. There's no point of discussing
18 the variability in terms of the chemical
19 quantification. That is precise. It's ± 2 percent at
20 the most in a good HVRCT. So all the problem is in
21 sampling of whether you sample exactly in the same
22 area again and again and again. You shift a bit to
23 the right or a bit to the left. This gives to
24 variations.

25 But apart from that, I haven't done the

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1 calculation but you understand from ± 10 percent what
2 the range is and you could do a guess of how many
3 volunteers you would need in order to see a difference
4 and to statistically be affirmative. This is the
5 difference.

6 DOCTOR LAVIN: And my concern is that each
7 and every vehicle combination and permeation that
8 you try would have a different variability associated
9 with it. Not just from the sampling measurement but
10 because the vehicles are different. And that's
11 something that will need to be controlled and this
12 would put a limitation on any new type of what we call
13 penetration methodology or new vehicle to enhance
14 absorption. Each of these will also be subject to
15 those kinds of sources of variation and this will make
16 it difficult potentially to try new vehicles with the
17 existing compounds and I see that as a major area of
18 research that's ongoing now. This method will,
19 because of its over-sensitivity, may throw the baby
20 out with the bath water.

21 DOCTOR SCHAEFER: Then it's up to FDA to
22 say okay, that's the range we accept.

23 DOCTOR LAMBORN: Kathleen Lamborn,
24 Pharmaceutical Sciences. I'm not quite sure I
25 understand the question that you're asking, Bill,

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1 because we're working for bioequivalence you always
2 within any comparison are not looking at different
3 vehicles always contrasting to the brand name or the
4 original innovator that you want to modify. So within
5 that, you will have a degree of experience so you're
6 not working with that range of variability within a
7 particular experiment. Is that what you're thinking
8 about?

9 DOCTOR LAVIN: No. My comment is
10 basically, like I stated, in this trial design that
11 had been done here, there are different vehicles.

12 DOCTOR LAMBORN: That was just done, as
13 I understand it, to demonstrate the particular
14 difference. By definition, you would never be
15 comparing two different vehicles. It has to be the
16 same vehicle for the purposes they're planning to use
17 this. There would not be two different vehicles in
18 the experiment.

19 DOCTOR LAVIN: My point is if you had one
20 experiment with one vehicle and you had another
21 experiment with a different vehicle in it, that that
22 second experiment with a different vehicle might have
23 a different sample size because that vehicle
24 introduces a different source of variation. So my
25 concern is that from experiment to experiment you have

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1 to be very careful about what vehicle it is depicting
2 in order to properly hone in on what the sample size
3 is and what the sources of variation are. So it's an
4 issue of each one of these has to be taken one at a
5 time as opposed to --

6 DOCTOR LAMBORN: Yes, but you have to
7 remember you're working with one innovator and then
8 you're trying to demonstrate one or more changes to
9 that innovator and, by definition, therefore, it's not
10 from one extent to another. It is one from product to
11 another that you would have to be dealing with
12 identifying the variability.

13 DOCTOR LAVIN: Right, I understand that.

14 DOCTOR TAYLOR: Thank you very much,
15 Professor Schaefer. We need to move on. The next
16 speaker will discuss procedures and validation and
17 Doctor Shrivastava will make that presentation.

18 DOCTOR SHRIVASTAVA: Good morning,
19 everybody. I'm going to cover the procedure and
20 validation aspects of the proposed DPK guidance, as
21 Doctor Shah pointed out earlier.

22 This is the overview of what I will be
23 covering. DPK methodology in brief, tape stripping
24 methods validation. There has been -- going on so I
25 think there will be time to cover all these things.

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1 And the critical concentration. I will give some
2 lists of critical concentration in the bioequivalence
3 study and some parts in summary.

4 So before we go into the methods, I would
5 like to begin with a couple of remarks concerning
6 bioequivalence studies. First of all, bioequivalence
7 studies are conducted in healthy subjects. I'm
8 talking about the systemic drugs and I will compare it
9 with the DPK approach later. These are studies in
10 healthy subjects in a crossover manner by treating the
11 subjects with test and reference. This may sound very
12 elementary but I think it is very appropriate that I
13 point this out to put the things in proper
14 perspective. And these test reference products are
15 applied at two different times within a period of,
16 let us say, one week or four weeks depending on the
17 product. And then comparing the drug concentration
18 and blood. That may not necessarily be the site of
19 action.

20 And then we compare, of course, these
21 metrics, CMAX. There you see AUCI and the test
22 product has to meet the criteria 90 percent confidence
23 interval. This is in systemic drug.

24 Next one please. In the DPK approach we
25 have tried to match that as much as possible and here

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1 we are looking into the uptake phase, the steady state
2 phase, and then elimination phase and we have
3 incorporated all this in our DPK approach for modeling
4 the stratum corneum. Again, the metrics are the same.
5 We've got the CMAX, TMAX, and then AUCs.

6 May I have the next one please. This
7 gives some similarities and differences between the
8 TPK approach and the DPK approach. The sampling
9 tissue in case of TPK is the blood whereas in the DPK
10 we have stratum corneum. The reference testing time,
11 as I indicated, is one to four weeks apart in case of
12 TPK and here we have concurrent application on the
13 same subject with the same time. The site of action
14 in case of TPK is remove or maybe close sometimes but
15 in case of DPK it is right in the vicinity. Right
16 near the site of action more or less. We don't know
17 the site of action most of the time, but it is very
18 close.

19 And the assumptions in both cases are the
20 drug reaches at the site of action. The drug, we know
21 that from the historical point of view as well as a
22 lot of studies have been done for the TPK but whereas
23 for the DPK there is still a lot of questions floating
24 around. However, we have lot of data that has been
25 generated by Doctor Schaefer's group and also -- and

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1 Latti, they have done some very preliminary work and
2 very basic studies, very eloquently they have shown
3 that the amount present in the stratum corneum
4 predicts as to how much the drug will go through the
5 body system.

6 If that is the case, it implies that
7 whatever goes through the body system is also going to
8 go to the site of action and that's why I consider
9 that the assumption in DPK as well holds. May I have
10 the next one please.

11 Going back to the methodology, the
12 methodology uses the tape stripping method and it uses
13 very heavily. So for those who do not know what is
14 tape stripping methods, you apply the drug on the
15 surface of the skin in a certain area and then you
16 allow certain exposure time, remove the excess drug
17 from the surface and then harvest the stratum corneum
18 layers by using adhesive tapes, 10, 20, whatever you
19 have come of it, and then quantitate the drug in the
20 tape strips. May I have the next one please.

21 As I said, DPK methodology uses the tape
22 stripping method so this is a brief description of
23 what is DPT methodology we are talking about. I just
24 went over a little bit but I'll add a little bit more.
25 Here, it uses the tape stripping method. Then we have

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1 here, as I said, uptake through the steady state and
2 elimination phases are included incorporated in that
3 DPK methodology. The skin sites are treated with
4 infinite amounts of test or reference products and the
5 test and reference treatments are concurrent, side by
6 side and in the same subjects. After a period of
7 time, excess drug is removed and as the schedule time,
8 stratum corneum layers are harvested and the amount of
9 drug in the stratum corneum is determined.

10 As with any methodology, you have to do a
11 number of SOPs and this is no exception for DPK. Here
12 also, before you conduct a DPK study, you have to go
13 through some of the development process and that's
14 where you have to come up with all this parameters as
15 to what things should be included in the study and how
16 you are going to perform the study.

17 First of all, you want to come up with
18 some kind of surface area which is uniform and most
19 probably you will select maybe forearm or maybe back
20 or some other area which suits. Then you have to find
21 out as to how many sites you will need for the study.
22 Two years ago we had a workshop where we recommended
23 that at least we need eight, but then it depends on
24 how much area you have available, you can increase the
25 number of sites. This will also depend on how many

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1 points you want to collect on the uptake phase or
2 during the elimination phase, etcetera. So depending
3 on that, you will have to determine how many number of
4 sites you will need and you have to have enough space
5 on the arm or back, whatever you have selected.

6 Also, you have to come up with the size of
7 the site, the treatment site, as to what size the site
8 is going to be. One centimeter, two centimeter, one
9 and a half, whatever. But this will all depend on
10 your sensitivity, analytical sensitivity as well as it
11 will also depend on the product that you are testing.
12 It may be .01 percent or maybe one percent. So
13 depending on how concentrated the product is, how much
14 concentration it has, it will depend on those things
15 as to how much it gets into the stratum corneum,
16 etcetera. So there are a number of factors that we
17 have to figure out, evaluate as to what the size of
18 the site is going to be.

19 Then you have the uptake phase. You have
20 to figure it out as to how much time it takes for the
21 drug to reach the steady state. Now, once you have
22 figured it out, then you can have the drug removed.
23 Let us say if it is four hours. You remove the drug
24 at four hours and then from that time onward, you
25 follow the elimination phase. Now you have to find

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1 out how long is the elimination phase going to be. It
2 could be 24 hours, it could be 48 hours. So you have
3 to find out as to how much time it will take for the
4 drug from the stratum corneum to go to almost zero, at
5 least which will give you a good pharmacokinetic
6 profile.

7 Then you also have to come up with the
8 excess drug removal procedure because if you have any
9 excess drug left on the surface of the skin, it can
10 make life very hard for you because in the data you
11 will have all kinds of data and a lot of variability.
12 So you have to come up with a very good excess drug
13 removal procedure. Number of tapes that you will need
14 to harvest the stratum corneum which will give you the
15 majority of drug that is in the stratum corneum. So
16 all these things have to be determined on some of the
17 initial experiments that you ran before you go into
18 the bioequivalence study.

19 Next one please. Once you have
20 established all those SOPs, standard operating
21 procedures, then you have to validate the methodology
22 and, in this case, we have two methods to validate.
23 Analytical method as well as tape stripping method.
24 They are both very subjective so, of course, the
25 analytical method is very well understood and it has

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1 been documented in so many workshops and all that
2 stuff. So we'll not go into that. But I'll cover
3 only the tape stripping methodology validation.

4 Now, as I said earlier, you have to
5 standardize the tape stripping methodology first, come
6 up with what kind of tape you want to use, what size
7 of tape you want to use, and how much pressure you are
8 going to use to apply to the tape and how quickly or
9 slowly you are going to remove the tape from the
10 surface of the skin or the site. So all these things
11 have to be standardized very precisely because there
12 is another problem maybe in this case. I don't know
13 if you realize it or not.

14 You have to remember that in the studies
15 one individual may have 12 sites on each arm so 24
16 sites on one person. If you have 36 subjects, you've
17 got to understand what will be the problem if you have
18 to harvest so many tissues and each site is being
19 harvested with, let us say, 15 or 20 tapes so you want
20 to make sure that you are not too ambitious in the
21 beginning and by the time you get to the 36th subject
22 and you are so tired next day, you know, there is a
23 lot of variability. So you've got to be very, very
24 careful and do the things right.

25 After you have standardized the

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1 methodology, you have to also standardize the drug
2 removal process. Of course, as I said earlier, if the
3 excess drug removal is not complete, then it can foul
4 up the experiment because it is still going on from
5 the surface of the skin into the stratum corneum and
6 it is fouling up the results. You have to determine
7 the accuracy, the precision, the reproducibility.

8 When you have more than one investigator,
9 you do need to make sure that they are comparable, the
10 results are comparable. You can not use two or three
11 investigators doing the study and, if they are not
12 available to you, have a problem. You want to make
13 sure that you have a good sensitivity and the
14 sensitivity in this case, we are talking about a dose
15 response curve sort of thing. And you have to
16 determine that. Then you also want to determine the
17 steady state time, as I mentioned, four hours, eight
18 hours or six hours or two hours, depending on the
19 product.

20 The same thing with elimination phase
21 duration. Another thing in this case you have to do
22 is the stability of your drug under testing condition.
23 If the drug like -- or something decomposes on the
24 surface of the skin, you have a little problem. You
25 have to figure it out as to how to handle that. Make

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1 sure that it is decomposing or, if it is decomposing,
2 then you have to come up with the stability profile
3 and also -- duration products, etcetera.

4 Finally, also you have to establish the
5 uniformity of the test surface. In other words, inter-
6 arm or intra-arm differences should be established.

7 Now I will get into some of the critical
8 considerations in BE study. First of you, you have to
9 select healthy skin and uniform skin surfaces.
10 Randomize the uptake and elimination phases, randomize
11 the test and reference products on the medial and
12 lateral sites of the arm, as we'll see in a minute.
13 Then randomize the exposure time to various sites on
14 the arm and then treat the skin sites with infinite
15 amount of test and reference products.

16 Going to the uptake phase, our uptake arm,
17 you allow the pre-selected time for time point and at
18 the end of the uptake time, you remove the excess
19 drug. After that, you harvest the stratum corneum
20 with additional tape strips and then pull all the
21 tapes or you can do it individually if you want, if
22 you have that kind of sensitivity, but I wouldn't
23 recommend that extra burden. But pull them all and
24 then you have the amount of drug in the stratum
25 corneum, total amount. That is the uptake phase.

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1 Now do the same thing with the elimination
2 phase. Elimination phase here will begin at the
3 maximum time, uptake time, and after the uptake time,
4 in this case, you remove the excess drug at the
5 maximum excess time at each time point from each site
6 and then at the designated elimination time you remove
7 the stratum corneum original tape strips and again
8 pull the tape strips and quantitate the amount of drug
9 in the stratum corneum.

10 May I have the next one please. This
11 shows the schematic of the treatment for subject #1
12 and these are two arms. This is one arm and this is
13 another arm. I didn't label it but let us say left
14 and right, whatever. Then what I was saying is that
15 you have to randomize the elimination phase, then the
16 uptake phase and in the uptake phase you can test and
17 reference on side by side we are treating and so you
18 can randomize this site and this site with the testing
19 reference and the treatment times can be randomized
20 this way. I like to keep the control separately
21 because of contamination problems and all that, so I
22 think in the interest of good data it might be a good
23 idea to just keep it separated.

24 May I have the next one. In summary, I
25 think the methodology can be very useful and, as

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1 Doctor Schaefer has just pointed out, we have a good
2 method in the literature and a 20 percent of CV is not
3 difficult to achieve. So it can be achieved and I
4 have seen some of the data from -- The differences are
5 only 10 percent, 10 to 20 percent. So it all depends
6 on you, how you conduct the study and it can be
7 achieved.

8 DPK study in -- assessment of in vivo drug
9 release, drug diffusion, permeation, metabolism,
10 elimination over the time period. If you look at it,
11 I only talked about the uptake, steady state and
12 diffusion but if you really look deeply, it does go
13 beyond that because it takes into consideration the
14 release. It starts right from the release. You can
15 see the differences between the two drugs, the test
16 and the reference, right from the release from the
17 matrix, that is partitioning from the matrix, then
18 diffusing through the stratum corneum, going into the
19 deeper layers, and then metabolism, elimination and so
20 on and so forth. So it does incorporate all those
21 things. That's what I'm trying to say in this first
22 bullet here.

23 This compares the kinetics of test and
24 reference products in stratum corneum reservoir, as
25 Doctor Schaefer has already indicated earlier, then

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1 compares the rate and extent of drug uptake,
2 elimination in the stratum corneum. Test and
3 reference are treated side by side in the same
4 subjects at the same time. Unlike systemic drugs, DPK
5 parameters are compared concurrently at or near the
6 site of action.

7 Thank you very much for your attention.

8 DOCTOR TAYLOR: Thank you. This
9 presentation is open for discussion by the committee.

10 DOCTOR GOLDBERG: Arthur Goldberg. You
11 said in the arm you separate the test and the
12 reference because there's possible cross contamination
13 with the excessive reference.

14 DOCTOR SHRIVASTAVA: No. I did not.

15 DOCTOR GOLDBERG: You showed the dots, one
16 line being test, one line being reference.

17 DOCTOR SHRIVASTAVA: Right.

18 DOCTOR GOLDBERG: You said you preferred
19 not randomizing those.

20 DOCTOR SHRIVASTAVA: No. I did say that
21 you should randomize those lines, but I said for the
22 control in the interest of contamination problems in
23 the methodology, I said keep the control little bit
24 away from the rest of the sites. Do you understand?

25 DOCTOR GOLDBERG: Yes.

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1 DOCTOR TAYLOR: Any additional questions
2 from the committee?

3 DOCTOR BRAZEAU: I think that the issue of
4 this method is training personnel to do it.

5 DOCTOR SHRIVASTAVA: Exactly.

6 DOCTOR BRAZEAU: What type of manpower or
7 womanpower is required to get somebody to feel
8 competent to get to those variation levels?

9 DOCTOR SCHAEFER: It takes at least one
10 Ph.D., one technician, three months to do the basics,
11 that is to do the validation, establish the procedure
12 and to do a first pilot study with tape stripping.
13 That's the minimum. There, people have to work very
14 hard. Normally, working people in Europe would take
15 six months, I would say.

16 DOCTOR MINDEL: Doctor Shrivastava, in one
17 of your early slides you showed uptake, steady state
18 and elimination phase in a TPK. Were those idealized
19 data or actual measurements?

20 DOCTOR SHRIVASTAVA: Idealized.

21 DOCTOR TAYLOR: Any additional questions
22 from the committee?

23 DOCTOR KILPATRICK: This is a great deal
24 of work. Has any work been done in an attempt to
25 minimize the number of serial strips taken? I'm

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1 most precision to the estimates, CMAX or AUC or
2 whatever it is you're trying to get to. This requires
3 quite a lot of work for a simulation for something
4 like that.

5 DOCTOR SHRIVASTAVA: It will be good idea
6 to get enough samples. We want to get a good profile.
7 As I indicated earlier, we have discussed about this
8 quite a bit and at least we need eight sites, four for
9 the uptake and four for the elimination phases.
10 Otherwise, it becomes very few points to really get a
11 good profile.

12 DOCTOR TAYLOR: Doctor Shah, do you have
13 a comment on that?

14 DOCTOR SHAH: My general comment is it
15 should be dependent upon how your pilot study is done.
16 That's why we have two phases in the study, the pilot
17 study that determines what's the optimum amount of
18 spacing and then use that optimum spacing for your
19 bioequivalency study.

20 DOCTOR TAYLOR: Any other questions?

21 DOCTOR LAVIN: Yes. What are the
22 acceptable inter and intra site variabilities that
23 were in your overhead? You indicated what represents
24 a release speck for those CVs.

25 DOCTOR SHRIVASTAVA: Well, I would say

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1 that if you have 20 percent, 25 percent, I think
2 you're in good shape. There is no set limits and
3 actually, depending on how good your methodology is,
4 actually it is going to help you in selecting the
5 number of subjects for the study also. So some of
6 those things actually will help. If you have a good
7 technician or the investigator is very good, then
8 actually it will reduce because of the low intra
9 subject variability. You will not need as many
10 subjects to conduct the study.

11 DOCTOR LAVIN: My experience is that when
12 you have 20 CVs that are in the 20 to 25 percent
13 range, you get large sample sizes in order to rule
14 that out. It's a common theme we seem to be
15 mentioning here but I'm concerned that if that CV
16 can't be lower than five percent, you're in a
17 situation where you're going to have to have a lot of
18 samples, a lot of testing, a lot of repeat
19 experiments. The sources of variation, everything
20 starts with the sources of variation. This is an
21 exercise identifying the sources of variation. If the
22 variation within those sites on the same arm at the
23 same time is high enough, that's going to preclude the
24 ability to detect any kind of difference. It'll take
25 away the sensitivity to be able to detect the

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1 difference and it'll also make it easy to say that
2 there is a difference when there really isn't one. So
3 I'm concerned that the CVs are large, just from what
4 you've shared with me.

5 DOCTOR TAYLOR: Doctor Shah, do you want
6 to comment?

7 DOCTOR SHAH: Yes. I would suggest that
8 Professor Lynn Pershing is coming back later on and
9 she would be coming back to address this, any
10 questions concerning intra sites permeability and if
11 we can wait for a few more minutes because she will
12 give you the information based on her own experience
13 what has been done in her laboratory to conduct such
14 studies.

15 DOCTOR TAYLOR: Thank you. One last
16 question.

17 DOCTOR DiGIOVANNA: You showed a nice
18 slide correlating this procedure with the standard way
19 pharmacokinetics would be done, I guess, with an oral
20 or intravenous drug and you call it stratum corneum
21 with blood. But in a way that sort of denigrates our
22 thought of the skin as a very complicated organ. Of
23 course, I'm a dermatologist so I think it's very
24 complicated. But the stratum corneum really doesn't
25 correlate very well in that paradigm because it's not

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1 the same sort of a reservoir in health and in disease.

2 So if I take an aspirin whether I have a
3 fever or whether I don't have a fever, my blood level
4 is relatively the same and not dramatically changing.
5 But if I use the stratum corneum as a reservoir, let's
6 say, for a steroid in health, that's very different
7 than it is in psoriasis or eczema because what's
8 happening to that reservoir is its increased
9 proliferation and increased shedding of the stratum
10 corneum in addition to its decreased barrier would
11 sort of be like me taking an aspirin, getting
12 intravenous fluids and a diuretic at the same time but
13 also affecting the ability to get that aspirin to
14 penetrate directly through to my central nervous
15 system or wherever it's acting.

16 So I think that that is a complication
17 that we need to keep in mind, that the process isn't
18 exactly correlative.

19 DOCTOR SHRIVASTAVA: I agree with you.
20 For that kind of information, we go to the correlation
21 between clinical and some of the others and the
22 assumption that I mentioned about. In this case, just
23 like in the systemic drug, we have assumptions. We are
24 making the same kind of assumption here also. Now,
25 the idea here is to establish the bioequivalence of

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1 two products so the assumption is that if the two
2 products in healthy skin are acting in the same way
3 more or less, then it is also possible that in the
4 diseased skin also they will act exactly the same,
5 more or less the same.

6 DOCTOR DIGIOVANNA: I think what you're
7 asking is if the two products get into and out of the
8 stratum corneum in the same way, then we assume that
9 they're going to in diseased skin get to the site of
10 action whether it be the hair follicle, the eccrine
11 gland, the blood vessel, the keratin sites in the
12 basal layer or whatever that may be.

13 DOCTOR SHRIVASTAVA: That's right. Thank
14 you.

15 DOCTOR TAYLOR: Thank you for your
16 presentation. What I'd like to do now is to go ahead
17 and take our break that's scheduled at 10:00. We'll
18 return at 10:25. That's 15 minutes for the break.

19 (Whereupon, off the record at 10:05 a.m.
20 for a 25 minute break.)

21 DOCTOR TAYLOR: The next presentation
22 speaks to DPK and clinical studies using antifungals
23 and the first presentation is by Doctor Mary Fanning
24 who will discuss some of the clinical studies.

25 DOCTOR FANNING: Thank you very much. My

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1 presentation and then the one of Lynn Pershing that
2 will follow is going to deal with the whole issue of
3 sensitivity, relative sensitivity of clinical studies
4 versus DPK studies, in evaluating an approved generic
5 product when it's compared to its innovator which is
6 kind of the forum in which we're talking about
7 applying this technique.

8 The drug I'll be talking about is
9 miconazole nitrate vaginal cream two percent given
10 over seven days and I will very, very briefly, as
11 briefly as possible, show you the data of a
12 bioequivalence study with clinical end points which is
13 the current standard for evaluating vaginal products
14 that was submitted in support of an AMDA, analyzed
15 according to criteria that the FDA has developed that
16 are known to industry and accepted and subsequently
17 was approved.

18 So what I'm going to give you here are the
19 basic criteria for enrollment, the evaluations
20 following enrollment, the end points, and kind of the
21 bottom line results of the study which I'd like you to
22 hold on to to compare to the results of the DPK study.
23 So if I could have the first slide, Vinod.

24 The criteria for an evaluable patient was
25 that they were enrolled and completed a day seven and

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1 day 37 followup visit. In order to be enrolled, they
2 had to have signs and symptoms of vaginitis. They had
3 to have a positive KOH smear and a positive candida
4 culture. They then had to go on to seven days worth
5 of treatment and, at the end of that treatment on day
6 seven, either they had to have no further clinical
7 signs and symptoms or improvement with a negative KOH,
8 negative candida culture in order to be considered
9 cured at that point.

10 They were then seen about a month later
11 and once again, in order to qualify as a clinical
12 cure, they had to have no signs or symptoms of
13 vaginitis and a mycological cure was a negative KOH
14 and a negative candida culture. If there was
15 discrepancy, particularly on the last visit, between
16 the KOH and the candida culture, the culture was
17 considered more reliable.

18 If I can have the next slide. This is
19 the sort of bottom line data. I'm sorry it's a little
20 bit busy but I'll walk you through it as best I can.
21 Here we have the results of the test or generic drug
22 compared to the reference or the innovator drug and,
23 if you look at clinical cure on the second visit,
24 you'll note that it's 92 percent for the test, 87
25 percent for the reference. Mycological cure at that

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1 point is also very high, 96 and 96 percent, and both
2 of these meet confidence intervals.

3 The clinical cure at the third visit one
4 month after completion of treatment is a little less
5 which occurs in these types of studies. It's 86
6 percent for the test, 84 percent for reference.
7 Mycological cure high for the test again at 86
8 percent, a little lower for the reference at 78
9 percent.

10 The third -- cure has a slightly lower
11 numerator in both test and reference and these
12 individuals are people who met cure criteria for
13 clinical and mycological cure at all the visits. So
14 they were sort of cured at every point that one looked
15 at. The innovator had a cure rate by those criteria
16 of 67 percent and the generic drug had a cure rate of
17 76 percent. The competence intervals are met on the
18 negative end. There's some suggestion perhaps of
19 slight superiority of the generic drug. But in making
20 its recommendation for approval of this product, the
21 medical officer and the statistician considered the
22 cure rates of all of the parameters and felt that this
23 would meet bioequivalence criteria.

24 So that's my presentation of the clinical
25 data and now Doctor Pershing will present the DPK

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1 data. I'd be happy to clarify any issues about the
2 clinical study.

3 DOCTOR TAYLOR: Thank you. We'll move
4 directly to the DPK applications by Doctor Pershing.

5 DOCTOR PERSHING: I'm Lynn Pershing from
6 the University of Utah. I'm going to talk about the
7 test and the reference products then that were
8 evaluated according to DPK in our laboratory. Next
9 slide please. We're going to discuss this data in
10 terms of the pilot study, a validation study, and a
11 pivotal bioequivalent study. Next slide.

12 These are the results of the pilot study
13 and there's two things we want to achieve in a pilot
14 study. We want to first pick the appropriate time
15 points for assessment. That is, time points for the
16 uptake part of the curve and also the elimination. We
17 also want to establish for the statistician intra
18 subject variability. So to do that, we generally test
19 the reference against itself in the same people in the
20 same study period. In this case, we use either the
21 inner or the outer aspects of the ventral forearm at
22 multiple sites along the forearm and, as you see from
23 the data, they reduce very well.

24 This tells you that this product is very
25 reproducible within a subject. The elimination time

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1 profile never does reach zero even after 24 hours.
2 That's typically true for topical drugs. The other
3 thing I want to point out is that elimination in the
4 skin is much slower than you'd expect looking at
5 plasma profiles and so the time intervals you want to
6 look at in the elimination phase are much more spread
7 out in time than you would expect from a plasma study.

8 So this is the statistical evaluation of
9 the reference listed product, Monistat 7 vaginal cream
10 two percent, against itself. We looked at Cmax, Tmax,
11 AUC over the uptake phase as well as the entire
12 profile 0 to T. What you see when you compare the
13 ratio versus the outer is a ratio about one between
14 the two products for Cmax with a confidence interval
15 around 22 percent. That's an intra subject
16 variability of about 22 percent. Tmax occurs at about
17 2.3 hours for the outer skin sites, at about 2.5 for
18 the inner sites. Therefore, the same formulation is
19 responding very similarly in its delivery of the drug
20 to the human subjects in the same individuals.

21 AUC over the uptake phase showed a ratio of
22 about 0.97, again very reproducible, with an intra
23 subject variability of around 18 percent. You see
24 over the entire pharmacokinetic profile from 0 to T
25 the ratio is about 0.91 and about a 34 percent intra

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1 subject variability. We're using Cmax as the intra
2 subject variability to calculate how many subjects
3 would be required in a pivotal bioequivalent study.
4 Using these data would suggest you need about 22
5 people to achieve statistical significance and
6 discrimination.

7 Another clear as mud information for you
8 is that you should really validate your method of drug
9 removal and understand how much of the drug is
10 actually going to be in the stratum corneum that you
11 have to analyze. In this case, we've looked at
12 various compartments of the skin site and in the
13 application removal situation. The first three bar
14 series here are cotton applicators, the first one, the
15 second one and the third one. We used three
16 independent dry cotton applicators and we found this
17 to be a superior way to remove residual drug.

18 If you look at the first cotton
19 applicator, it contains both at the inner and the
20 outer sites about 32 to 35 percent of the drug
21 applied. The next cotton applicator is significantly
22 reduced and then the third cotton applicator is even
23 more reduced. The two that we used to distribute the
24 drug around the surface area of the skin site contains
25 anywhere, in most of our drug studies, between 10 and

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1 20 percent. Data not shown here is the tape guard
2 that we used to protect the skin site from accidental
3 drug removal and that also contains between 10 and 25
4 percent in a typical study.

5 What is very important to see in this data
6 is that what's on the surface of the skin of the drug
7 is much greater than what was in the skin. If you did
8 not have an appropriate drug removal system, you would
9 see these be much, much higher. For miconazole
10 nitrate in this particular reference listed product of
11 vaginal cream, the total amount of the stratum corneum
12 represents one and a half to two percent of the drug
13 applied. That is typical for topical drug products.

14 If we expand that skin stripping data to
15 separate the first from the combined two through fifth
16 skin stripping or six through 10, you see a beautiful
17 concentration gradient through the stratum corneum.
18 According to -- diffusion, you would expect a
19 concentration gradient of the topical drug in the
20 stratum corneum as you go from the outer to the inner
21 aspects of the stratum corneum.

22 So in the pivotal study we analyzed 24
23 subjects. Remember our statistics in the pilot study
24 from intra subject variability data suggested we
25 needed at least 22. And you'll see that the test

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1 product in green is much less in its pharmacokinetic
2 profile compared to the reference listed drug. If we
3 statistically analyze these data, we see that
4 according to Cmax our ratio would be about .7 and the
5 90 percent confidence intervals, which you can't read
6 here but I'll tell you what they are, is about 54 to
7 79 percent. Although that 90 percent confidence level
8 is very narrow, it is shifted outside that acceptance
9 criteria we use for Cmax according to the proposed
10 guidance which is 70 to 143. So according to the Cmax
11 parameter, these two products would fail.

12 Tmax is about two hours for the test and
13 about two hours for the reference. That's a median
14 Tmax. They look relatively equivalent. The AUC data
15 here, which you can't see at all, for the uptake phase
16 the ratio is about .7 with a confidence interval again
17 very narrow but outside the acceptance criteria for
18 bioequivalence for this parameter which is 80 to 125.
19 If we analyze from 0 to T, we see the same thing, a
20 ratio of about .5 and a confidence interval that's
21 very narrow but outside the acceptance criteria.
22 These data then, the DPK data, would say that these
23 two products are not bioequivalent.

24 So the issue remains in the contrast
25 between the clinical study and the DPK work, how much

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1 difference in DPK can you have and still predict
2 bioequivalence and do differences in DPK predict
3 differences in bioactivity?

4 We developed in the laboratory a number of
5 years ago a bioassay, a growth inhibition bioassay
6 using candidadol species that is most selective to
7 miconazole and our fungal drugs. It's a growth
8 inhibition assay where you submit increasing
9 concentrations of the drug to the assay and measure
10 the zone of growth of inhibition. As you would
11 expect, as you increase the concentration, you
12 increase the zone of inhibition.

13 As any Emax model, you would expect that
14 after a particular concentration, if you increase it
15 further, you see no difference in the pharmacodynamic
16 effect. This assay is linear, however, only up to 2.5
17 micrograms per square centimeter. Therefore, all your
18 data must be analyzed in the linear portion of your
19 curve. If any skin stripping sample was above 2.5
20 micrograms per square centimeter, you would have to
21 dilute that sample before submission to the bioassay.
22 So let's see what happens when we do that.

23 What I want to tell you is in this assay
24 the DPK response and the discrimination, the
25 statistical discrimination between different

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1 concentrations by a nova is 1.25 micrograms per square
2 centimeter which correlates to the bioassay biological
3 response of 0.33 centimeters zone of growth
4 inhibition. What this means is the following.
5 Between your diluted skin stripping samples of test
6 versus reference at the same time point, you would
7 have to have -- this is that creeping phenomena, Hans
8 -- you would have to have a difference in your test
9 versus reference in your diluted sample of greater
10 than 1.25 micrograms per square centimeter to be
11 statistically different.

12 What I want to tell you is that 50 out of
13 the 168 pairs of skin strippings had skin stripping
14 drug contents greater than two and a half micrograms
15 per square centimeter and, therefore, were diluted to
16 a similar extent and then submitted theoretically then
17 to the assessment doing this bioassay. In the end,
18 only one pair out of the 168 paired samples of test
19 and reference showed a statistical difference. The
20 bioassay data, like the clinical efficacy data,
21 suggests that there is no significant different
22 between the test and the reference.

23 So we have DPK, clinical efficacy, safety
24 human trials as well as very specific in vitro
25 bioassays and DPK was the only method that could

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1 differentiate and discriminate between these two
2 products. The lack of the human clinical study and
3 the bioassay studies to differentiate these two
4 products is likely due to the fact that topical drug
5 products deliver much more drug than is required to
6 achieve a maximal pharmacodynamic effect.

7 In conclusion, dermatopharmacokinetics is
8 more discriminating and more sensitive to elicit
9 differences between topical drug products than
10 clinical efficacy or bioassay methods.

11 One last statement is the following. This
12 is a very, very important consumer issue and that is
13 this. The differences we measured in DPK between
14 these two products still gave a similar clinical
15 efficacy and bioassay result. That is a consumer
16 safety benefit. DPK will pick up differences that you
17 can't in those other two methods. This is a producer
18 risk because it would fall outside acceptance criteria
19 for bioequivalence, but it is not a consumer risk.
20 They would both be considered equivalent for efficacy
21 and for safety. Thank you. I apologize for those
22 slides.

23 DOCTOR TAYLOR: Thank you. Are there any
24 questions?

25 DOCTOR WALKER: I guess I don't know

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1 enough about how you compare what happens on the
2 forearm with what happens in the vaginal vault because
3 don't you have to take into consideration pH changes,
4 the normally occurring bacteria and what not that are
5 in the vaginal vault that may have some effect on the
6 drug?

7 DOCTOR PERSHING: In general, and I
8 collaborate with someone who evaluates mucosal
9 membranes -- we find that actually drug partitions
10 into stratum corneum better and more discriminatorily
11 than a mucks membrane will. So you'd see even less
12 difference in the vaginal tissue than you would in the
13 skin. So again, skin errs on the side of more
14 discrimination and a better opportunity for us to be
15 able to discriminate between the drug products than we
16 would in the vaginal tissue.

17 It is a problem and you're absolutely
18 right. There aren't too many women who are willing to
19 submit to 20 biopsies in that particular area, so it's
20 very difficult to prove that point but isolated tissue
21 research suggests that in fact the skin is more
22 discriminating than vaginal or mucosal tissue.

23 DOCTOR MINDEL: Joel Mindel. Since the
24 DPK method is the method that has to prove itself, why
25 is it that the conclusion couldn't be that it was the

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1 inaccurate methodology and the other two were the
2 accurate ones?

3 DOCTOR PERSHING: Because I validated the
4 analytical assay. You can't validate clinical studies
5 really well. The analytical aspect of DPK is
6 extremely demanding for validation and so we feel very
7 good in terms of our skin stripping validation, the
8 short validation work I showed you here, that the
9 methodology in the collection of samples, the analysis
10 of samples, is very highly controlled and reproducible
11 and acceptable. But it's very difficult. In the
12 bioassay I can do those strict measures because it's
13 again an analytical assay, but in clinical, how do you
14 when go to an investigator, how do you validate their
15 ability to determine their cures other than the fungal
16 culture and the KOH? I think the bottom line here is
17 that we deliver more drug than we need to to get a
18 maximal effect. So the differences we saw in the --
19 reference, even though it's lower, is clearly
20 sufficient to produce the maximum effect.

21 DOCTOR MAYERSOHN: If you were to make a
22 recommendation to the agency in this particular
23 example, what would you recommend?

24 DOCTOR PERSHING: Recommend as far as
25 what?

1 DOCTOR MAYERSOHN: Acceptance. Are these
2 going to be too high?

3 DOCTOR PERSHING: What I'm finding with my
4 work is that 80 to 125 is likely too stringent for
5 acceptance criteria for determination of
6 bioequivalence. The inherent variability -- and this
7 is a very important issue -- skin is inherently
8 highly variable. I challenge anyone on a day to day
9 basis or even along the forearm to find an average in
10 a population. Coefficient of variation of any
11 parameter they chose to measure that was less, an
12 inter subject variability average, of less than 25
13 percent. My forearm is really reproducible. I'm
14 about five percent. But I'll show you in the open
15 public hearing that as you go between people,
16 different people have different variabilities and the
17 critical aspect here is that we can do both
18 formulations simultaneously in the same person at the
19 same time to minimally reduce that variability.

20 DOCTOR MAYERSOHN: What's your
21 recommendation for this product?

22 DOCTOR PERSHING: For the product?

23 DOCTOR MAYERSOHN: Yes, for this
24 comparison.

25 DOCTOR PERSHING: Okay. Based on the data

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1 that I showed you today, I think they're actually
2 bioequivalent based on the clinical efficacy study,
3 the bioassay which I think is probably the best, and
4 the DPK work. So you can see differences in DPK that
5 you wouldn't see differences clinically.

6 Now, the issue really is this. If I only
7 had DPK data, I would reject this. Well, that's a
8 producer risk. Right?

9 DOCTOR MAYERSOHN: But you're comparing
10 dermal absorption to vaginal absorption. Is that
11 right? You're using skin as a surrogate for vaginal
12 absorption. Is that fair?

13 DOCTOR PERSHING: I think it's more than
14 fair. I think it's more discriminating than vaginal
15 tissue. So I will pick up differences that would then
16 fail because of bioequivalence that the vaginal tissue
17 would not. So in other words, it's a producer risk.
18 They may fail at getting their product approved, but
19 the public is safer for it.

20 DOCTOR TAYLOR: We have two questions on
21 this side of the table now. Doctor McGuire and then
22 Doctor DiGiovanna.

23 DOCTOR MINDEL: This one is brief. Where
24 is the candida that you're trying to kill with
25 Miconazole? Is it surface? Is it within the first

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1 micron? In other words, if you have a drug that shows
2 very good DPK characteristics, it penetrates rapidly
3 and well and then is eliminated slowly or rapidly, how
4 would that effect its efficacy clinically? Do you
5 want something that shows good DPK characteristics or
6 do you want something that sits on the surface and
7 kills the yeast? It really depends upon where the
8 yeast is or the yeast are. Where are they?

9 DOCTOR PERSHING: That's right. For
10 antifungal infections, they are thought in dermatology
11 to be superficial. I think some of the new research
12 shows that it's also within the stratum corneum. But
13 in general, we view that an antifungal infection is
14 superficial on the surface.

15 DOCTOR MINDEL: So you want something with
16 poor elimination.

17 DOCTOR PERSHING: Well, yes, but remember,
18 we're looking here at bioequivalence so all we really
19 want to show is that the elimination is similar. But
20 you're right. Topical drug therapy in this case.
21 You'd like something that hung around for a while.

22 DOCTOR DiGIOVANNA: I think Joe touched on
23 the beginning of the point I wanted to make and maybe
24 I missed something, but you ended up saying that
25 dermatopharmacokinetics was more discriminatory but is

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1 it relevant? I mean is that discrimination predictive
2 of efficacy? I didn't quite see that connection here,
3 and I think that's what Joe was trying to get at.

4 DOCTOR PERSHING: It's better.

5 DOCTOR DiGIOVANNA: But is it better at
6 the same thing or at the thing you want?

7 DOCTOR PERSHING: Well, okay. I guess the
8 bottom line is that one of the key issues in
9 dermatopharmacokinetics is is it adequately
10 discriminatory to differentiate between two drug
11 products? The goal of standard here is a clinical
12 study. I think what we're trying to show is this.
13 That in a clinical efficacy study you may show no
14 difference that DPK can show a difference. That means
15 that yes, DPK has the ability to be highly
16 discriminatory and pick up differences that you would
17 normally not see. That is, to me as a consumer, a
18 great relief because that means even though they might
19 be the same clinically, if I had to make a decision
20 only on DPK work, I would say no, you're not making
21 it.

22 Now, that might not get to the market but,
23 for goodness sake, it sure wouldn't be a lack of
24 efficacy then to the subjects and it wouldn't be toxic
25 either and so from a consumer viewpoint, I think this

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1 is a very important issue. We actually want DPK to be
2 more sensitive than a clinical efficacy study.

3 DOCTOR DiGIOVANNA: But I think we want it
4 to be more sensitive at measuring what we want to
5 measure and, in a sense, I almost get the feeling that
6 this is kind of like well, I lost my keys on
7 Twinbrook Parkway but I'm going to go look for them on
8 Fisher's Lane because that's where the light is. We
9 have a test. It can measure something but is it
10 measuring the end point we're looking for which is
11 efficacy? I'm not sure I see that. I accept the fact
12 that it is discriminatory. I'm not certain that that
13 correlates with its efficacy, that it's discriminating
14 what we're looking to discriminate.

15 DOCTOR PERSHING: When you see two plasma
16 PK profiles that might be different, do you assume
17 that they are efficaciously different?

18 DOCTOR DiGIOVANNA: I think that what
19 we're talking about there, because of my aspirin and
20 I'm sorry about that --

21 DOCTOR PERSHING: I know, but you know
22 what I'm saying?

23 DOCTOR DiGIOVANNA: I know what you're
24 saying. They're assumptions and the assumptions vary.

25 DOCTOR PERSHING: Right, and the

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1 assumption here, luckily for the antifungal, is that
2 wow, the target site really is right there. You don't
3 have to go to Fisher's Lane because that is the target
4 site. I lost my keys there and, therefore, that's
5 where I will look. And so I think for antifungals
6 it's very clear.

7 DOCTOR TAYLOR: Doctor Lavin.

8 DOCTOR LAVIN: There's a graph I'd love to
9 see. I'd love to see the DPK data on one axis. I'd
10 like to see the blood data on the other axis, and I'd
11 like to see highlighted whether they're responders or
12 not on the graph. Then I'll believe what I'm hearing.
13 That would be neat to see. Do you have that?

14 DOCTOR PERSHING: Okay. First of all,
15 topical drugs aren't absorbed extensively, so it's
16 rare that you can actually get a blood level from a
17 topically applied product.

18 DOCTOR LAVIN: But in this experiment here
19 that you did where you were showing you had the AUC
20 calculated two ways, show me the data done both ways
21 where the data are paired and then let's see for each
22 of those points on the pair -- I'm assuming that you
23 said that you had that data.

24 DOCTOR PERSHING: No, I don't have any
25 blood data. Okay. What would you want as X and Y?

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1 DOCTOR LAVIN: I'd like to see the DPK
2 data on one axis basically for each patient, each
3 patient is a point on the curve, and then on the Y
4 axis the other measure. You said you could draw blood
5 in this experimental setting.

6 DOCTOR PERSHING: No. It would be the
7 bioassay result which would be zone of growth
8 inhibition. If you do that, you get a linear
9 correlation. As you increase the amount of drug,
10 actually what you do for this instance is take the
11 difference between the test and the reference PK and
12 you plot that against the difference in the bioassay
13 and that shows a linear correlation.

14 DOCTOR LAVIN: Yes, that would be
15 interesting to see and then also to see who basically
16 had the response, who had the clinical response versus
17 who didn't on that as well because then you'd have
18 your answer to whether or not you're doing better. In
19 other words, do you have better separation? You'd be
20 able to see by the clustering which way the data are
21 showing. Right now we have one set of data in the
22 right hand and this set of data in the left hand and
23 we've not joined the two together.

24 DOCTOR PERSHING: Well, I think in the
25 public hearing session I'll show you those

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1 correlations that I've done in psoriasis in another
2 antifungal study where we did all these things at
3 once. This is a retrospective study of a product that
4 was already approved based on a clinical study. So
5 that's important to know.

6 DOCTOR TAYLOR: Doctor Williams, did you
7 have a comment you wanted to make?

8 DOCTOR WILLIAMS: Yes. I just wanted to
9 ask. You did show a difference, Lynn, in terms of DPK
10 and were these formulations Q and Q the same in terms
11 of five percent and then what was your hypothesis as
12 to why it was showing such a big difference in terms
13 of DPK?

14 DOCTOR PERSHING: I wish I had the
15 ingredients comparison. I do not. I'm sorry. Did
16 Mary find that? It's interesting. It wasn't listed
17 on the reference tube. It was listed on the test tube
18 but not the reference for the inactive ingredients so
19 I don't have that data. I'm sorry.

20 DOCTOR TAYLOR: Okay. Any other question?
21 We'd like to thank you very much. I'd like to move
22 ahead now to Doctor Jonathan Wilkin's presentation.

23 DOCTOR WILKIN: Doctor Taylor, members of
24 the two committees, I've altered my title somewhat so
25 I can get more to the point, take advantage of the 15

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1 minutes. I would put myself in the category that
2 Vinod presented earlier of the premature. I think DPK
3 is premature to accept for a guidance at this time.
4 I have 15 minutes and if you look over the schedule
5 this morning, you'll find over two hours for the
6 supportive discussions of DPK and so I have to take
7 advantage of these 15 minutes. I have to really focus
8 in on just one or two targets to really think about.

9 And so I'm willing, especially for the
10 purposes of doing that, to think about the initial
11 stages of validation, the first stage being that one
12 can have a reproducible method in a single laboratory
13 and then the second stage being that the method can
14 become reproducible at different laboratories. I
15 think that it's quite plausible that DPK has that kind
16 of potential. So that's the level of a controlled
17 artifact, that level of validation, and I would think
18 that we could proceed from that point.

19 Having said that, to understand the
20 meaning and regulatory utility of this controlled
21 artifact, one needs something else. You either need
22 evidence from experimentation that indeed DPK measures
23 up to the gold standard of the clinical tests or, on
24 the other hand, you need to be able to derive it from
25 first principles and, in the case that we see in the

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1 guidance, we're led to believe that we can derive it
2 from first principles from the plasma area under the
3 curve.

4 Doctor Shah and Doctor Shrivastava's paper
5 is in the briefing package for the committees and this
6 is a figure taken from that. As you can see, the
7 reference is to dermatopharmacokinetics and it's
8 described as kinetics of the drug in the skin. As it
9 turns out, it really isn't in the skin. It's focusing
10 on a very small part of the skin, the stratum corneum.
11 We're to see the plasma AUC and here it says skin
12 concentration versus time profile and that really
13 should be stratum corneum. Stratum corneum, at least
14 to dermatologists, is not the same thing as the skin.

15 This is Netter's drawing. That could be
16 focused just a tad. The skin extends down to where
17 the butter starts down here and this is the collagen
18 and up here is the viable epidermis and on top of that
19 you see in this cartoon that the stratum corneum looks
20 something like baklava. It's in nice, neat, ordered
21 layers. So at any rate, the stratum corneum is not
22 the skin. Dermato refers to the skin. You could
23 think of a lot of other words for what we're talking
24 about today. I won't use them because I think DPK is
25 firmly entrenched in the literature at this point.

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1 But when I think about DPK, I will be thinking about
2 stratum corneum.

3 So the key question turns out to be is the
4 DPK AUC of topical dosage forms analogous to the
5 plasma AUC of oral dosage forms? I call this the
6 grand analogy. Again, stratum corneum is not the same
7 thing as skin. We mentioned that. I think one of the
8 key problems is that it ignores the follicular
9 pathway. The stratum corneum is not the sole pathway
10 and it's difficult to see in the literature that it
11 actually can predict what the follicular shunt
12 contribution is going to be. The stratum is not a
13 real compartment the way the blood is. It's not well
14 mixed. It is not in equilibrium with the actual
15 target.

16 Again, the cartoons typically show it as
17 being in this very orderly baklava kind of structure,
18 but the fact is is that there are a lot of furrows,
19 a lot of irregularities and the fact that one gets a
20 similar amount on each tape strip is really an
21 artifact of the tape stripping. It's not really that
22 one is excavating layer by layer down through the
23 stratum corneum. And then some of the members of the
24 committee have already considered the concern about
25 how the stratum corneum really is absent in diseased

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1 skin. It's absent in the rip and the vaginal mucosa
2 which are intended sites for this guidance document.

3 If one thinks about oral dosage forms,
4 they go into solution in one of the fluids in the
5 gastrointestinal tract, often the gastric juices as I
6 have here, and they go into solution and then they
7 bathe up against the gut wall and the solvent for that
8 solution is the biological fluid which is kept in
9 homeostasis so from one person to the next it's a
10 pretty similar kind of fluid. So the vehicle
11 literally up against the gastric mucosa is a fairly
12 constant vehicle. And then it goes through the gut
13 wall and it goes into the blood. The blood is well
14 mixed and the blood is in equilibrium with the target
15 organ.

16 I thought I'd quote Doctor Schaefer here
17 as an expert who could speak to this. He's written
18 earlier that "Plasma levels produced by two generic
19 formulations should be similar at equilibrium as the
20 plasma level/tissue level ratio will remain constant
21 at equilibrium." So I think he is agreeing that this
22 equilibrium notion is important. So equilibrium,
23 homogeneity, and good mixing.

24 Contrast that with healthy skin. Here we
25 have the active in a vehicle and if it's a solution,

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1 it's going to be thought of differently for generic.
2 We're really talking about semi-solids today. So they
3 are multiphasic structures and there's going to be a
4 continuous phase and a discontinuous phase typically
5 and it will be the continuous phase that abuts up
6 against the stratum corneum and the active will come
7 from the continuous phase into the stratum corneum.
8 It will partition in. So there's not this
9 intermediacy of a solution of constancy as in the
10 gastrointestinal tract.

11 The second difficulty is that on the skin
12 the vehicle has two pathways. We're talking today
13 about DPK which is only going to look at the stratum
14 corneum but, in fact, the vehicle can go -- the active
15 can go through the stratum corneum or it can go
16 through the follicle and it can go to the variety of
17 parts in the skin and many of the ones that we're
18 really interested in, drugs we're interested in, we
19 like to see going down to the superficial dermis which
20 is where the blood vessels are which is also seen with
21 the vasoconstrictor test. Those are the blood vessels
22 that are involved in that.

23 One of the questions that has already been
24 raised is that functionally and anatomically intact
25 stratum corneum does not occur in the skin disease and

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1 so what one really sees in skin disease is something
2 different. Again, I'm quoting Doctor Schaefer. I
3 have a handout that the committee has at the table
4 where I've quoted some of the other experts who were
5 invited here today. I happen to use Doctor Schaefer's
6 words because they're very pithy and they fit on a
7 slide. So I hope he doesn't think I'm picking on him.
8 I really like the expression.

9 But what he indicates here is when a
10 dermatologic drug is used, it is usually applied to
11 diseased skin which may not have the same permeability
12 as healthy skin and to simulate diseased skin, the
13 stratum corneum can be removed. So here is our model
14 of the vehicle containing the active sitting on skin
15 and disease and there may not be much of a stratum
16 corneum barrier in that particular setting.

17 Okay. If you could lower that just a tad
18 so we could start at the top. I just want to point
19 out that we're looking at topical absorption on this
20 side, oral absorption on this side. The gastric
21 juices, the gastrointestinal canal fluids are more
22 constant than we can expect the vehicles which will be
23 in the topical products, the differences between the
24 reference listed product and the generic can be very
25 inconstant. It may be due to actually the inactive

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1 ingredients. It may be that it is different in active
2 ingredients. It may be that it's the same inactive
3 ingredients, that they're there in a very different
4 proportion and it's also possible that somehow the
5 generic company would manage to come on the exact
6 recipe in terms of ingredients and the quantity of the
7 ingredients and still be able to do something
8 different in the manufacturing process to achieve this
9 complex multiphasic structure that is the topical
10 vehicle. So I would say it's much more inconstant
11 than the fluids of the GI tract.

12 I think that the stratum corneum for me is
13 the analog of the -- mucosa. I mean it's the barrier.
14 It's what one is going through. The stratum corneum
15 is only one of two paths to the target and doesn't
16 necessarily predict the other. I haven't seen any
17 evidence that it predicts the follicular path.
18 Healthy is certainly not the same thing as disease.
19 It's not well mixed. There is no equilibrium with the
20 target and it's absent in some of the places that
21 we're really interested in like skin disease, lip and
22 vaginal mucosa.

23 I don't think there is a cognate for the
24 plasma blood which again, is a single path to the
25 target if a drug is in the systemic circulation, it's

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1 going to the brain or to the kidney. It's going by
2 way of the blood if it's an oral drug. Healthy is
3 pretty much the same as diseased. It's not thought
4 that there are major differences in the plasma AUC in
5 people with headaches and people without headaches.
6 It's well mixed and there is an equilibrium with the
7 target end organ.

8 Next slide please. There's one additional
9 item and that is only rarely would someone use a
10 topical product one time. Virtually all use is
11 multiple applications. If Doctor Schaefer will
12 forgive me, I quoted him again. "The metabolic
13 activity and permeability of the skin may be changed
14 under the effect of repeated exposure to the product
15 during a toxicity or a clinical study." So I think
16 it's important that we consider this aspect as well.

17 There was an AAPS FDA workshop and in the
18 briefing materials for the committee under Tab 2 at
19 the very back you can actually see parts of this
20 paper. It's Bioequivalence and Topical Dermatological
21 Dosage Forms Methods of Evaluation of Bioequivalence.
22 There's a page missing. It's page 168 and so I wanted
23 to bring to the attention of the committee one of the
24 sentences that is found on page 168 and that is,
25 "Before a DPK method is adopted as a basis for

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1 bioequivalence, it must be shown that differences in
2 DPK capture or reflect significant clinically
3 important differences in formulations." I see that as
4 the final stage of validation and that could happen
5 even in the absence of getting to DPK from first
6 principles. That is, you wouldn't have to have the
7 analogy with the plasma AUC. One could get there by
8 raw pragmatism. It actually works because one has
9 done a series of studies.

10 The kind of evidence needed really, I
11 think this should be done blinded. I would think
12 there should be some group, possibly the Office of
13 Generic Drugs could do this, could send out three
14 bottles blinded to an investigator who could look at
15 the reference product, known bioequivalent product and
16 something very similar that could be a bio-
17 inequivalent product and the different therapeutic
18 classes because there are different target sites
19 within the skin. I think that kind of information
20 would be the right kind of information to have. The
21 information we have to date, certainly DPK as a method
22 for BABE would be compatible with some of the data we
23 have but it's under-determined by the data. It's
24 necessary that the data have turned out the way they
25 have, but by themselves I think they're insufficient

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1 to make the case.

2 In the last study we saw, the one with the
3 antibiotics, really, what kind of an answer could have
4 come out at the end of the day? DPK could have looked
5 exactly like the clinical outcome or it could have
6 been different, and I was thinking when I heard that
7 if I only had that argument when I was an
8 undergraduate, I could tell the professor that if I
9 didn't get the exact answers that he was looking for,
10 that it was because I was more discriminating in my
11 thinking about it.

12 I don't think DPK can be derived from
13 first principles through the grand analogy of the
14 plasma AUC. I believe it's under-determined by the
15 current evidence and I think that it really shouldn't
16 move forward until we have adequate evidence, this
17 final stage of validation that we know that it really
18 can detect clinically meaningful differences in
19 products. Thank you.

20 DOCTOR TAYLOR: Thank you very much. This
21 presentation is open for discussion.

22 DOCTOR KILPATRICK: John, if you want your
23 pragmatic validation, would you advise that to be done
24 on normal skin or diseased skin?

25 DOCTOR WILKIN: Actually, I thought I was

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1 pretty obvious about that. I think that the analogy
2 doesn't work for normal skin. It doesn't work for
3 normal stratum corneum. But in terms of pragmatism,
4 I mean if one is not getting there with first
5 principles, I mean the truth is is that if someone
6 could actually go out and paint this on tree bark and
7 show that you could actually make the discrimination,
8 I think we could get there pragmatically.

9 DOCTOR TAYLOR: Are there additional
10 questions?

11 DOCTOR BRANCH: Can you comment on the
12 question of the idea of producer risk. Let's take the
13 example that was shown with the Miconazole study where
14 bioequivalence was shown. Here we had a clinical
15 study that actually took 50 people in both arms and
16 that's a fairly substantial study for bioequivalence
17 and the critique that you could level at it is that it
18 was under-powered and that's because of the variance
19 that comes into the end point measures.

20 Now you're going to a technique that has
21 got a greater level of precision and which, if I
22 understand you correctly, you would not be concerned
23 that if bioequivalence were shown with this technique,
24 you'd be comfortable with that going through to a
25 patient population. The issue is where you don't show

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1 bioequivalence. Then how do you interpret that?
2 Well, right now without the availability of that
3 particular test, you have to go for the clinical study
4 with all the cumbersome nature and the lack of
5 precision of that.

6 So it seems to me that what you're
7 offering to industry if this guidance is adopted is a
8 relatively high risk approach because it's going to be
9 hard to show equivalence. But if you've got
10 equivalence, you've got a rapid shortcut to not have
11 to go through the clinical testing. If you show
12 nonequivalence, you've got the same options that you
13 have right now of doing the clinical study. So it
14 seems to me that what the whole exercise is doing is
15 offering a greater range of choice, a potentially
16 faster, more efficient system for industry. And I see
17 absolutely minimum risk to the public community by
18 going for a higher precision technique. So I'm really
19 confused as to why you're taking role that this
20 approach is no use.

21 Could you sort of respond to the public
22 interest nature of this and the potential advantage to
23 the pharmaceutical industry if they actually get
24 within that range.

25 DOCTOR WILKIN: Sure. I'd be happy to.

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1 I think actually we probably agree on multiple points.
2 I would agree that the clinical tests can be more time
3 consuming, certainly more resource consuming, and I
4 would agree that they're probably more imprecise. I
5 think at the end though what I would say is would you
6 rather have an imprecise answer to the right question
7 or a precise answer to the wrong question? What I
8 really haven't heard is that DPK is really telling us
9 the kind of information that we need and that is can
10 it detect clinically significant differences? I mean
11 the tests that we have seen so far weren't designed
12 really to query that point.

13 DOCTOR BRANCH: I think that those of us
14 who were here yesterday, there was a very nice
15 presentation from the floor in the open session of
16 the constraints that go to or the tensions that are
17 present in developing policy for approval for
18 bioequivalence of therapeutic relevance versus the
19 producer trying to produce something within a defined
20 set of criteria. There is a coming together that the
21 FDA has to resolve with that.

22 But what I think you're addressing is the
23 clinical relevance issue requires clinical trials to
24 answer that question. If that's what industry really
25 want, then the whole of this is redundant but they can

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1 expect to do clinical trials of sufficient power to be
2 able to answer the question. What you're asking for
3 is a generic equivalent to something that's already
4 been proved. So it seems to me that what we're
5 talking about in this overall discussion is a step in
6 the right direction to try to and reduce the amount of
7 burden in terms of being able to get generics on the
8 market. The question is how to do it.

9 If you take something that has absolutely
10 no risk to the public, it actually sets the goal post
11 higher, then it seems to me that this is a very
12 reasonable, logical way to proceed. If there were
13 false negatives from this that you got, if that was
14 the danger, then I'd take the opposite tack. But all
15 that I've heard so far is it's going to be much harder
16 to get within those goal posts but if you got within,
17 then your confidence is going to be the same and
18 you're taking a surrogate marker. It's a surrogate
19 marker approach. You're saying the skin in the
20 forearm is equivalent to or a surrogate marker for
21 what's happening in the vagina. That's part of what
22 this phase of bioequivalence is all about. I don't
23 see where the problem comes.

24 DOCTOR TAYLOR: Any additional questions?

25 DOCTOR MINDEL: In a functional way, the

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1 sentence about the washing. "In case of certain oily
2 preparations such as ointments, washing the area with
3 a mild soap may be needed before skin stripping." I
4 know I'm asking this to the audience that I want to
5 answer, but how would you determine whether a
6 preparation is oily enough that it should be washed
7 away with a mild soap and what would be the effect on
8 the data of washing away with a mild soap?

9 DOCTOR WILKIN: Actually, this is Doctor
10 Shah's but I think any time that you moisten the skin,
11 you enhance generally percutaneous penetration. If
12 the drug is already on the skin and then you're
13 moistening it after the fact, often it will drive more
14 drug through with that second washing. That's one of
15 the reasons why folks who have really toxic agents
16 that easily penetrate the skin, when they go to
17 emergency rooms, they might not be sent to the shower
18 which could actually drive a lot of the drug in.

19 I think it's in North Carolina people get
20 what they call green tobacco disease and the folks
21 that get extremely ill from that, which is from
22 nicotine on the skin, are the ones who, when they
23 start feeling ill, go into a shower and try to wash it
24 off but what they really do is they drive more
25 nicotine in.

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1 DOCTOR MINDEL: What bothers me is this
2 oily aspect of the ointments and why is it important
3 to remove them with soap under certain circumstances?
4 I mean you're going to be the -- this whole problem of
5 the ointment on the skin, removing it, getting a
6 reasonable sample, this whole aspect bothers me a
7 great deal and I don't see how functionally the FDA
8 can make certain determinations that this ointment
9 shouldn't be washed away and other ointments should be
10 washed away.

11 DOCTOR WILKIN: Again, I'm not the speaker
12 who should be defending that. I mean I started out
13 saying that I had 15 minutes so I was going to limit
14 my focus, my target. There are other things that I
15 could talk about. That could have been one of them.
16 I'm not going to argue with your point or explain it
17 differently. I think that falls to Doctor Shah or
18 Doctor Shrivastava.

19 DOCTOR TAYLOR: Why don't we delay that,
20 what I perceive might be a more prolonged discussion,
21 until we get to the end of the presentations so we'll
22 have all the data and then you can bring that up again
23 at that point because we're still having trouble
24 getting through two additional presentations. Did you
25 have another comment?

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1 DOCTOR LAMBORN: I just wanted to see if
2 I could get a clarification following the question a
3 minute ago. If I understood you correctly, the reason
4 that you are concerned about this assay is because, in
5 spite of the data that we heard earlier, you perceive
6 that there might very well be instances where there
7 would be apparent equivalence due to the DPK but
8 where, because of the fact that it would be moving to
9 a different surface or a diseased area, you might in
10 fact have inequivalence at those other locations. Is
11 that where your concern is?

12 DOCTOR WILKIN: I would say the essence,
13 I mean I have two concerns. One is I can't, of
14 course, get there from first principles for the --

15 DOCTOR LAMBORN: Right, but let's
16 assume--

17 DOCTOR WILKIN: Just looking at the data--

18 DOCTOR LAMBORN: -- the pragmatic one.

19 DOCTOR WILKIN: Yes. Just looking at the
20 data part of it, I don't see that the evidence is
21 complete at this stage that there really is sufficient
22 evidence to say that DPK is going to detect clinically
23 important differences in two products.

24 DOCTOR LAMBORN: Okay. I think that
25 that's addressing what your question is. Thank you.

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1 DOCTOR DiGIOVANNA: I just wanted to make
2 a comment about the adverse risk to the consumer.
3 From the perspective, as I see it, at least this
4 point, if there is an assay that determines that a
5 generic is bioequivalent and that assay doesn't
6 measure appropriately what one wants to measure, which
7 is the concern that's been raised about this, and a
8 product is approved that ends up being clinically
9 substandard, then I think there's a substantial risk
10 to the consumer, not only in cost but also in delay
11 or lack of treatment and all the medical consequences
12 thereof. So I think there is a real issue with
13 respect to answering the right question.

14 DOCTOR TAYLOR: We're going to move on
15 now. Thank you very much for your presentation. Now
16 the final two presentations for the morning. We'll
17 start with DPK compared to standard approaches,
18 Professor Schaefer, and I'm going to ask you to try to
19 stick to the time.

20 DOCTOR SCHAEFER: First of all, after the
21 joke of Doctor Wilkin, I have to rearrange my
22 overheads.

23 First, I think everybody will agree that
24 what you see on the right slide after 1,000 minutes in
25 the skin of -- is the relevant issue. It's the

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1 concentrations in the skin, we measured in vivo in
2 humans in biopsies with the stripping of the left side
3 and concentrations in the skin in the -- tissue on the
4 right side. The point is is there correlation between
5 the right side and on the left side on normal skin.
6 That is the point we want to examine.

7 Now the next please. It's only to say
8 that we have done this in quite a number of instances
9 and had I known about the discussion today, I would
10 have brought more slides of this kidn because it's
11 only to tell you that, for example, with this -- zone,
12 we have done the same in normal and diseased skin and
13 seeing this correlation.

14 Next please. To answer questions which
15 were in the room. These are the kinetics.
16 Testosterone. Again a different compound. Horny
17 layers 100 times higher concentrations in the
18 reservoir and this is what happens subsequently in the
19 epidermis and the dermis. These are the true kinetics
20 on human skin in vivo.

21 Next please. Here's another one of the
22 same kind. This is another drug. I think it's
23 amphelin. Concentrations the horny layer, epidermis,
24 dermis. That's what Vinod showed and you see the
25 correlation between the two of them. Skip that one,

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1 Vinod. Next one.

2 This is the most important for me today
3 because what does it say? A) on top to the right and
4 on the left side is complete analysis. It is on
5 animals in vivo applied compounds under different
6 conditions and I tell you under which conditions. Two
7 animals and analogy is complete -- after four days
8 relative to stripping after 30 minutes. What you see
9 on the top is different compounds, correlation between
10 stripping after 30 minutes and including blood,
11 including -- including urine or excretion. Every and
12 any body compartment. So it's only stratum corneum.
13 It's correlated. Take stratum corneum aside and take
14 the rest of the body. That's what you see.

15 On the right side, four compounds at five
16 different concentrations. A clear cut correlation
17 between what is applied to the skin, what enters into
18 the reservoir and what happens subsequently. Complete
19 biolance, masked biolance in four days. On the left,
20 different -- alcohol and propylene glycol and --
21 different also recalls, several different anatomic
22 locations is on the right side. This is in humans.
23 On the right side, this has been done at Maibach's lab
24 with Andrew Rougier and Dupree and -- They have done
25 these assays with Hobart Maibach's approach which is

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1 not concentrations in the skin. It's concentrations
2 in the serum and concentrations excreted by the urine
3 and again, now you see we're coming very close to the
4 systemic compartment, the blood compartment or the
5 global body compartment and there's a clear cut
6 correlation between the two of them.

7 So in other words -- next please --
8 technicality. Only reason to show you this one is to
9 give you an impression how it looks really. The
10 concentrations in the different stripping layers now
11 with two sunscreens. You see the true concentration
12 profile layer by layer. In other words, this answers
13 the question how many tapes you have to take. Very
14 few in order to get this correlation. Only to tell
15 you that technical details which you have addressed
16 which you have asked for are already approached and we
17 won't have the time today to tell you about the
18 technical details of how this can be quantified, how
19 variabilities can be excluded. Only to show you one
20 approach which has been done in Berlin by Doctor
21 Weigmann and Doctor Lademann.

22 Next please. Here's still another
23 distribution in percentage in the horny layer of
24 sunscreen substances. The next please. What they
25 did, they investigated the absorption profile of tape

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1 strips and where they can measure the amount of
2 stratum corneum that is of corneocytes adhering to the
3 tape because it's not the number of the tapes that's
4 relevant. It's not the weight of the tape which is
5 relevant. It is the number of corneocytes, the mass,
6 which is relevant. And they found out that where you
7 see corneocytes aggregate at that site, at that wave
8 length, you can measure and what you see it -- the
9 next slide please -- what you see is the rate line
10 from tape one to tape 17. It's almost linear. In
11 other words, when you take the absorption at -- I
12 think it's 220 nanometers -- then you have a
13 quantitative measure for the mass of corneocytes, the
14 mass of material adhering whereas when you take the
15 weight, it is the blue one. There is, you see quite
16 clearly, where there is still -- adhering to the tapes
17 in terms of mass but no corresponding or not
18 sufficient corresponding mass of corneocytes whereas
19 when you go down to strip five, it becomes parallel.

20 Later on, of course, it goes down because
21 there's less and less material, adhering becomes more
22 and more wet. It's only to tell you that these things
23 have already been approached. This is under way.
24 There are publications under way. There's more work
25 under way. We're trying to work very hard on this to

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1 standardize this. Next please.

2 So we come back to the point. If we
3 believe -- and I might make asterisk in the
4 discussion. If we believe that concentration in the
5 target tissue corresponds to clinical efficacy and if
6 I can convince you that concentration in the target
7 tissue is strictly correlated to the reservoir that's
8 shown in vivo on animals, on humans, in different
9 models and under mass balance conditions, if we
10 believe that, then we can state and we must state that
11 there's a quantitative link between the horny layer
12 reservoir and the subsequent penetration and
13 permeation. That is subsequent process independently
14 of whether this skin is normal or whether it's
15 diseased.

16 Next please. So it comes back to the
17 question. Can we under these conditions, conceived
18 conditions, under which DPK, as assessed by the tape
19 stripping technique, would not detect pharmacokinetic
20 differences between two preparations. I clearly state
21 you assume that there is a link between concentrations
22 and clinical activity. The only thing I'm saying,
23 that is I can not conceive conditions under which the
24 pharmacokinetics would not be depicted by the
25 stripping technique. Thank you very much. We have

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1 time for maybe a couple of questions from the
2 committee, if there are any.

3 DOCTOR MCGUIRE: Doesn't it depend upon
4 where the target is? If the target is within the
5 stratum corneum, then the elimination phase or rapid
6 elimination actually works against you.

7 DOCTOR SCHAEFER: Yes. Rapid elimination
8 in the skin under these conditions normally doesn't
9 exist. Kinetics is almost always the same. I can't
10 give you exceptions, the exception being a -- acid
11 test of similar compounds. We know the maximum is
12 about three hours to five hours.

13 DOCTOR WALKER: I see why you think this
14 is a good method from some points of view, but I have
15 a problem understanding how we can say that we're
16 determining equivalence using a surrogate for vaginal
17 preparations where it's in the mucosa versus the skin,
18 where there's a horny layer versus no horny layer.
19 Maybe what you're saying, Doctor Pershing, about it
20 may be making us a little bit more discriminating is
21 true, but I don't think that we can say that we can go
22 by that alone. I think that it's imperative where
23 there's such a difference in the surface that the
24 clinical trial has to be done. Maybe I'm naive about
25 that. Maybe somebody can tell me why my thinking is

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1 incorrect, but it just doesn't seem like you can
2 compare apples and oranges.

3 DOCTOR SCHAEFER: Sorry, I can not because
4 I have no experience. I can not answer the question.

5 DOCTOR TAYLOR: Let's save that one for
6 the end, as well, and we'll have some general
7 discussion and have the other individuals that have
8 presented be able to make some comments.

9 Let's move on to the last presentation for
10 the morning and it's correlations and clinical
11 relevance, Doctor Howard Maibach.

12 DOCTOR MAIBACH: Thank you, Doctor Taylor,
13 members of the committee, members of the agency, and
14 colleagues. I apologize to those of you in the back
15 that I am facing the front, but that is the way the
16 hardware is rigged today.

17 My assignment simply is not for the
18 dermatologists who know this very well but for
19 somebody on the outside to explain to the non-
20 dermatologists the report card, the voracity of
21 clinical trials or cutaneous biometrics as relates to
22 clinical trials.

23 The first point is that, as an article of
24 faith, as an assumption and hardly a fact, most
25 dermatologists believe today that the quality of semi-

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1 solid formulations available to the consumer and to
2 the patient is distinctly better than the quality a
3 generation or two generations ago. There is no clear
4 data. The experiments haven't been done. But it's
5 probably a reasonable assumption.

6 Secondly, most people who are not in this
7 room, certainly most practicing physicians and
8 pharmacists and other scientists and the consumer,
9 firmly believe that even if they don't understand
10 anything about any type of pharmacokinetics, that they
11 do have confidence in the clinical trial. And I, too,
12 make the same assumption, that if I could only have
13 one of the two techniques, which is not the case
14 because clearly dermatopharmacokinetics is going to
15 survive and prosper no matter what the group does
16 today because it's a scientific method of significant
17 prowess and power. But if I can only use one today,
18 I accept that the gold standard, the platinum or the
19 diamond standard, is the clinical trial.

20 Now, let's talk about what we know then
21 about the power of the clinical trial because, of
22 course, then that is what the consumer is depending
23 upon us for. There is no doubt that the clinical
24 trial is superb in telling the difference between an
25 active and a placebo. It's probably not as good as we

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1 would like for many reasons, which are the subject of
2 a new textbook which will be available in a few months
3 called *Cutaneous Biometrics*. But when you go through
4 the cutaneous biometrics, you will see there are many
5 examples of drugs that the consumer thinks that works,
6 the dermatologist thinks that work, but if you take a
7 look at the data, they don't work nearly as well as we
8 would like. Well, one can just say that that
9 is a complex issue, but it's still the best that we
10 have available today.

11 Secondly, if you take a look at the
12 efficacy data, one of the most troubling parts of it,
13 so much so that it got into *The New York Times*
14 magazine section two or three weeks ago, is the fact
15 that when we dermatologists do clinical trials, we see
16 panaceas all over the place. The panacea that we see
17 is the remarkable response of the placebo in the
18 clinical trial. Now, *The New York Times* editorialist
19 and writer chose to say that it was some mysterious
20 hormone yet to be identified. I take it certainly in
21 biometrics of skin, very often it's the subjective
22 measurements that we must use today for most of these
23 trials and, in fact, if you took a look at the most
24 objective studies of clinical efficacy, you find that
25 in the objective studies the placebo isn't quite as

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1 powerful as it is in the subjective studies.

2 Now, the one area though where the
3 clinical trial has noticeably been weak has been in
4 the area of something that all pharmacologists and all
5 toxicologists hold as just as much of a belief, if not
6 more of a belief, than the New Testament to the Old
7 Testament and the Koran put together, and that is the
8 ability to show a difference, something called a dose
9 response relationship. As recently as several months
10 ago in a very important article in *The New England*
11 *Journal* and *The New England Journal* doesn't publish
12 too many dermatologic efficacy articles, clearly a
13 drug was effective in atopic dermatitis but in a very
14 large study, much larger than the ones demonstrated
15 here today, the clinical measurement systems, the
16 metrics were not sufficient to show a dose response
17 occurred.

18 Now, if you take a look at the report card
19 of all of the English publications because somebody
20 has done this and I don't want to do it for the
21 American or Czech publications, but it is available
22 for the English publications in one journal. If you
23 take a look at the ability to show the difference
24 between any two drugs or any two formulations, the
25 overwhelming majority of the publications show we

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1 can't show a difference. Now, the purpose of the
2 particular article that I'm referring to, it's
3 Williams in *The British Medical Journal*, is not that
4 the metrics were so bad but that the insufficient
5 numbers of subjects were used so that the power was so
6 weak that our statisticians every time will say,
7 Howard, don't even do the experiment because there
8 isn't sufficient power to do it.

9 Now, what are the weaknesses in our
10 clinical trials? #1, we need more objective
11 techniques and those are being developed and
12 bioengineered in other areas. #2, in the clinical
13 trial paradigm that we use today, we are stuck with a
14 validation problem that Doctor Wilkin mentioned and
15 that is going from one laboratory to another. Most of
16 our clinical trials are multi-center trials where each
17 individual grader is seeing a different subjective
18 response and, furthermore, when I get the chance, not
19 as often as the people in the agency get the chance,
20 to read the reports, very often more than one grader,
21 if I look at the signature, was done at each study
22 site. So you're adding enormous diversity of
23 subjective measurements.

24 Then lastly, obviously a disadvantage of
25 the multi-center studies is because you're losing

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1 power with the weakness of the metric, the many
2 graders, you need many larger numbers of subjects and
3 the statisticians who look at this with us all the
4 time are constantly warning us about that.

5 In terms of the clinical trials between
6 telling the difference between any two fuitively
7 similar formulations, there's another problem.
8 Recently the agency approved an important formulation
9 which I'm sure is biologically equivalent in which the
10 two formulations were 92 percent effective. To my
11 personal taste with the weakness in our metrics today,
12 when I read papers like that -- this one I didn't
13 read, I read it in a summary basis of approval -- I
14 feel much more comfortable when there's a third leg
15 and the third leg is, of course, the clinical leg
16 where there's a placebo which is a test of the
17 observer to make a valid observation.

18 Now, in fact, the clinical trials are the
19 standard that everything that we've done since 1963 is
20 dependent upon. The clinical trials are surely going
21 to improve. Namely, yesterday or the day before the
22 agency had a workshop on metrics and psoriasis. I
23 haven't read the minutes yet, but I'm hoping that when
24 I read them I'm going to be absolutely enlightened to
25 make those trials more efficient than they were

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1 before.

2 Secondly, I believe that, although one has
3 great limitations in the paired comparison methodology
4 in clinical trials of left versus right in the arena
5 of toxicology, I am not yet convinced that we can't
6 creatively use paired comparisons to make more
7 effective clinical trials than we have before.

8 And then thirdly, as I had mentioned
9 earlier, I am confident that within five to 10 years
10 that, in fact, the objective measurements will greatly
11 aid the subjective measurements and make the clinical
12 trials more powerful.

13 Now, what do I see for the future, the
14 future 36 months from now or five years from now?
15 Well, I think it should be clear to all of you that
16 the clinical trial is not going to disappear because
17 it is the standard that society is dependent upon.
18 But #2, I think that the dermatopharmacokinetic
19 approach -- and clearly there's room for far more
20 validation and there's more room to improve the
21 technology and we see some of that already -- it's not
22 going to go away because it has a power and a
23 simplicity that the clinical trials don't have.

24 But in the end, I think that what all of
25 us do in this room today can really be viewed the big

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1 picture is very simple. When individual
2 bioequivalence is worked out three or four years from
3 now, when Doctor Williams has his meeting to display
4 to the universe of science what individual
5 bioequivalence is shown for oral drugs, by then
6 hopefully dermatology and dermatopharmacology and
7 dermatotoxicology will have enough information so that
8 we'll understand the integrity and the validation
9 aspects of each of the clinical trials, the integrity
10 and the validation aspects of any of the kinetic
11 methods, but in the end the days that somebody can
12 show a better method, science will adopt it and I'm
13 sure the agency will adopt it and I'm sure the
14 practicing physician will adopt it.

15 I hope I've been suitably brief and
16 delivered you to your lunch on the appropriate time,
17 Doctor Taylor. Thank you.

18 DOCTOR TAYLOR: Thank you. That completes
19 the presentations. I'll open up the floor for
20 discussion by the committee at this point. We've had
21 quite a bit of discussion already but we have, I
22 think, time for some additional.

23 DOCTOR BRAZEAU: Well, as I've been
24 listening to these presentations this morning, it goes
25 back to some of the questions that we've been asking

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1 or were asked earlier by Roger. What do we want to
2 know? What assumptions are we willing to make? And
3 how sure do we want to be? I think I'd like to
4 address the last question. How sure do we want to be?

5 I see in this dermatopharmacokinetics a
6 method that is more sensitive, a method that goes back
7 to what's been discussed earlier about potential
8 safety issues. I think that's a major component here.
9 I'd much rather err on the side of being cautious than
10 err on the other side, and I think that we've got a
11 technique here that allows us to have the sensitivity,
12 allows us to quickly check a generic versus an
13 innovator product and remember, if my understanding is
14 correct -- and maybe, Roger, I'm wrong -- the
15 assumption is the generic can show bioequivalence and
16 therapeutic equivalence if it's the same product and
17 that generic products shouldn't have to go through any
18 more rigor versus the innovator product. I think
19 we've got a useful technique that we need to go
20 forward with and implement in various techniques. We
21 do need more data, but I think the data is going to
22 show that this technique is going to be valuable.

23 DOCTOR TAYLOR: Thank you. Yes, Doctor
24 Lavin.

25 DOCTOR LAVIN: One request that I have is

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1 that it be reproducible from one site to another so
2 that one could trust the results, that there would be
3 a protocol, that there would be training, that there
4 would be standardization and that there would be
5 experience so that one could trust the results
6 consistently from one center to the other, and I think
7 that that will probably be the key to making it be
8 able to be accepted.

9 DOCTOR TAYLOR: Doctor Lamborn.

10 DOCTOR LAMBORN: The thing I could use
11 some help on from those who are from the Dermatology
12 Committee, I think that from my perspective we've
13 shown that in some instances -- and it appears some
14 good data -- that if we can get the validation
15 straightened out that you can -- it is sensitive -- is
16 there a logic that says though that there are
17 circumstances when the kinetics of how these agents
18 would work when they're going to be applied to
19 diseased skin or to other surfaces, that it is not
20 safe to assume that it will detect the differences.

21 In other words, I understand that the
22 technique itself is quite sensitive. That part has
23 been demonstrated. But of the specific examples like
24 the vaginal or others where there's an argument for
25 why this would not carry over.

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1 DOCTOR TAYLOR: Who would like to respond?

2 DOCTOR DiGIOVANNA: The one argument I
3 would think of that seems the strongest to me is
4 analogous to the difference between normal skin and
5 vaginal mucosa is that you're measuring uptake and
6 elimination from the stratum corneum which is either
7 a very different character undergoing very different
8 behavior and, in some cases, hardly there at all. So
9 you're measuring a different process, and I would
10 think that is the major, most intuitive argument to me
11 that what you are measuring isn't there.

12 DOCTOR TAYLOR: Any other responses to
13 Doctor Lamborn's question? Doctor Branch.

14 DOCTOR BRANCH: It seems to me that what
15 we're suggesting is a surrogate measure for clinical
16 response and it should be subject to all the criteria
17 and all the evaluation that goes for any surrogate
18 measure. How many false positives, how many false
19 negatives? Is it a good index? I think the danger
20 -- I'm not sure exactly how Anders work, but I think
21 there is a responsibility from industry to provide the
22 FDA with both positive and negative data as the
23 experience accumulates and there would be a real
24 danger if industry hangs on to data which it really
25 doesn't want to show because I think the issue of can

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1 you get equivalence by this method that actually puts
2 products on the market that create different
3 therapeutic responses, that's an extremely important
4 piece of information. Converse, the false positive
5 and false negative rates are the key issue as to the
6 long term acceptability of this. It still seems to me
7 that if this is introduced, you're still not
8 preventing industry from going and doing the gold
9 standard, the clinical trial. You're just giving them
10 an option to get a short cut there. It seems a
11 reasonable approach.

12 DOCTOR TAYLOR: Doctor Shah.

13 DOCTOR SHAH: I'll try to give some
14 examples again what we discussed earlier with respect
15 to the -- discussions that products which are
16 clinically equivalent didn't show equivalent
17 dermatopharmacokinetics. Now, in terms of the
18 corticosteroids, as we discussed earlier, the two
19 corticosteroids clobetasol from the innovator company
20 and the USP product are both determined to be
21 equivalent by the FDA standard. What other standard
22 we have, that has been accepted to be equivalent.
23 Now, there is no dispute on that. When we did the DPK
24 on that, we find it to be exactly the same. There is
25 no difference between the two.

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1 Going back to the Temovate E and Temovate,
2 since it is known that those two products are not
3 interchangeable, again we showed the data that the
4 products from the DPK point also are not
5 interchangeable. They are distinctly different. So
6 again, we do have some data and I would suggest and I
7 would be going along with the Doctor Lamborn and
8 Doctor Branch's indications. This is a really
9 sensitive matter and we need to go and try and have
10 the data. If we do not have this kind of an approach,
11 it's going to be very difficult for the generics to go
12 out and say that. We also heard from Doctor Maibach
13 indicating that it is really difficult to find a dose
14 proportionality area, in which cases we are seeing the
15 dose proportionality with the glucocorticoids. You
16 have 20, 30, 40 differences in the concentrations.
17 It's exactly the same pharmacodynamic response and
18 maybe nearly the same kinds of things with several
19 other cases.

20 But with the DPK we have an excellent
21 chance of showing a very good dose proportionality.
22 We can really distinguish between the different
23 concentrations.

24 DOCTOR TAYLOR: Thank you. Yes, Doctor
25 Wilkin.

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1 DOCTOR WILKIN: I'd like to respond to one
2 of the comments that Doctor Shah made and that is the
3 comparison between the Temovate cream and the generic
4 product. It's true, as he says, that the FDA will
5 accept these as equivalent and so I think we have to
6 take that on one hand. But on the other hand, think
7 about the mechanism how this occurred. It's with the
8 multi-point Stodden MacKenzie assay, so one is looking
9 at vasoconstriction and when one is looking at
10 vasoconstrictor potency of topical corticosteroids,
11 and these are super potent topical corticosteroids,
12 there's only so much power that one can achieve.

13 So as one continues higher strength
14 corticosteroids, more potent corticosteroids, there's
15 this horizontal asymptote. I mean you can't get super
16 power. There's only one level of power that you can
17 achieve and so there's a curvilinear relationship at
18 the very end and the fact that it didn't show may mean
19 something a little differently. I think the assay is
20 probably more accurate. The multi point Stodden
21 MacKenzie assay is probably more accurate and more
22 linear when it's looking at the lower potency
23 corticosteroids.

24 DOCTOR TAYLOR: Thank you. Doctor
25 Kilpatrick.

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1 DOCTOR KILPATRICK: Kilpatrick from DODAC.
2 In some sense, I'm going to be reiterating what the
3 last three speakers have been saying, as far as I can
4 understand them. I'm still convinced that the
5 randomized clinical trial is a necessary standard, but
6 I'm beginning to see the DPK as an adjunct to the
7 clinical trial in the following sense. If we turn
8 things around on their head a little bit, the clinical
9 trial could come in first focused not at multiple
10 doses but at a given dose thought to be effective and
11 safe and, having established efficacy and hopefully
12 safety, DPK would then be used to establish a dose
13 response relationship. This is off the top of my head
14 but I don't know whether it's a feasible situation or
15 not.

16 DOCTOR TAYLOR: Would someone like to
17 respond to that? Doctor Williams.

18 DOCTOR WILLIAMS: I think that's an
19 interesting suggestion and if it's all right with the
20 chairman, I'll make some general comments. First of
21 all, I found this discussion very useful and very
22 helpful and, as you can see, I'm trying to not say
23 much because I really want to be the recipient of what
24 the committee has to say. Second of all, I think one
25 of the ways the committees could help us would be to

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1 kind of give us ideas about -- I'm going to use the
2 wrong word here -- validation of the surrogacy of DPK,
3 and I'll tell you why that's the wrong word in just a
4 second.

5 I like that thought and I might ask the
6 committee if we could show that there was a dose
7 response to DPK where we couldn't show it in the
8 clinic, because we all recognize it's hard to show a
9 dose response in terms of clinical effect sometimes,
10 would they find that compelling in terms of quote
11 "validating the DPK approach"? I think I'm really
12 following up on your suggestion.

13 DOCTOR TAYLOR: Additional comments from
14 the committee?

15 DOCTOR WILLIAMS: We may actually have
16 some of that data already in the welter of information
17 that I've seen this morning.

18 DOCTOR MCGUIRE: What concerns me is that
19 one is measuring only one very small piece of the drug
20 interaction with the skin or with the patient. You're
21 measuring absorption, movement and elimination from a
22 membrane that the properties of which are pretty well
23 known but which is pretty badly damaged in most of the
24 diseases you're going to be treating. I'm not
25 speaking for any piece of the committee other than

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1 myself, but that's my major concern. I think that a
2 physical chemist could find molecules that have
3 absolutely no pharmacologic activity that mimic
4 exactly some of the active molecules that we're
5 dealing with. Of course, that's not the way the DPK
6 is going to be done, but if you're just looking for
7 molecules with those characteristics of absorption and
8 elimination, you could certainly find those.

9 Full stop. I was expecting to see some
10 data on comparing concentrations on uptake, absorption
11 and elimination this morning, and I don't know if
12 we're going to see them this afternoon. The nod is
13 yes.

14 DOCTOR SHAH: Yes. You will be seeing
15 some more data with respect to the dose
16 proportionality but maybe could I just bring back one
17 major question. What we are looking here is comparing
18 test product with the reference product in the same
19 type of formulation which has nearly the same
20 component or qualitatively, quantitatively does the
21 same composition. That is what we are here primarily
22 discussing with respect to the bioequivalency
23 determination.

24 DOCTOR McGUIRE: And Vinod, my concern is
25 that you are measuring characteristics of that

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1 molecule that may not be the most important ones for
2 its pharmacologic activity because you're measuring
3 its interaction with a compartment in the skin that is
4 damaged in the patient.

5 DOCTOR TAYLOR: Doctor Goldberg.

6 DOCTOR GOLDBERG: In response to that, I
7 think that what we're really looking at is not the
8 differences in drug response or transfer out of the
9 stratum corneum into the Z state but we're looking at
10 essentially the change in stratum corneum
11 concentration as a function of the dosage. Once the
12 drug enters the stratum corneum, the data seems to
13 support the fact that it will behave in a way -- I'm
14 sorry. Let me go back. Once the drug enters the
15 stratum corneum, it doesn't know whether it came from
16 product A or product B and it will perform the same
17 way once it enters the stratum corneum. What we're
18 looking for are differences in the rate and extent to
19 which it enters the stratum corneum. That's a dosage
20 form effect as opposed to what happens to the drug
21 after it enters the stratum corneum.

22 So the surrogate we're looking at is does
23 the dosage form affect the transfer beyond the stratum
24 corneum? I don't think it does. I think that's
25 independent of the dosage form. That's a function of

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1 the drug itself.

2 DOCTOR DiGIOVANNA: Somehow I don't
3 understand that in that I would think that one would
4 want to take into account the site of action of the
5 drug and not necessarily how it gets into and out of
6 a compartment. The characteristics of that motion may
7 be totally irrelevant to how that drug acts at the
8 active site. I guess that's why I don't understand.

9 DOCTOR GOLDBERG: The transport into and
10 out of the active site is a function of the drug/body
11 interaction. That has already been shown by efficacy
12 studies to work. So the question that I have is does
13 it enter the stratum corneum at the same rate from
14 product A and product B? I think that is very clearly
15 shown by GPK data.

16 DOCTOR TAYLOR: Doctor Williams.

17 DOCTOR WILLIAMS: One other thing I might
18 ask the committee to ponder and I'm going to ask maybe
19 Vinod and Tony, if he's here, to watch me closely in
20 terms of what I say. But the agency has already come
21 to a conclusion regarding post-approval changes for
22 these products via a document called SUPAC-SS. That
23 applies to both pioneers and generics and I can tell
24 you that our recommendation in that document is that
25 any manufacturing and site change can be handled, not

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1 even with DPK but with in vitro release provided you
2 stay within the five percent excipient range that you
3 see in the current guidance, the draft guidance, and
4 that your particle size doesn't change.

5 So if you ask what the agency has already
6 concluded, we've concluded that under those
7 circumstances we are willing to rely not even on DPK
8 but on in vitro release. Now, I guess I'm hearing a
9 lot of concern from certain segments of the joint
10 committees that may call us to reopen that question.

11 DOCTOR LAMBORN: I have a question for
12 the agency. Just clarification, a followup on the
13 issue of the current standard for clinical trials. It
14 was mentioned that you could have circumstances where
15 you're getting 90 percent efficacy apparently in the
16 clinical trial which is used to demonstrate
17 equivalence and the real question is would you in some
18 of those circumstances be ending up demonstrating
19 equivalence to placebo equally if there had been a
20 placebo component in that trial. I'm assuming that
21 the comparisons that are required for the generic
22 equivalent in fact do not include a third arm. Is
23 that correct, that their standard would be just simply
24 -- whoever can answer the question.

25 DOCTOR FANNING: Let me just answer to

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1 that because I actually review those studies and, in
2 most cases, placebos are included.

3 DOCTOR LAMBORN: They are included.

4 DOCTOR FANNING: They are included for
5 that very reason.

6 DOCTOR LAMBORN: Okay. Thank you.

7 DOCTOR TAYLOR: Doctor Wilkin.

8 DOCTOR WILKIN: I'm in the review division
9 for dermatologics and so I have looked over the SUPAC-
10 SS which is when innovators are changing their
11 vehicles in some way and they are generally quite
12 limited changes and, depending on what level of
13 change, there are different levels of things they must
14 do. I had the view in reading this guidance that
15 Doctor Shah has given to us that it's much more open
16 for these generic products.

17 I'm looking on page three of the guidance
18 and here's the section where it's talking about
19 inactive ingredients and under B it says, "Waiver of
20 bioequivalence" and it directs us to the Code of
21 Federal Regulations. It says, "In accordance with 21
22 CFR 31494A9V," and then there's this adverb,
23 "generally the test generic product intended for
24 topical use must contain the same inactive ingredients
25 as the reference listed drug." I'm wondering about

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1 the adverb "generally." I thought I knew what the
2 meaning was.

3 When I look at 21 CFR 31494A9V, it reads
4 like this. "Inactive ingredient changes permitted in
5 drug products intended for topical use. Generally, a
6 drug product intended for topical use shall contain
7 the same inactive ingredients as the reference listed
8 drug identified by the applicant under paragraph" and
9 then it gives another section of this section.
10 "However, an applicant may seek approval of a drug
11 product that differs from the reference listed drug
12 provided that the applicant identifies and
13 characterizes the differences and provides information
14 demonstrating that the differences do not affect the"
15 and the word here is "safety of the proposed product."
16 It really is not talking about efficacy.

17 And then I think at the very beginning
18 when Doctor Williams was talking about pharmaceutical
19 equivalence, he emphasized at that point that really
20 the inactives do not absolutely have to be the same
21 nor do they have to be in the same proportion.

22 DOCTOR TAYLOR: Is there a response to
23 that?

24 DOCTOR WILLIAMS: I think Jonathan is
25 raising a good question and I'm looking now that this

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1 five percent seems to relate to solution. What did
2 SUPAC-SS say? Was it all formulation?

3 DOCTOR SHAH: Yes. SUPAC-SS is referring
4 to the formulations, the brand name company has a
5 formulation and then when they make the changes in
6 terms of the inactive ingredients, how much of the
7 variations are allowed. It is maybe one percent, two
8 percent, five percent or, in extreme cases, up to 10
9 percent but in those cases they have to do the in
10 vitro drug release. Beyond that, they will have to do
11 the bioequivalency studies when those changes are
12 made.

13 Sometimes, as I made the presentation
14 earlier indicating that generally the generic
15 manufacturer goes and does the reverse engineering.
16 They try to identify and quantitate all the
17 ingredients which are in the brand name product.
18 Sometimes some of the names of the things aren't --
19 and that's what the word generally means. It may not
20 be containing every ingredient because it is not
21 identifiable. It could not be detected. But we as a
22 reviewer have the information of every ingredient,
23 every component in exactly all the proportions.
24 That's why the word generally comes up there.

25 DOCTOR TAYLOR: Doctor Wilkin, do you have

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1 a rebuttal to that?

2 DOCTOR WILKIN: No. Actually, I'm in full
3 agreement with that and I actually agree with that
4 section of the guidance because it goes on to say that
5 one can have a waiver of bioequivalence if it is a
6 solution. I just wanted to emphasize that a solution
7 is very different from a semi solid that is a multi-
8 phasic structured vehicle. It really doesn't matter
9 in a solution if you have the same inactive -- if you
10 have the same inactive ingredients and they're there
11 in the same proportion, it really doesn't matter how
12 you manufacture it. If you have a salt solution of
13 five percent, it doesn't matter whether you put the
14 salt in the beaker first or you put the water in the
15 beaker first. Whichever way you do it, you're going
16 to end up with the same salt solution. Solutions are
17 very predictable. But these are multi-phasic
18 structures and I don't think Q1 Q2, the list of
19 ingredients and their proportions actually determines
20 the properties ultimately of the vehicle.

21 DOCTOR TAYLOR: Doctor DiGiovanna.

22 DOCTOR DiGIOVANNA: Doctor Wilkin almost
23 took all of what I was going to say and that is that,
24 Doctor Shah, you refer to these inactive ingredients
25 and it's difficult for us dermatologists to express

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1 how we feel when we hear that. Many of us have used
2 preparations that are listed as generic equivalents
3 and many dermatologists will tell you such and such
4 preparation doesn't work and it may be listed as
5 equivalent.

6 Dermatology has a long history of
7 compounding, most of it before my time unfortunately
8 because I enjoy creativity and compounding is somewhat
9 like witchcraft or cooking or somewhere in between.
10 A number of years ago, I had the pleasure of visiting
11 with a dermatologist in Paris who was using some
12 ancient solution -- I believe it was called Yesner
13 solution -- to do a peel and I was rather fascinated
14 by this. She gave me the name of the person to go to
15 in Paris who could actually make this for me and we
16 had a very long conversation.

17 This is someone who was explaining to me
18 that unless you make this preparation exactly correct
19 using the exact right machine and getting the exact
20 particle size and adding the ingredients in the exact
21 proper way, it was like Julia Childs. You either got
22 a good cake or you didn't. I think that's some of
23 what we find so difficult here, that you can have the
24 same preparation with indistinguishable differences
25 according to the list of ingredients but a very

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1 different end product.

2 The concern here is that it may interact
3 with the stratum corneum the same way with certain of
4 its characteristics. It may not interact with the
5 target the same way.

6 DOCTOR TAYLOR: Since you brought up
7 cooking, that reminds me that we have to go to lunch.
8 So we're going to break for one hour. Return
9 approximately 20 minutes after one to continue.

10 (Whereupon, the hearing was recessed at
11 12:20 p.m. to reconvene at 2:20 p.m. this same day.)

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1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 2:25 p.m.

3 DOCTOR TAYLOR: The afternoon session is
4 an open public hearing of the issues that we have been
5 discussing this morning. We have nine individuals who
6 have indicated they would like to make some comments.
7 I'm going to ask that the speakers stick to the number
8 of minutes that they were given. In fact, you will be
9 on a timer and you can see it on the podium. It will
10 be green, then yellow, then red. The red is to
11 indicate that you're to stop.

12 At any rate, our first speaker is Doctor
13 Prakash Parab. He's a Senior Principal Scientist from
14 Bristol Meyers Squibb presenting on behalf of PhRMA.
15 You can proceed now.

16 DOCTOR PARAB: The major issues with
17 dermatopharmacokinetics is the -- that
18 dermatopharmacokinetics can not be used as a universal
19 surrogate for topical bioequivalence/bioavailability
20 because DPK has yet to prove its correlation to
21 clinical efficacy and systemic safety. Most important
22 is systemic safety. Topical product activity is a
23 composite of drug substance and vehicle excipients.

24 There are technical issues which will
25 limit the ability of the assay to be validated in

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1 terms of reproducibility, precision and so on. It is
2 a misconception and this is very sensitive. We have
3 a lot of questions on this.

4 In vitro release using a synthetic
5 membrane as a surrogate for topical bioequivalence and
6 quality control test has already been rejected by the
7 SUPAC-SS Committee and AAPS/FDA Workshop in 1997, so
8 they -- to drop from this guidance.

9 AAPS/FDA Workshop was held in 1996 to
10 discuss bioequivalence of topical dermatological
11 dosage forms. The consensus of the meeting identified
12 that the method of DPK assumes the excipients are
13 pharmacologically inactive, the stratum corneum
14 concentration time curves are directly related to the
15 concentration time curves of the active drug in the
16 epidermis and dermis and, lastly, that differences in
17 DPK captures or reflect significant clinically
18 important differences in formulation. However,
19 available data in humans indicate that these
20 assumptions have not been verified and, in some cases,
21 are contraindicated.

22 I will discuss briefly the limitations of
23 DPK with respect to appendages -- and body site
24 variations. Next slide. This table shows the stratum
25 corneum concentration, follicular concentration for

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1 three compounds at different times. You see that
2 stratum corneum concentration goes on increasing
3 whereas follicular concentration goes on decreasing.
4 Most importantly, follicular concentrations are very
5 high. The follicular concentration to stratum corneum
6 concentration can be from two to 37. Thus, the
7 stratum corneum concentrations do not predict
8 follicular concentration and DPK can not be used for
9 BA/BE for follicular availability drafts.

10 This particular table shows the steroids,
11 four different steroids, and its absorption through
12 scar skin and the surrounding normal skin done in
13 vitro and the normal skin had hair follicles and --
14 units where the scar skin did not have and you can
15 see that -- absorption for normal skin which had hair
16 follicles is significantly higher for all the --
17 compounds than that of the scar skin devoid of hair
18 follicles. This again shows the importance of
19 appendageal transport.

20 Now let us look at the skin accumulation.
21 There is no difference between scar and normal skin
22 for skin accumulation although -- absorption is
23 different. Therefore, there is no correlation between
24 skin accumulation and systemic absorption. Thus, DPK
25 can not predict systemic toxicity at a systemic

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1 exposure.

2 Now the rate -- effects. The rate of
3 excipients are not pharmacologically inert. Look at
4 the Retin-A vehicle. It causes 36 percent reduction
5 on all lesions whereas when you put active -- it goes
6 to 55. So you see a 60 percent -- effect. Look at
7 the Rogaine. -- 11 percent of the subjects showing
8 moderate to dense hair growth. When you put -- it is
9 26. Again, you see 40 percent -- effect. Thus, the
10 excipients in topical products are not
11 pharmacologically inert. They can affect the clinical
12 efficacy and safety. So it is a composite of the
13 active drugs and the vehicle.

14 Therefore, it's very important -- this
15 point is very important that the quantitative
16 composition of the reference product, the quantitative
17 composition should be less than ± 5.0 percent of that
18 of the reference product according to the SUPAC-SS.

19 Again, what is site variation? Site
20 Ciclopirox lotion is effective in interdigital tinea
21 pedis. Go to the most resistant area. It doesn't
22 work much. So DPK measures on volar forearm which is
23 moderately permeable may can not -- is less permeable
24 areas such as elbow and knee and more permeable areas
25 such as face and scalp.

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1 Let us review some of the DPK publications
2 with clinical end points which are given as a
3 reference in the guidance as a support. The authors
4 looks at the stratum corneum concentration at three to
5 four hours for four Bentameeethasone products and
6 plotted them against cumulative skin blanching and
7 plot a correlation of .9935. When we looked at the
8 details of this paper, we found that this correlation
9 was obtained with a clinically irrelevant dose of 159
10 mg/cm² under occlusion for 24 hours. The clinically
11 relevant dose is 2 mg/cm². Next slide please.

12 So the question, the validity of the
13 conclusion that the stratum corneum concentration
14 represents the concentration at the site of action,
15 that is the dermis in this case.

16 Now let us look at another paper where the
17 authors incorporated betamethasone dipropionate at
18 different concentrations in a cream product and looked
19 at the stratum corneum concentrations. They went on
20 increasing and plateaued at .05. But however, they
21 looked at skin blanching. There was no difference
22 between .02, .04, .05, .06 for skin blanching. So no
23 correlation was found between stratum corneum
24 concentration and skin blanching for dose response
25 studies. All the dose responses like dose duration,

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1 varying concentrations and film thickness.

2 Next slide. Let us review some of the
3 acyclovir data. The authors looked at stratum
4 corneum, epidermis and dermis concentration of
5 acyclovir after oral and topical administration to the
6 nude mouse which has been grafted with human skin. If
7 we look at all the three cases, stratum corneum,
8 epidermis and dermis, the concentrations by topical
9 are very high, 44, 11 and 57. So one can assume that
10 acyclovir is very effective topically in -- infection
11 but it is not true. Oral administration is more
12 clinically effective. So this poor correlation
13 between stratum corneum concentrations and clinical
14 effectiveness indicates that in general stratum
15 corneum concentrations kinetics may not represent the
16 kinetics of the drug at the target site, that is the
17 epidermal-dermal junction in this case.

18 Validation issues. Six subjects. Site A
19 and adjacent site B. When you do 24 stripping in
20 subject C you can get hardly 100 micrograms whereas
21 adjacent site you can get about 1,300 micrograms and
22 also there is huge intra-subject variability. Skin
23 stripping is not well-controlled. The large inter-
24 and intra-subject variability. Percent of SC removed
25 is unknown for each site. Therefore, inappropriate to

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1 normalize the dose concentration/cm² and also drug in
2 the stratum corneum is gradient, not homogeneous, so
3 it can not be normalized by weight also.

4 This lack of data validating the proposed
5 DPK method as a reliable, precise, accurate predictor
6 of clinical safety and efficacy, therefore, BA/BE.
7 The proposed 10 strips only represent a small portion
8 of the stratum corneum. TEWL data shows that there is
9 a barrier inside the stratum corneum. At least 25
10 strips had to be removed in Type II and III, 60 strips
11 in Type IV and V. So this bring up the question of
12 the proposed 10 strips accurately reflects stratum
13 corneum concentration. To reach the deeper layer, one
14 has to strip 30 strips and these 30 strips will cause
15 pain, scarring, and hyperpigmentation. Look at the
16 scar and hyperpigmentation caused at 41 days.

17 Next slide please. So summary of the DPK.
18 Correlation between DPK and clinical safety and
19 efficacy must be demonstrated for each particular
20 class of compound, each formulation, and each
21 indication. There is lack of data suggesting
22 correlation between stratum corneum and target sites
23 such as epidermis/dermis/hair follicle and there's
24 clear data that DPK may fail to predict delivery to
25 hair follicles and vehicle is not controlled, so

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1 qualitative and quantitative composition should be
2 similar.

3 Next slide. Single dose DPK studies on
4 healthy adult arm will not predict equivalence in
5 diseased skin, geriatric and pediatric age groups,
6 multiple dose conditions, and so on. The current
7 guidelines do not address whether these assumptions
8 hold true for combination products, especially when
9 the active ingredients have different targets. DPK is
10 inappropriate for vaginal, nail, transdermal, and
11 mucosal products.

12 Next slide please. The last conclusion
13 slide. PhRMA concludes that DPK is a research tool
14 which is currently not validated and is unproven
15 surrogate for clinical safety and efficacy.
16 Scientific consensus exist that in vitro release
17 methodologies are not surrogate for BA/BE. PhRMA
18 urges the FDA to withdraw this guidance until the
19 proposed methodologies are either modified or
20 supported by a coalition of government, industry, and
21 academic scientists. PhRMA proposes the formation of
22 working group to develop recommendations based on
23 scientific consensus.

24 Thank you.

25 DOCTOR TAYLOR: Well, actually you have a

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1 minute left.

2 DOCTOR PARAB: I was scared that I would
3 not get to my last slide.

4 DOCTOR TAYLOR: Do I look that mean?
5 Well, we have a minute if the committee has some
6 questions that would clarify his presentation, you can
7 make them during this one minute.

8 DOCTOR DiGIOVANNA: I was particularly
9 struck by your slide showing the difference between
10 absorption into the skin and skin scrapings and hair
11 follicles and I wonder if you have any information --
12 and how different it is with different products -- any
13 information on acne-related products such as retinoids
14 or such as anti-bacterials, products where the goal,
15 the intent, is possibly to deliver the anti-bacterial
16 to the hair follicle or to deliver the retinoid
17 possibly in some cases to the sebaceous gland or in
18 cases, for example, where one might want to deliver a
19 drying agent to the eccrine sweat duct.

20 DOCTOR PARAB: We have reviewed the data.
21 There's only very limited data on follicular delivery
22 relating to stratum corneum. So that I have
23 presented. Maybe in case we want -- we have approved
24 that for those compounds. There's no data available.

25 DOCTOR TAYLOR: The question took one

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1 minute.

2 DOCTOR PARAB: Thank you very much.

3 DOCTOR TAYLOR: Okay. Thank you very
4 much. Now the next presenter is Doctor Richard Guy.
5 He's the Scientific Director, Center for Inter-
6 university Research. That's the best I can do.

7 DOCTOR GUY: Close enough. Thank you.

8 We've obviously heard a lot about what the
9 pros and cons of this technique are during the course
10 of the day and I'd like to try and highlight what I
11 see as some of the issues which need to be addressed
12 and some of the things which remain in question. I
13 should point out that my presence here has been
14 sponsored by Galderma which might give you some idea
15 of what I'm about to say.

16 However, it could easily have been
17 sponsored by the Director of the Dermatology Division
18 here at FDA, having listened to his presentation
19 earlier today. So the assumptions which have been
20 made here in developing the guidance for DPK are
21 listed here. The normal intake skin stratum corneum
22 is usually the rate determining barrier. The
23 concentration drug in the stratum corneum is related
24 to that which diffuses into the underlying viable
25 tissue. And looking at levels of dermatological

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1 effect in the stratum corneum level seems to be much
2 more useful and relevant than using plasma
3 concentrations.

4 Next slide please. The questions I'd like
5 to ask. Is this document a useful guide for doing
6 what you'd like to do? Are the key issues of the
7 methodology and validation adequate for acceptance?
8 Have some additional and unjustified assumptions been
9 made in developing this guidance and, as a surrogate
10 to the clinical studies, is what we have currently
11 useful or not?

12 Next slide please. My conclusions, before
13 I go on to justify them, is I think the adoption of
14 ideas in this guidance is premature but that the basic
15 premise could be used at least for some specific drug
16 classes and that things need to be designed
17 specifically to figure out if it is a good idea or
18 not.

19 Next slide. The analogy has been made to
20 oral and this point has already been made. The drugs
21 delivered orally usually don't have the GIs as is the
22 of action whereas that's not the case for topical
23 drugs at -- Skin disease we know can alter barrier
24 function. And so is the use of DPK on normal skin
25 relevant? The answer, I think, is unknown. Maybe it

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1 is, maybe it's not, but we need some data to decide.
2 And that requires the correct DPK procedure to be
3 developed and validated and then tested specifically
4 for specific drugs or the drug disease classes,
5 combinations.

6 Next slide. Methodology. A fixed number
7 of tape strips removes the root amount of stratum
8 corneum. Absolutely not. We know that's not the
9 case. Skin or stratum corneum thickness variability
10 means that we don't remove with a fixed number of
11 strips a fixed fraction of the stratum corneum. If
12 we're going to use this technique for bioequivalence
13 assessment, we need to make a fair comparison. That
14 means we really need to know how much of the barrier
15 is being taken off.

16 For example, if you do blood levels for
17 oral bioequivalence, you always take a thick volume of
18 the blood. You always inject the same volume onto the
19 HPOC card. You don't inject a random amount. So I
20 think one needs to measure the amount or the fractions
21 of total stratum corneum taken off during tape
22 stripping, and that needs to be quantified by some
23 technique, and that may involve weighing tape strips,
24 it may involve protein determination. Maybe we can
25 get some information from the measurement of

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1 transepidermal water loss during this stripping
2 procedure.

3 Next slide please. Let me just give you
4 some data here. Here's transepidermal water loss on
5 the Y axis as a function of strip number using a
6 series of different tapes in this particular case, and
7 you can see that different tapes have different
8 effects. However, if we instead put the same data as
9 a function of the mass of stratum corneum removed, and
10 that's been converted to a thickness, assuming a
11 density, one can see that the different tapes actually
12 all behave in a very uniform. When we express it as
13 the cumulative amount of skin removed as opposed to
14 strip number, we get much better relationship between
15 the two observations.

16 Next slide please. Now we can actually
17 take the inverse of the transepidermal water loss and
18 plot it against the thickness of stratum corneum
19 removed, and the intercept on the X axis at that
20 inverse TESL versus SC removed gives us the thickness
21 of the membranae, and this is something we published
22 two years ago in the biophysical journal. As you can
23 see, there's a variability in the thickness of stratum
24 corneum. This is all ventral forearm, normal human
25 subjects.

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1 Next slide. What's also interesting,
2 here's transepidermal water losses of function of
3 amount of stratum corneum removed in six different
4 individuals, and you can see that they have really
5 quite different skin thicknesses or stratum corneum
6 thicknesses because the TEWL takes off at different
7 values of the depth of stratum corneum removed. But
8 if I now look at the top curve, and it really
9 expressed that data as the relative removal. That is
10 to say, what percentage of the stratum corneum has
11 been removed? There's really a very nice correlation.
12 I think now one can begin to make respectable
13 comparisons between different people.

14 Next slide. So it's also true that the
15 amount of stratum corneum removed will be influenced
16 by the vehicle composition. We have a penetration so
17 that will change the -- of the stratum corneum. That
18 will allow easier removal of the membrane by tape
19 stripping. So again, a fixed number of tape strips
20 won't remove equivalent amounts of stratum corneum,
21 and that will therefore prevent you from making
22 quantitative comparisons. And the solution is exactly
23 the same as what I've said before.

24 Next slide. Once again, our subjects have
25 been treated with different formulations containing

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1 different materials and again, plotting the data as
2 tape strip number spreads out the results. Here, if
3 I correct them to stratum corneum depth, you can see
4 that certain compounds such as urea, sodium laurel
5 sulphate, have a much bigger impact on how much
6 stratum corneum or ease of stratum corneum removal.

7 Next slide. But again, this is just with
8 isopropyl marasthate as one of the principal vehicle
9 constituents. If we go from depth removed to relative
10 removal, once again there's a reasonable correlation
11 amongst all the different individuals.

12 Next slide please. Throwing away the
13 first two tape strips because they contain quote
14 "unabsorbed drug," what about the washing procedure?
15 How should that be done? Does that not remove the
16 unabsorbed drug? Does this upper stratum corneum
17 float magically above the body? I doubt it somehow.
18 Where's the justification and evidence for doing that?
19 Where are the results that compare when these first
20 tape strips are or are not included? I hear they're
21 measured, but I never see the data with or without
22 them being included. And, of course, these things
23 often contain significant and variable amounts of
24 drug. This needs some sort of peer review. What
25 about material trapped in skin -- We're going to hear

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1 from Tom Friends and Doctor Lehman later on. Again,
2 this needs to be tested correctly with the right sort
3 of experiment.

4 Next slide. So I think this remains a
5 relatively immature methodology, but it has some real
6 potential. There are many aspects that require
7 development, assessment, and validation before I think
8 a useful guidance can be issued. I would ask the
9 committee to think about what was done in order to
10 approve the use of blood levels and dissolution
11 testing for all products. I'm sure that wasn't
12 decided just because somebody thinks this looks like
13 it's going to be a good idea. A number of things have
14 already been mentioned by everyone in terms of what
15 things need to be addressed to make this work
16 successfully.

17 Next slide. Drugs that act specifically
18 at the follicle sebaceous gland. The guidance quotes,
19 "There is a positive correlation between stratum
20 corneum and follicular concentrations." We've just
21 heard Doctor Parab say where are the facts to support
22 that. It's very difficult to measure follicular
23 concentrations precisely and unambiguously. What
24 about products that target to the follicle? If I make
25 a generic with a specific goal to target to the

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1 follicle, surely my plan is to get more of the drug in
2 the follicle than in the stratum corneum. In that
3 case, wouldn't there be an inverse correlation between
4 the stratum corneum level and the follicular level?
5 So perhaps that's an interesting point that should be
6 addressed, particularly by some of the developers of
7 the more recent and effective anti-acne preparations.

8 The kinetics of follicular uptake are
9 clearly different from that of the stratum corneum
10 uptake. It's been accepted in the literature since
11 the days of Shiplien and Blank that follicular uptake
12 is more rapid than stratum corneum transport. So that
13 means that we have timing issues if we're going to in
14 fact support this initial hypothesis that's stated in
15 the guidance. So again, I think we need to review
16 critically whether these things are related. We need
17 to meticulously evaluate the methodology for
18 follicular isolation and how you assay what's there
19 and then design some proper studies to test the
20 hypothesis.

21 Next slide. Damaged stratum corneum. If
22 the stratum corneum is frankly damaged, it's suggested
23 that the tape stripping procedures are -- or I would
24 suggest the tape stripping procedure is unlikely to be
25 useful. Does the in vitro release test help? I'm not

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1 sure. And is this a relevant test? I guess we're
2 going to talk about this later on, so let me continue
3 because we're getting close to the end here.

4 So I think there are some important
5 questions. Is it applicable to all dermatologicals?
6 I think that needs to be demonstrated. Is it
7 applicable vaginally? I'm not sure that the evidence
8 presented this morning makes me think that that's the
9 case. The use of healthy subjects has been discussed
10 considerably during the course of the day.

11 Stratum corneum concentration as predictor
12 of the amount of drug absorbed. We heard Hans
13 Schaefer quote the work of Andrew Rougier and his
14 colleagues. I think these references have been taken
15 somewhat out of context because Rougier's goal was
16 certainly not to establish bioequivalence in his
17 measurements. And should we be thinking about ways to
18 look chronically at the dosing of these substances,
19 given, as Doctor Wilkin pointed out this morning, we
20 rarely use these. Acutely, they're used under chronic
21 conditions.

22 The last slide is my conclusions. So I
23 think this is a laudable idea, but I think this
24 issuance of the guidance is clearly the cart before
25 the horse. I think that there are many questions left

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1 that need to be answered in terms of justifying what's
2 been proposed. I think there's been a mistake made in
3 terms of citing evidence which uses studies that have
4 not been designed to test the key hypothesis which are
5 made in the guidance, and I think that's a shame
6 because I don't think it helps the people that would
7 like to see this move forward to make their case. And
8 as a result, I think you're hearing and have heard and
9 will hear valid criticisms being voiced against this
10 procedure.

11 So there are procedural issues which need
12 to be addressed, and I cite a couple of examples here.
13 And I think obviously there has to be eventually
14 correlation between efficacy and this methodology for
15 assessing bioavailability or bioequivalence and
16 specific tests to really find out if these hypotheses
17 are appropriate or not, for which drugs, and which
18 drug classes. Thank you.

19 DOCTOR TAYLOR: Thank you very much.

20 The next speaker is Deborah Miran. She's
21 representing Generic Pharmaceutical Industry
22 Association. You may proceed.

23 MS. MIRAN: Good afternoon. I am Deborah
24 Miran representing the Generic Pharmaceutical Industry
25 Association. Thank you for the opportunity to present

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1 our remarks regarding FDA's DPK drug guidance.

2 GPIA is made up of some 40 member
3 companies including both independent generic owned
4 manufacturers and brand owned generic manufacturers.
5 Our membership also includes contract research
6 organizations which routinely perform bioequivalence
7 studies for both brand and generic manufacturers.

8 My comments today will be general focusing
9 on the attributes of the study design, specifically
10 suitability for bioequivalence testing for generic
11 topical drugs.

12 In general, GPIA supports the DPK approach
13 described in the draft guidance as a means of
14 establishing in vivo bioequivalence for an ANDA. GPIA
15 lauds the effort of the topical dermatologics drug
16 product working group of the DCAA in both the research
17 of the study design and the development of the draft
18 guidance. For many years, the pharmacokinetic
19 approach which measures blood, plasma and urine drug
20 concentrations has successfully served as an in vitro
21 approach for bioequivalence determinations and
22 systemically absorbed drugs. From the PK design,
23 important metrics such as Cmax and AUC can be
24 determined.

25 In the instance of a dermatologic drug

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1 product, the DPK approach can also provide a mechanism
2 in which drug concentrations can be measured in the
3 stratum corneum layers of the skin. Like the PK
4 design, a stratum corneum drug concentration time
5 curve can be constructed and a Cmax and AUC
6 determined.

7 Over \$1 billion of important off patent
8 dermatologic drug products were available for generic
9 drug development and ANDA approval as low cost
10 alternative for patients which this guidance is
11 finalized. Therefore, GPIA believes this guidance
12 should be generally applicable to all topical
13 dermatologic drug products in all therapeutic
14 categories.

15 It is GPIA's scientific opinion, which now
16 has been documented with the Miconazole nitrate study
17 and others, that DPK is a more discriminating test
18 than clinical end point design or even the sensitive
19 and specific pharmacodynamic bioassay. GPIA believes,
20 after seeing the data presented today, especially the
21 protocol and methodology use of the Miconazole nitrate
22 study, that the validation, specifically precision and
23 reproducibility, can be achieved for the DPK design.
24 Clearly, DPK is a more discriminating test for
25 bioequivalence.

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1 For example, in the Miconazole nitrate
2 study, the clinical approach showed no statistically
3 significant differences between the two products for
4 micrological and clinical cure while the DPK design
5 clearly showed statistically significant differences
6 between the test and reference. Neither acceptance
7 criteria are met in this instance while the
8 coefficient of variation was quite acceptable at about
9 20 percent.

10 This data, together with the knowledge
11 that the skin surface is highly variable, suggests
12 that FDA's proposed acceptance criteria of 75 to 133
13 percent for Cmax can be justified. Additionally, GPIA
14 suggests that a wider limit for AUC should also be
15 adopted until such time as more data suggests a
16 tighter criteria is warranted.

17 Finally, I wish to offer a few thoughts on
18 the in vitro release methodology. While GPIA realizes
19 this test is no surrogate marker for bioequivalence,
20 neither does the SUPAC-SS nor the draft DPK guidance
21 describe its use for this purpose. But rather, it is
22 a useful tool as a good first step in the development
23 process to determine if a product should proceed to
24 next stage DPK testing. It is also an acceptable
25 comparative measure for pre- and post-change

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1 evaluation and between higher and lower strengths
2 which are similarly formulated in a product family.

3 Generic drug developers are fully aware of
4 the important role of structure forming incipients in
5 the performance and penetration of drug products.
6 Accordingly, GPIA agrees that, whenever possible, the
7 generic equivalent should be formulated as closely as
8 possible, both qualitatively and quantitatively, to
9 the reference listed drug.

10 However, absent access to information
11 about the quantitative composition of the reference
12 listed drug, matching the quantitative component must
13 remain flexible within the constraints of FDA's
14 inactive ingredient guide.

15 In summary, GPIA supports this draft
16 guidance as a means to open up the regulatory pathway
17 to ANDA approvals for products that heretofore have
18 been unavailable. But, more importantly, GPIA
19 supports the guidance because, for the first time, it
20 really suggests a design that is sensitive and
21 specific and suitable as a rigorous measure of
22 equivalence between a proposed generic product and the
23 marketed brand product. Thank you.

24 DOCTOR TAYLOR: Thank you. We have a
25 minute and a half left, so if there are questions

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1 that might clarify the presentation from the
2 committee, you can ask at this time. There being
3 none, thank you very much.

4 The next speaker is Doctor Stephen
5 Wisniewski. He's Manager of Technical Research Center
6 at J&J. You may begin.

7 DOCTOR WISNIEWSKI: Thank you, sir. I'd
8 like to thank the committee for allowing us to speak
9 today. For maybe a little more of a change of pace
10 for the committee, we'd like to comment on the
11 guidance directed to the use of in vitro release
12 approaches for lower strength approvals.

13 To that end, we would like to present data
14 today that will show you that in vitro release testing
15 is not proven as a reliable marker for approval of
16 lower strength generics and that comparisons of Retin-
17 A cream to a generic tretinoin cream showed different
18 in vitro release profiles which demonstrated that they
19 were not bioequivalent when compared on an initial
20 study, yet bioequivalent when compared on a repeat
21 study. We believe that this methodology is not
22 justified as a replacement for clinical trials.

23 So, in accordance with in vitro release
24 workshop recommendations and SUPAC guidelines, we
25 developed an in vitro release test for tretinoin

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1 creams because they're available at multiple strengths
2 and, in the U.S., available as Retin-A cream from
3 .025, .5, and .1 percent, and a Canadian cream called
4 Vitinoin cream which is marketed at the same
5 strengths.

6 The next slide shows data generated from
7 our in vitro release test and again, we're plotting
8 cumulative amount versus the square root of time and,
9 according to theory, this plot should be linear, and
10 it's shown to be so here with good fits at all
11 strengths. You can see that the method we've
12 developed also differentiates cleanly between the
13 three strengths. Again, as the strength decreases,
14 the release rate decreases.

15 Next slide. We've repeated the study and
16 that data is shown here. Again, there's statistically
17 significant differentiation between all three
18 strengths and each run or each study, the paired
19 studies have been shown to statistically the same.
20 Next slide.

21 On this slide we compare side by side data
22 for the release rate of tretinoin from both Retin-A
23 cream and Vitinoin. You'll see with the Vitinoin
24 cream that our method again adequately distinguishes
25 the release at all strengths, and these differences

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1 are significant. You'll also notice that the release
2 rate from Vitinoin cream is much lower than Retin-A
3 cream, and in each strength that release rate is about
4 half that of Retin-A cream.

5 We would like to interject at this point
6 that we find it hard to believe that a simple in vitro
7 test carried out over a period of six hours can
8 adequately reflect the complexities seen in the
9 clinical trial where vehicle effects can affect the
10 stratum corneum and where multiple dosing occurs over
11 a period of days, weeks, or possibly even months.

12 So back to the guidance and how we would
13 treat the data from these experiments. Let me
14 summarize them for you at this time. The release rate
15 of tretinoin from Retin-A cream and Vitinoin cream
16 decreases again as the strength decreases, again
17 significant. Release rate of tretinoin is
18 significantly higher at all strengths for Retin-A
19 cream versus Vitinoin cream, again according to SUPAC-
20 SS statistical methods. Duplicate runs of Retin-A
21 cream passed SUPAC-SS guidelines at all strengths.

22 So back to the guidance. The guidance
23 recommends for this comparison that we take release
24 rates of the reference products at hi/lo strengths and
25 that ratio should be approximately equal to the

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1 release rate for the test products at hi/lo strengths
2 or taking the cross products that this ratio here in
3 equation two should be approximately equal to one.
4 We've used statistical methods from SUPAC-SS
5 guidelines, the Wilcoxon Confidence Intervals, to
6 evaluate this data.

7 On this graph we've plotted the release
8 rate versus tretinoin strength and we've included the
9 hi/lo strengths for comparison here. We've taken
10 ratios for Retin-A at study one, the ratio being 3.53,
11 for study two 3.31, and for the Vitinoin cream the
12 hi/lo ratio is 3.02. Taking the 90 percent confidence
13 intervals specified by SUPAC and a bioequivalence
14 range of .80 to 1.20 as delineated in the current
15 guidance, we made a comparison between Retin-A cream
16 and Vitinoin for study one and the range is 1.00 to
17 1.26 and we would conclude in this case that the lower
18 strength Vitinoin is not bioequivalent. When we make
19 a comparison for study two, the range is .91 to 1.15
20 and, in this case, the lower strength Vitinoin is
21 bioequivalent.

22 So we'd like to conclude again that in
23 vitro release testing is not proven as a reliable
24 marker for approval of lower strength generics and
25 that comparisons of our test creams, Retin-A cream and

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1 a generic tretinoin cream, showed different in vitro
2 release profiles that were not bioequivalent when
3 compared on an initial study and yet bioequivalent
4 when compared on a repeat study. So we believe that
5 this technique is not justified as a replacement for
6 clinical trials.

7 And I would like to acknowledge the
8 efforts of my coworkers who have performed the in
9 vitro release studies and the statistical evaluations.
10 Thank you.

11 DOCTOR TAYLOR: Thank you. Are there any
12 questions of clarity from the committee?

13 DOCTOR McGUIRE: Joe McGuire. I missed
14 the details of the release. What is the technique?

15 DOCTOR WISNIEWSKI: Using a Franz cell
16 setup, a synthetic membrane is used to support a
17 quantity of formulation.

18 DOCTOR McGUIRE: Okay. That's the piece
19 I missed. Thank you. I got it.

20 DOCTOR TAYLOR: Thank you.

21 The next speaker is Doctor Elizabeth Duell
22 from the University of Michigan who is representing
23 the Academy of Dermatology.

24 DOCTOR DUELL: Thank you. John Vourhees
25 was the individual who originally was designated to

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1 give this, but he has the happy task of having the
2 JAHACO group at the University of Michigan so that he,
3 as chairman of the department, has to be there. I've
4 been associated with the department for a number of
5 years now. I'm actually a biochemist by training and,
6 since we have done a lot of in vivo analysis of
7 epidermal tissue, we were essentially asked to present
8 the information that we have.

9 On the next slide is essentially the
10 comments that the academy had sent to the FDA, and the
11 academy is dedicated to quality patient care, higher
12 standards in clinical practice, education, and
13 research. The members' interest is that all topical
14 products that they prescribe are safe, effective, and
15 that generic formulations are bioequivalent and have
16 the same bioavailability as brand products.

17 With this respect, they do have problems
18 with the dermatopharmacokinetic approach to establish
19 bioequivalence and question whether or not
20 measurements in the stratum corneum give you a true
21 feel for what is going in the viable area of the
22 tissue. A drug product must penetrate through the
23 stratum corneum into the viable area, both the
24 epidermis and dermis. They just want to ensure that
25 techniques measurements for drugs in the viable skin

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1 and that that technique in fact can be done with
2 reproducibility.

3 What I would like to present is some of
4 the information that we have from in vivo systems. On
5 the bottom half, the one that's marked retinal means
6 that it was retinal treated tissue, and that is one in
7 which all of the stratum corneum has been removed.
8 You can see that there's none left here as opposed to
9 what just happened to be a -- treated one, but this
10 whole area up here is the stratum corneum, the viable
11 part in both cases are here and, of course, this is
12 the dermal part down in here.

13 Next one please. And the areas that we
14 actually have been looking at are twofold. We happen
15 to be working with retinoids for quite some time and
16 we looked at the metabolism of retinol to retinoid
17 gases and induction of an enzyme that's called 4
18 hydroxylase that actually decreases the retinoid gas
19 activity. Retinoid gas actually exerts its effect by
20 binding to receptors that are in the nucleus, so we're
21 talking about strictly the viable part of the cell.

22 Next please. And one of the things that
23 we did was to apply various retinoids, the red one to
24 retinoid acid and blue is retinal and the yellow is
25 retinol at the various concentrations listed. What

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1 we're measuring is the 4 hydroxylase activity. And as
2 you increase the amount of retinoid acid that has been
3 applied topically, you do get a reduction of the
4 enzyme activity in a linear fashion. With both
5 retinol and retin aldehydes, since they are not the
6 direct compounds, it actually reaches a point at which
7 you get no further induction of the activity.

8 Next please. One of the other things we
9 did was supply specifically either 9-cis, 13-cis or
10 all-trans to the top of the skin, the stratum corneum,
11 removed all of the stratum corneum. We didn't leave
12 any of it. And then measured how much was there. You
13 can see that compound actually goes through the
14 epidermis. You can have a wide variety of changes
15 occurring. The retinoic acids are known to be able to
16 isomerize so, even though we started out with 9-cis,
17 by the time it reached the viable area we actually
18 have a significant amount of all-trans and some 13-cis
19 as well. If you apply 13-cis, you actually wind up
20 with more all-trans as a final product. If you start
21 out with all-trans, the majority still stays but there
22 is some conversion.

23 Since I periodically get questioned about
24 whether or not we can use the stratum corneum as
25 opposed to having to go through the tape stripping

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1 which is very difficult if you truly want to get rid
2 of all of it and becomes very painful as it gets more
3 towards the viable areas, we did just a few pilot
4 studies to see whether or not we could start to use
5 something like the tape stripping. Of course, most of
6 the compounds that I've dealt with had been very
7 lipophilic type of compounds so that normal aqueous
8 solutions don't do anything. I worked with things
9 like acosanoids, retinoids and also with cyclosporin
10 for a while.

11 So what we usually wind up using are very
12 organic solvents like chloroform methanol and we tried
13 that on one of the plastic discs and we actually wound
14 up totally dissolving it. All of the combinations we
15 used, and we tried five different ones, all of them
16 gave us the gelatinous areas as the adhesive actually
17 came off of the discs and you can, to a certain
18 extent, increase the volume of your extraction and
19 minimize this but you still have a gummy material at
20 the bottom. The ones that actually did manage to give
21 acetosupernatan was a combination of the acetone
22 butanol heptane isoamyl.

23 And since we didn't have other means of
24 trying to figure out how much stratum corneum we were
25 taking off by using this, what we decided to do was to

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1 weigh the individual ones and we had several packets
2 so we just sort of did a random checking. And within
3 any given sheet the reproducibility was reasonably
4 good but if you got between different sheets, while
5 this sounds like a small amount and it is in reality
6 rather than grams, if you compare it to the amount
7 that we actually got when we tried stripping the
8 epidermis, the difference there was at least four or
9 five times larger than what we were taking off which
10 meant to us that we had to weigh each one individually
11 before and after stripping.

12 And then we did try applying .25 percent
13 all-trans retinol in athenol to the top, left it sit
14 there for four hours and then tape stripped the area
15 and we wound up using 11 discs. One of my research
16 associates and I did this. And between weighing the
17 discs before actually doing the tape stripping and
18 then reweighing each one, it wound up taking us two
19 hours to do it and we found variations anywhere from
20 a tenth to roughly .7 milligrams in the different
21 discs as we had tape stripped. We usually did five
22 strippings per disc except for the first one which we
23 did only one.

24 Next please. These are actually the
25 numbers that we got. What we did was add a very small

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1 amount of tritiated retinal which did not add
2 significant weight to the vials to determine the
3 recovery. So we knew how much we started out with
4 putting it into the solvent mixture that we were using
5 and then at the end we actually determined the
6 recovery. In the first two in which there was only
7 one disk, you don't lose much in that layer. But the
8 last two we actually used five disks per vial.

9 As you can see, we lost 20 percent of the
10 radioactivity into that particular fraction which can
11 not be put through the HPLC. We make the assumption
12 that we have lost the equivalent amount of whole
13 material that was in there, and then these are the
14 numbers that we got so that it varied somewhere
15 between two and three thousand nanograms per milligram
16 wet weight. By the time we got down to this one which
17 at this point would have been roughly 30 to 40
18 strippings, the concentration did decrease. We used
19 a second alternative organic solvent on this set and
20 did pretty much the same type of thing and once again,
21 when you have more than one of the discs, we wound up
22 with a reasonable amount of material staying in the
23 gelatinous pellet.

24 The numbers for the first two are
25 relatively same. This one, of course, is smaller

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1 concentration than in the previous person. As a
2 comparison, this is what we found if we applied
3 retinol topically, totally tape stripped, and then
4 measured the amount of retinol that we could find in
5 the viable parts of the tissue. After six hours, we
6 wound up -- this is actually expressed in grams so if
7 you put a decimal point here, it's equivalent to the
8 other one so that essentially there was five nanograms
9 per milligram at six hours in the actual viable part.
10 By 24 hours, it actually reached the peak at roughly
11 20 and by 96 hours, it's back down. That can be
12 either because less is penetrating, more is being
13 metabolized or more is being suppressed into other
14 areas.

15 So at least in terms of the sorts of
16 things that we've done, if you actually remove all of
17 the epidermis, it is really a very tedious process and
18 gets painful towards the end so you don't too often
19 get people volunteering a second time and, while
20 compounds can be extracted from the tape stripped
21 area, the amount present in there may still be
22 difficult to correlate to the viable area and what is
23 truly there. Thank you.

24 DOCTOR TAYLOR: Thank you.

25 The next speaker is Doctor Kim Spear from

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1 Spear Pharmaceuticals.

2 DOCTOR SPEAR: I would like to thank the
3 committee and Doctor Wilkin for the opportunity to
4 make some comments. I am a practicing clinical
5 dermatologist in Fort Myers, Florida. I represent
6 myself. My partner is Geneva Pharmaceuticals. That
7 is a generic pharmaceutical company. And we've been
8 involved in developing a generic tretinoin or Retin-A
9 for the last five years.

10 Why has skin stripping been suggested for
11 acne bioequivalence? The current belief is that acne
12 studies can not be done and show bioequivalence so
13 skin stripping has been proposed in this guidance to
14 help the generic industry. At the last FDA Advisory
15 Committee of March 20th, Doctor Flynn, as reported,
16 said, "We don't have the convincing clinical
17 validation comparison that makes us comfortable, but
18 we also don't want to require the generic industry to
19 have to do comparative clinical trial at enormous
20 cost, and that is our dilemma." So this is trying to
21 be put forward.

22 Does stratum corneum stripping predict
23 activity in sebaceous glands? The draft guidance
24 admits that for anti-acne drug products, target sites
25 are the hair follicles and sebaceous glands. The

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1 draft guidance tries to make the case that stratum
2 corneum predicts the amount of drug absorbed and,
3 therefore, it predicts the amount in sebaceous glands.
4 There's really no proof of this and a lot of this
5 discussion today has been around this central issue.
6 There is a leap of faith to say that stratum corneum
7 equals amount in body and so the amount of body equals
8 the amount down in the pilot pilosebaceous unit which
9 is the activity of the drug. The effect is very drug
10 specific, as well.

11 Skin stripping and epidermal action drugs.
12 Topical anti-fungals have epidermal action. Topical
13 anti-virals have epidermal action. Epidermal action
14 drugs. Now you can make a better case that stripping
15 the epidermis predicts bioequivalence but
16 pilosebaceous action drugs can never be sure that skin
17 stripping is predicting what is happening. Acne
18 bioequivalent studies, double blind comparative active
19 acne bioequivalent studies can be done with reasonable
20 cost.

21 I'm here to report that Spear
22 Pharmaceuticals with the Geneva Pharmaceuticals has
23 successfully shown bioequivalence with an identical
24 generic. The success is dependent on one reviewer at
25 one site. Doctor Maibach already made comments that

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1 there's inter reporting from multi sites and also
2 multi reviewers. Our generic, to let you know, is
3 qualitatively and quantitatively identical and is
4 manufactured to have the same viscosity. It is
5 identical as we can make it. We have one ANDA for
6 each strength that has been filed. We've been quiet
7 about our product until we're approved, but I thought
8 it was important to present this at the committee
9 since they're trying to embrace a different method.
10 Here are the results.

11 Here is the .025 percent Retin-A in the
12 blue versus our generic in the green. There are 412
13 patients that were enrolled in this study. This is a
14 very large study. Actulaly larger than Ortho studies
15 when it was approved. You can see week zero, two,
16 four, eight and 12. There are no statistical
17 differences. This is the .1 percent study, 398
18 patients, 0, 2, 4, 8, 12, no statistical differences.

19 To highlight, acne study results at 12
20 weeks, let's look at the percent reduction of total
21 lesions. In the .1 percent study with 398 patients,
22 Retin-A had a 71.1 percent reduction at 12 weeks. Our
23 generic had a 71 percent reduction. Bioequivalence
24 analysis is done by a two one-sided t test using a 90
25 percent confidence interval of Westlake. This has

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1 been the method most embraced by Doctor Sherman of the
2 FDA. Bioequivalence must be between delta of 80 to
3 120 percent. Our results, 90.5 to 114.1 percent.

4 Comparing the .025 percent study, it's
5 interesting. You'll notice Doctor Maibach also
6 mentioned that it's difficult in any study to know
7 differences in concentration of the same drug. Here
8 we have shown that there's a difference for the .1
9 percent strength versus the .025 and our .025 is equal
10 to .025. And again down at the bottom, the important
11 point is are you within 80 to 120 percent of your
12 delta, and we are.

13 Let's talk about in vitro release now for
14 just a moment as applies in this document and as in
15 SUPAC-SS and I must compliment Doctor Shah for his
16 wonderful work in putting the SUPAC-SS together. He's
17 done a very good job and actually this guidance itself
18 is a start. It is a way to discuss these issues. The
19 draft guidance supports the use of in vitro release.
20 We agree that if there are only two strengths, waiver
21 by in vitro release of clinical bioequivalence for the
22 lower strength does make some sense. However, there's
23 three strengths. Bioequivalence studies should be
24 done on the high and low and maybe waiver of the
25 middle strength.

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1 The agency, the FDA, has a long history of
2 bracketing as the safest method to show different
3 strengths and to allow waiver of both lower strengths.
4 With only one bioequivalent study of the top strength,
5 we do not feel this is sufficient.

6 Here's our in vitro membranae release. As
7 you can see, the green here is Retin-A. The blue is
8 our generic. This is .025 percent, .05 percent, .1
9 percent. You can see there's a linear correlation
10 between the strengths and within each there's no
11 statistical difference. Another way to look at it is
12 that you take the 36 different wells, if you will, and
13 you look at #8 and #29 and rank them accordingly and
14 it should be between 75 and 133.3 percent. For the
15 .025 percent our ranking was between that, 84.5 to
16 106. When we looked at .05, our ranking was between
17 that. When we looked at .1, our ranking was between
18 that.

19 So using SUPAC-SS method looking at in
20 vitro release, we do show equivalency or -- excuse me
21 -- the word that is better used, as Doctor Shah points
22 out, is sameness. Again, this test is not for
23 bioequivalence. This is a test for sameness.

24 Summary of our position. Acne
25 bioequivalence studies can be done without excess

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1 expense to the generic industry. If acne biostudies
2 are done on the high and low strengths, waiver of
3 biostudies in middle strength with in vitro release is
4 reasonable. Skin stripping may make sense for anti-
5 virals and anti-fungals but embracing skin stripping
6 as a surrogate for acne studies is always suspect as
7 it is not measuring what is happening in the
8 pilosebaceous unit.

9 Thank you.

10 DOCTOR TAYLOR: Thank you very much.

11 DOCTOR DiGIOVANNA: May I ask a question?

12 Doctor Spear, I enjoyed that very much and it's a
13 little bit of a surprise to me to have someone
14 representing a generic industry with this approach.
15 But my question for you is that I've heard a lot of
16 discussion today about the enormous cost of clinical
17 trials to do what you've just done. Can you give us
18 a sense as to approximately how much what has been
19 done in this situation has cost?

20 DOCTOR SPEAR: More than I make in a year.

21 DOCTOR DiGIOVANNA: That would be more
22 than twice what I make.

23 DOCTOR SPEAR: It is expensive but the
24 point is it is not -- you're talking about a product
25 that is used in America in large number. You're

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1 talking about Retin-A is approximately a \$125 million
2 a year product. A generic for that, there is going to
3 be profits made. Interestingly, right now there is a
4 generic that's being sold. It is, of course, Avitas
5 .025 percent. But Avita was approved as an NDA and
6 Alpharm, who has an agreement with them, actually
7 cloned it and are seeing that as a generic, although
8 it has two different inactive ingredients.

9 But to address your question, it is
10 expensive but if there are rewards to be made, this is
11 a nation of risk takers and people will take that risk
12 if the rewards are there. It is not beyond the range
13 of expense.

14 DOCTOR DIGIOVANNA: I assume it's not \$125
15 million.

16 DOCTOR SPEAR: No. No. We're under \$2
17 million.

18 DOCTOR DIGIOVANNA: Thank you.

19 DOCTOR MAYERSOHN: The basis for your
20 comparison, Doctor Spear? The conclusion of sameness
21 was based upon characterization of the lesions. Is
22 that right? Number of lesions?

23 DOCTOR SPEAR: No. Excuse me. In vitro
24 release --

25 DOCTOR MAYERSOHN: No, no. In vivo.

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1 DOCTOR SPEAR: In vivo.

2 DOCTOR MAYERSOHN: Your earlier slides.

3 DOCTOR SPEAR: The acne studies?

4 DOCTOR MAYERSOHN: Yes.

5 DOCTOR SPEAR: This was a standard 12 week
6 study of counting lesions. You'd count inflammatory
7 lesions, non-inflammatory lesions, total lesions. Is
8 that what you're getting at? We count lesions so it
9 is a standard way that we're doing in the industry
10 now. Most all products that are approved, Different
11 gel, Retin-A mitro, all the methods use a 12 week
12 study in which you really look at total lesions and
13 percent improvement in total lesions.

14 DOCTOR MAYERSOHN: And that was the basis
15 for your statistical --

16 DOCTOR SPEAR: That is the basis of the
17 statistical comparison. Yes.

18 DOCTOR MAYERSOHN: I don't remember seeing
19 any variability characteristics for your bar graph.

20 DOCTOR SPEAR: The way that you look at
21 bioequivalence today is whether or not, if you look at
22 the mean, the mean of your improvement over 12 weeks
23 at each week, 0, 2, 4, 8, 12, you look at the delta
24 with a two one sided t test and is it between 80 and
25 120 percent of the mean? And if your product is

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1 between 80 and 120 percent, then you can statistically
2 say that you are equivalent. Just like with blood
3 studies, the same number.

4 DOCTOR MAYERSOHN: So this apparently is
5 a very reliable end point to use.

6 DOCTOR SPEAR: If you have designed the
7 acne study well, it's a very reliable end point.

8 DOCTOR MAYERSOHN: And you have one person
9 who does the reviewing?

10 DOCTOR SPEAR: Yes.

11 DOCTOR MAYERSOHN: This is a very valuable
12 person. I suggest you increase his salary.

13 DOCTOR SPEAR: Thank you very much.

14 DOCTOR TAYLOR: Thank you.

15 The next speaker is Doctor Lynn Pershing,
16 University of Utah.

17 DOCTOR PERSHING: I wanted to spend some
18 time, since there's been a big question about skin
19 stripping, the actual methodology and its
20 reproducibility. I want to give some examples on the
21 validation of that. When we first started this
22 project almost 10 years ago at the FDA, we saw that
23 when we compared biopsies and histology versus the
24 amount of skin that was removed by weight, weight
25 removed, if we look at the number of layers of stratum

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1 corneum removed with numbers of tape strippings, you
2 follow the green, you see that it increases with
3 number of tape -- I mean -- how do I say this? Layers
4 of stratum corneum, the number of layers removed
5 increased the number of skin strippings and the number
6 of tape strips that were required followed that very
7 nicely.

8 You see that all these overlap which has
9 to do with the total amount of stratum corneum that
10 could be removed with tape stripping depending on this
11 particular adhesive used. I should say here that
12 different adhesives remove stratum corneum to a
13 different extent in a different profile. The bottom
14 line was that if you confirmed the amount of stratum
15 corneum removed with increasing number of tape
16 strippings, they also agreed with the number of skin
17 layers that were removed with the skin stripping as it
18 progressed from one to 10.

19 One of the issues that is often asked is
20 how different the arms are, inter arm, also intra.
21 The most important variable intra subject variability.
22 How reproducible is skin stripping within an
23 individual? What I want to show you here is the data
24 that came from the Miconazole nitrate study. We took
25 three subjects and we did four sites on each arm and

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1 we skin stripped them according to our methodology.
2 There was 10 skin strippings. And we shoed the mean
3 amount of skin removed and its variability on the
4 right arm. In this person it was 25 percent. There
5 was also 25 percent variability on the left arm. And
6 these two values are not significantly different.

7 On subject two there's a difference in the
8 coefficient of variation between the four sites on the
9 right and left arm, again, no significant difference
10 between the total amount removed. And on subject
11 three a little bit different for right arm, left arm,
12 but not statistically significant.

13 When we looked at inner versus outer
14 aspects of the forearm, this is very important because
15 in the draft guidance you'll see that if you're going
16 to do test and reference evaluation simultaneously in
17 the same person and you have multiple time points of
18 data that you want to collect, the only way you can do
19 that and have enough data points is to do inner and
20 outer aspects in the ventral forearm and you want for
21 a particular comparison, for instance of a two hour
22 treatment, that both the tests and the reference are
23 in the same anatomical location on the forearm.

24 What I want to show you here is in those
25 same three subjects inner versus outer variability of

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1 the Miconazole nitrate study. You see the left inner
2 versus the left outer. It's not significantly
3 different from each other. There are differences in
4 the variability on the right arm but again, because of
5 the variability, they're not significantly different.
6 As we go to subject two and three, we see the same
7 thing. So inner and outer aspects of the forearm are
8 much more reproducible than when you go along the
9 forearm.

10 These are five different subjects in a
11 different study where you have five skin sites along
12 the forearm going from the wrist to the anacubital
13 fossa. In subject one you see very good
14 reproducibility along the forearm although the amount
15 of drug per square centimeter in that subject was 38
16 percent. And as you go to the other subjects, you see
17 some subjects have very high variability and some have
18 pretty low variability.

19 In fact, if you did this with more and
20 more and more people, what you find is in a general
21 average population of 12 to 36 people, the coefficient
22 of variation in the stratum corneum removed and the
23 drug per square centimeter is going to be an average
24 of around 25 to 35 percent coefficient of variation
25 intra subject. Between subjects, if you compare one

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1 to five, the coefficient of variation obviously will
2 go up. It'll go up to 50, to maybe even 80 percent.
3 Within subject you have relatively good
4 reproducibility. Between subjects you have more
5 variability. That's just biology.

6 But what is important to remember here is
7 that a given subject -- this is subject #1 -- we
8 validated how much stratum corneum was removed from
9 that person at three sites on the forearm over a two
10 and a half period of time. It's relatively
11 consistent. The increases that you see here at time
12 #5 and #12 were during summer months when you get more
13 UV radiation and the stratum corneum thickens. But
14 other than that, over time if you took all these, the
15 coefficient of variation in that person is 23 percent
16 and that's pretty true to what we see in most people
17 when we follow them over a long period of time

18 This is another day to day reproducibility
19 where we did a study where we taped up the same
20 individuals, these seven individuals, at week zero,
21 two, six and 12 weeks. What I want to show you is
22 that as a function of time you don't see them
23 necessarily go up or down. You just see that people
24 within themselves are variable and a subject can be as
25 low as eight percent in the coefficient of variation

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1 and the amount of skin removed or as high in this
2 group of 44 percent. But note that in general people
3 are relatively reproducible on a day to day basis.

4 The other thing I wanted to address was
5 healthy versus diseased skin. This has been a healthy
6 component of our discussion today, and I wanted to
7 show you two clinical studies that we did where we did
8 DPK actually and followed clinical course of psoriasis
9 or tinea pedis as a function of therapy. Psoriasis
10 was done -- with topical corticosteroids and the tinea
11 pedis was done with topical cutanazole cream.

12 The first thing you would obviously want
13 to acknowledge is that in psoriatic skin you should
14 have much more stratum corneum than you do in the
15 matched subjects' uninvolved or healthy skin site or
16 uninvolved in this case and indeed, you'll see that at
17 the weeks of therapy the uninvolved sites have less
18 stratum corneum removed for 10 tape strips than the
19 psoriatic lesions did. In fact, there's a three to
20 five or even sixfold difference in the psoriatic
21 stratum corneum weight removed.

22 It is interesting to note that with
23 therapy the amount of stratum corneum goes down, and
24 that's a nice little built in bioassay saying that the
25 drug therapy likely worked. But nonetheless, we have

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1 more specific data. This is .05 percent betamethason
2 dioproyinate was the ointment. It was actually diaper
3 zone ointment and comparing it to a generic foosura
4 ointment. We saw that the DPK profiles over time were
5 actually nonsignificantly different and the clinical
6 target lesion scores were not significantly different.

7 In the case of the antifungal story, we
8 looked at moccasin-type tinea pedis on the plantar
9 surface of a foot and we've compared one, eight and 24
10 hours after a single dose and then one, eight and 24
11 hours after seven doses and we compared the amount of
12 stratum corneum removed in the forearm skin of those
13 people treated with the same dose as their fungal
14 infected foot. We saw there was a significant amount
15 of difference between the milligrams of stratum
16 corneum removed.

17 When we compare after a single dose in
18 humans, we see that when we normalize the drug content
19 for the amount of stratum corneum removed, we see that
20 the forearm data here in the bright pink was not
21 significantly different than the fungal foot. After
22 seven doses, the same was true. Even though it looks
23 like it's decreasing to a great extent, this is not
24 significantly different than the fungal foot
25 concentrations.

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1 If you compare the amount of drug per
2 milligram of stratum corneum removed in the single
3 versus seven dose study at both the arm and the fungal
4 foot against its activity, those extracts from skin
5 strippings submitted to a growth inhibition assay that
6 I discussed earlier, you see as you increase the
7 concentration you increase the growth inhibition
8 activity.

9 This has to do with method of drug removal
10 and we talked about that in the earlier presentation
11 but I guess here it is again. This is another study
12 that's not Miconazole nitrate just to show you that it
13 works with more than one drug and again, these are the
14 cotton applicators we used to remove residual drug.
15 How much is in the protective tape guard? How much is
16 in the tube we used to distribute the drug around the
17 skin surface area? And all of these being much
18 greater than what we see in the skin for SMI solid
19 cream. And further, there's no significant difference
20 to the right and the left arms.

21 The other issues that's addressed in the
22 guidance that I wanted to specifically address in
23 this talk here is that skin stripping is dose
24 responsive. If you take a drug and increase its
25 percent concentration in a solution and apply it to

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1 the skin and measure the amount of drug per square
2 centimeter, you see in all six subjects a dose
3 response. As you increase concentration, you increase
4 the drug content in the skin. That's with the
5 solution.

6 This is a study we did a number of years
7 ago with triamcinolone acetonide at 0.25, .1, and .5
8 percent. What I wanted to illustrate here is that
9 each person is dose responsive and yet the extent, the
10 difference in that slope can be quite significantly
11 different from one person to the next. Nonetheless,
12 the all demonstrate a dose response to concentration
13 applied.

14 And finally the last question that's been
15 coming up a lot is can you use stratum corneum
16 concentrations to predict what's happening in deeper
17 skin layers? What I want to show you here is topical
18 two percent Miconazole cream. This was actually
19 Monistat Derm applied to human skin that is
20 orthotopically grafted onto a nude mouse. In fact,
21 there is differences in stratum corneum compared to
22 epidermis and dermis and that is maintained as a
23 function of time in this model taking multiple
24 biopsies over time.

25 DOCTOR KILPATRICK: I'd like to, for the

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1 sake of consistency, make the same point that Doctor
2 Lavin and I made this morning about how easy it is to
3 design a study which shows your most commonly repeated
4 phrase, not statistically significantly different.
5 Sample sizes were low and again, to repeat Phil's
6 conclusion, you can't really conclude anything.

7 DOCTOR LAVIN: Thank you for the CVs.

8 DOCTOR TAYLOR: Thank you.

9 The next presenter is Doctor Thomas Franz,
10 Dermatologist, Palo Alto, California.

11 DOCTOR FRANZ: The work I'm going to
12 present is from non-sponsored research that was done
13 when I was a member of the faculty at the University
14 of Arkansas, so I'm here really representing myself as
15 a private dermatologist as well as truth and justice
16 and the American way.

17 I'm here to say that DPK works. I can
18 think of 1,000 reasons why things should not work and
19 years of experiments to look at the details, some of
20 which are well thought out and some of which are
21 irrelevant but when put to the test in our laboratory,
22 all's I can say is it works and try to just present
23 one simple example today because it illustrates two
24 specific points that have come up over the discussions
25 of the morning.

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1 One is the consideration of follicular
2 penetration and how it will confound analysis of the
3 data and the other is the number of tape strips to
4 remove surface drug. One of the classes of compounds,
5 corticosteroids have been repeatedly referred to as
6 follicular penetrating and, therefore, may be a group
7 of compounds for which tape stripping doesn't work.
8 Data has been presented that shows differences between
9 stratum corneum content as well as follicular content.
10 We decided to test this and went to the over the
11 counter market.

12 As you know, one percent hydrocortisone
13 and the lower strengths are available over the counter
14 without prescription, no data whatsoever on
15 bioequivalence are required. Given that caveat, one
16 could be assured that there will be differences in
17 bioavailability with one percent hydrocortisone
18 products on the market and so, in fact, we started
19 screening them to look for two one percent
20 hydrocortisone creams with differing bioavailability
21 and we used two assays that are considered to be not
22 relevant assays but literally assays that are used by
23 the industry, the industry that puts money into doing
24 these kind of studies. Therefore, they must have some
25 relevance.

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1 What we found is that there are two
2 products out there, Hytone one percent and Cortisone-
3 10, that's also a one percent product, that by human
4 cadaver skin assay have very, very different rates of
5 absorption and whether one looks at peak rate of
6 absorption through cadaver skin or area under the
7 curve total absorption, one sees about a five to six
8 fold difference.

9 I won't spend a lot of time on what
10 cadaver skin absorption is, but it's like it sounds.
11 You take a piece of cadaver skin, mount it on a
12 chamber, try and maintain somewhat physiological
13 conditions and, in my mind, there are two key
14 conditions that are the major controlling parameters
15 of in vitro absorption. One is the temperature and
16 the other is the relative humidity.

17 So these cadaver skin specimens are run
18 about 37 degrees with a 37 degree solution bathing the
19 underside of the skin. They're exposed to normal
20 ambient conditions just like in this room. A finite
21 dose of these compounds is applied to the surface of
22 the skin, normally in the range of two to five
23 milligrams per square centimeter, and then repeated
24 samples are taken from the dermal bathing solution
25 over time -- in this case, 48 hours -- and analyzed by

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1 HPLC for drug content.

2 We're using the unmodified --
3 formulations, no radioactivity, HPLC is sufficient to
4 look for non-degraded apparent drug. As you can see,
5 the differences between these two products are
6 considerable. So cadaver skin assay says these two
7 products are not bioavailable. If we look at total
8 absorption, roughly a tenfold difference at 48 hours.
9 If we look at peak flux rates, slightly greater than
10 sixfold difference between cortisone and Hytone. So
11 hydrocortisone is much more bioavailable from Hytone
12 than it is from cortisone.

13 We decided to verify this with another
14 accepted assay, the vasoconstrictor assay, and here
15 we're not talking about an assay that is generally
16 considered to be clinically relevant due to the work
17 of Stowton and Cornell. There seems to be no single
18 test, no single predictive test, as good as the
19 vasoconstrictor assay that tells us something about
20 clinical efficacy. For those that know the data, no
21 further discussion is needed. For those that don't
22 know the data, there's not time to discuss it here.

23 In fact, however, the agency does agree
24 with this because bioequivalence for corticosteroids
25 other than hydrocortisone are in fact approved on the

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1 basis of the vasoconstrictor assay. So it's
2 considered to be a relevant assay.

3 We did it in a manner -- essentially
4 hydrocortisone is a very weak vasoconstrictor so the
5 test has to be done the way Stowton did it. It can't
6 be used really using the new technique that the FDA
7 recommends. So we're talking about applying these two
8 steroids to sites. Both are applied to the same
9 forearm and both are applied to both arms of 18
10 volunteers. A finite dose is applied. The sites are
11 occluded with Saran for 16 hours in order to drive
12 enough hydrocortisone into the skin to produce
13 vasoconstriction.

14 At 16 hours the occlusion is removed. One
15 hour later by use of a chronometer the A scale reading
16 is taken as an index of balancing. Now, these studies
17 were actually done in groups of six subjects and the
18 differences between these two products are so great
19 that statically significant differences can be
20 achieved with six subjects, but this represents the
21 average of 18. Just as there is less bioavailability
22 of the cortisone as compared to Hytone, there is less
23 vasoconstriction -1.2 versus -1.9 and these are
24 statistically significant.

25 As you noticed, the scale that we have to

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1 deal with, the chronometer, doesn't have the magnitude
2 that these other tests have so it's a less sensitive
3 assay. But nevertheless, it validates the point that
4 the cadaver skin initially pointed up, and that is
5 these products are different. They do not have equal
6 bioavailability.

7 So then the next question is would DPK
8 give us the same answer? Now, many in this room would
9 say we need to be concerned about follicular
10 penetration. That's going to confound the results.
11 But rather than discussing it, we took the Harry
12 Truman approach and basically just decided let's put
13 it to the test.

14 Now, tape stripping is again done applying
15 a finite dose to demarcated sites on both forearms and
16 again, since we only have two products to test since
17 this is unfunded, unsponsored research, we didn't want
18 to spend a lot of money on this, so we used just six
19 subjects but we applied it to both arms so side by
20 side comparison of Cortisone-10 and Hytone on one
21 forearm, side by side on the other. These sites were
22 not occluded. These sites were tape stripped at eight
23 hours. Eight hours, if you remember from the first
24 slide, is in the middle of our flux curve. The steady
25 state rate of absorption has already been established.

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Huge differences between the products would be expected because you can not get absorption -- you can not get greater absorption from one compound without having a greater concentration in the stratum corneum. And so that's what we're testing. Do we see that greater concentration? We take, in this case, 22 strips. We're analyzing them in pairs. And again, these are taken at eight hours. These represent the first two tape strips commonly considered to represent unabsorbed drug on the surface and, as you can see, the results are equal. These are two one percent compounds. They should be equal.

This next is a grouping of five strips. They're pooled, extracted, analyzed, and again, we're seeing equality. No difference between Hytone and cortisone. We go five more strips. We're now at 12 and again, we see equality in concentration between the two vehicles.

What is happening now -- if you've ever seen the book that Hans Schaefer has co-authored, he has a nice statement in there that succinctly says, as Hans often does, what he means. The skin is not flat. That's the statement. There are furrows in the skin. And as one tape strips stratum corneum, one gets

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1 stratum corneum cells and one also gets unabsorbed
2 drug in skin furrows and those furrows go down quite
3 far. What we are seeing is drug in the furrows. One
4 percent is one percent. They've got to give the same
5 answer, and they do.

6 But after 12 strips, as we get into 17 and
7 then 22 strips, we finally begin to leave the furrows
8 behind, get into the middle portion of the stratum
9 corneum and now we see statistically significant
10 differences between the two products. This is a semi-
11 log scale here so, in fact, these are in a range of
12 two to threefold differences in concentration. So the
13 same answer that we got from two other independent
14 methods was, in fact, the answer that was achieved
15 with DPK and by this particular assay, it really
16 alleviates the problems that people have about
17 follicular penetration.

18 Here at least is one example that shows
19 yes, a portion of this may be going through the
20 follicle. That doesn't mean assaying the stratum
21 corneum doesn't give useful information. In fact, it
22 does. The vasoconstrictor assay measures skin
23 blanching. I've never seen in any textbook anybody
24 say that skin blanching has anything to do with
25 clinical efficacy. It's a pharmacodynamic endpoint.

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1 Here we're looking at a pharmacokinetic endpoint. It
2 may not be the most important one, but we're
3 addressing the question, are two products the same?
4 That, I think, needs to be remembered. I hear a lot
5 of arguments about comparing ointments in creams and
6 the problems that will cause and adding penetration
7 enhancers. It's irrelevant. We're talking about
8 compounds. We're talking about products that are
9 similar in Q1 and Q2. These products are virtually
10 identical, and then put them to the test. DPK works
11 and that's the bottom line.

12 DOCTOR TAYLOR: Thank you. Are there any
13 comments or questions? If not, we'll go to the last
14 presenter, Doctor Paul Lehman from the University of
15 Arkansas.

16 DOCTOR LEHMAN: There's more to
17 bioequivalence than just tape stripping, and a quick
18 and simple way of comparing different methodologies is
19 this very what I like to call an elegant chart to
20 compare the different methods that are available. The
21 simplest is -- release which tells you about the
22 availability of drug in the vehicle and that's about
23 all. There is a tape stripping method which presents
24 the kinetics within the stratum corneum but which can
25 not be observed without a release of product from the

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1 vehicle.

2 There's the cadaver skin assay which was
3 just discussed by Doctor Franz which measures the rate
4 and extent of absorption into the epidermis and
5 through the dermis but which can not happen without
6 the kinetics in the stratum corneum and a release from
7 the vehicle. There are various pharmacodynamic
8 methods, vasoconstriction being just mentioned, but
9 also transepidermal water loss is measured by the
10 pharmacological response, pharmacodynamic response.
11 But again, it can not be observed without some events
12 preceding it. And of course, the clinical trial which
13 is a cascade of events producing multiple
14 pharmacodynamic responses which are often unknown but
15 gives an overall picture. To a validity of the --
16 they must actually complement each other.

17 We had recently an opportunity to evaluate
18 this with a generic tretinoin cream at all three
19 available concentrations as compared to Retin-A at the
20 same three concentrations. First is presented the
21 membrane rate of release assay on the Franz diffusion
22 chamber with synthetic membranes -- generic product
23 with Retin-A at each of the three concentrations. We
24 saw using the SUPAC guidance method that there's
25 equivalence at each three strengths and that this

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1 method also demonstrates dose response across the
2 three strengths.

3 Using the finite dose cadaver skin assay,
4 essentially the same methodology just described by
5 Doctor Franz. Again the generic as compared to the
6 Retin-A. Six donors were used, each in at least
7 triplicate replicates for each product over a 48 hour
8 time period. This is demonstrating the amount
9 absorbed. There was equivalency found within the
10 strengths at the lower strengths, the middle and the
11 higher strengths and, as you can see, there is a dose
12 response that can be observed, so this method also can
13 differentiate those as well as show equivalency. This
14 method can also, although not shown here, demonstrate
15 the drug content within the epidermis and dermis as
16 well as the rate of penetration.

17 We had the fortunate ability of having a
18 pharmacocyte dynamic assay available as well for Retin-A
19 that measures two components, first being
20 transepidermal water loss. In this case, 34 subjects
21 over a 21 sovachronic dosing period. TEWL was
22 measured. Bioequivalence was demonstrated at each
23 different concentration. At least for the generic we
24 were able to demonstrate dose response as well.
25 Interestingly enough, the innovator did not show as

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1 good of a dose response suggesting that there may be
2 a problem here in the innovator product which is not
3 present in the generic product.

4 The second parameter that can be measured
5 with the pharmacodynamic assay is a desquamation score
6 or the time it takes before the surface of the skin
7 stratum corneum is peeled because of exposure to the
8 tritinoin products. This is days to full peel versus
9 the various concentrations. This is a much nicer
10 picture than the previous one in that at each
11 concentration bioequivalency was determined for both
12 generic versus the Retin-A and there is a nice dose
13 response.

14 This then is presenting three separate
15 methods, each demonstrating dose response capability,
16 each demonstrating generic versus innovator
17 equivalency. The question is how does tape stripping
18 fit into this? It should also then, if it has the
19 capacity to show bioequivalence, it should also show
20 bioequivalence. We also then did the tape stripping
21 study, a very carefully designed study, fully
22 validated on 24 subjects per concentration. There was
23 a six hour absorption phase and a four and a half day
24 elimination phase.

25 After a -- wipe, the initial 12 strips

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1 were discarded because we had previously decided that
2 that represented surface dose and the next 10 strips
3 were then taken, cooled and assayed. This graph
4 represents the area under the curve as measured for
5 both generic and innovator. Bioequivalence was
6 demonstrated at the low strength, at the middle
7 strength and at the high strength and, as you can see,
8 there is a nice dose response that can be demonstrated
9 by the tape stripping assay.

10 A second parameter that is of concern from
11 the tape stripping assay is the Cmax in the same sort
12 of subjects. Bioequivalence can be shown at low
13 strengths, middle strengths and the high strength and,
14 as you can see, there is a dose response available
15 too. So the tape stripping assay does support
16 bioequivalence when it's used in a properly validated
17 methodology.

18 The conclusion is simple and apparent.
19 Even if you have a multitude of choices when you
20 compare them all, we were able to demonstrate for
21 Retin-A versus generic cream that bioequivalence or
22 equivalence or sameness, however you want to call it,
23 the memory rate of release assay was confirmed, the
24 cadaver skin assay was confirmed, TEWL pharmacodynamic
25 assay was confirmed, and in concert with that, the DPK

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1 tape stripping assay also demonstrated the same
2 bioequivalence as the other methods.

3 If you don't have confidence in the tape
4 stripping assay, for whatever reason, then we would
5 suggest doing more than one approach. Do the tape
6 stripping assay with a pharmacodynamic or with a
7 cadaver skin assay. Certainly, two approaches are
8 much stronger than one approach.

9 Thank you for the time.

10 DOCTOR GOLDBERG: What was the cost of
11 doing those studies?

12 DOCTOR LEHMAN: Significantly less than a
13 clinical trial.

14 DOCTOR TAYLOR: Thank you. I'd like to
15 thank all of our speakers for the open public hearing
16 portion of the meeting. They have added significantly
17 to our hopefully understanding and appreciation of
18 what you and the industry and academia think about
19 what we're discussing.

20 The next hour we will be discussing some
21 followup issues to the morning session and the first
22 one will be given by Doctor Shah and it's in vitro
23 release approach and regulatory applications. So
24 Doctor Shah, you have the floor. I'm to remind you
25 that we're going to exert equality here and that, just

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1 as we timed the speakers from the floor, we're going
2 to time the speakers from the FDA as well.

3 DOCTOR SHAH: May I have the first slide.
4 The second part of the discussion now is going to
5 focus on the in vitro release and the regulatory
6 applications, especially focusing towards the lower
7 strengths. In the previous hour of the open
8 discussions, we did hear some comments on the lower
9 trend, whether it is valuable or not, and I'll come
10 back again to those issues at the appropriate time.

11 May I have the next slide please. For the
12 benefit of those who are not fully aware of what's an
13 in vitro release, I'll try to briefly summarize it.
14 It's an in vitro release system using the diffusion
15 cell system with a synthetic membrane and we measure
16 the release of the drug in the receptor medium. The
17 amount of the drug released was the square of times
18 plotted. It takes about four to five different points
19 and we did similar to the area under the curve or the
20 dissolution profile that you normally see. But then
21 we take all those data points and arrive at a single
22 time point at a single value which is known as the
23 release rate.

24 And I would like to show you some more
25 data where the release rate has been found to be

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1 highly reproducible. I do want to emphasize the fact
2 that the release rate is the property of the
3 formulation and we can not compare from one
4 formulation to the other formulation or one
5 manufacturer to the other manufacturer.

6 May I have the next slide please. This is
7 the -- system where this is a slightly modified --
8 Here we put the synthetic membrane on top of that. We
9 have the drug product and we measure the drug samples
10 from here taken at different time intervals. Next
11 slide please.

12 And this slide shows the interlot
13 variability. Actually, let me point out here we plot
14 here the amount of the cumulative amount of the drug
15 release was the square root of time. It's about six
16 hours time duration and you can see the
17 reproducibility from different lots from a single
18 manufacturer plus the reproducibility on the same lot
19 when it is done several times. In this particular
20 case, it was done for four times and you can see the
21 reproducibility of the system.

22 Coming back to the issue of the lower
23 strength. I would like to go back to what is in the
24 statute and what for the oral immediate release drug
25 products. For the oral immediate release drug

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1 products, the bioequivalent studies is done only at
2 the highest strength and the lower strengths are
3 approved based on the composition similarity and the
4 dissolution profile. Taking these assumptions and the
5 fact that it is in our statute that we should provide
6 them the way they were based upon the composition
7 similarity, what we are suggesting here and asking is
8 similarly for locally acting dermatological drug
9 products, a bioequivalence study needs to be done at
10 the highest strength and then the approval of the
11 lower strength based on the composition similarity and
12 the in vitro drug release rate.

13 Next slide please. We are making the
14 following assumptions here. That the formulation of
15 the two strengths from the given manufacturer differs
16 only in the concentration of the active ingredient and
17 there is no difference in the manufacturing process
18 and type of equipment used between the two strengths.
19 Now again, as you may recall, the strengths of these
20 types of products are somewhere between .1 percent
21 and .5 percent and what we are saying it if the
22 product is approved found to be bioequivalent by
23 whatever criteria you have at .1 percent, then the
24 slight change in the amount of the active ingredient,
25 .5 milligram percent is only changed. Nothing else is

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1 changed. It's the same manufacturing process, same
2 process in the same manufacturing unit. In those
3 cases, we can do the -- based on the in vitro release
4 data.

5 Also, the requirements are the reference
6 listed drug, the innovator or the brand name product,
7 is marketed at both strengths, in the higher strength
8 as well as the lower strength, and the generic product
9 is determined at the highest strength to be
10 bioequivalent. By whatever criteria we decide, it is
11 found to be bioequivalent to the innovator product
12 using the appropriate BE tests.

13 Just to summarize it very briefly how
14 exactly all the release rates come in the picture, for
15 higher strength, let's call that the release data to
16 be S1 and for the lower strength the release rate to
17 be S2. Using the well known and established --
18 equations, this equation provides the release rate
19 from the suspensions and this equation provides the
20 release rate from the solutions. If you want to
21 compare the release rate of S1 and S2, depending on
22 whether the product is in the pharmacosuspension, then
23 the release rate is directly related to square root of
24 the two concentrations and, if the product is formed
25 in the pharmacosolution, then the release rate between

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1 the two strengths is actually proportional to the
2 ratio of the two strengths.

3 I'll show you an example. This is an
4 example of a steroid where two different manufacturers
5 are involved. This is the highest strength release
6 rate. This is for the second manufacturer. But
7 within the same manufacturer this is the slope of the
8 lower strength and in this particular case it is this
9 one. If we take the ratio between the higher and the
10 lower strength in a given manufacturer, it is 2.69 in
11 one manufacturer. The other one is 2.74. If you
12 follow the guidance, what it says is this ratio or
13 this ratio should be very close to one and that's why
14 in this particular case it happens to be 0.98.

15 May I have the next slide please. In a
16 different set of examples, again taking a look into
17 the different products, hydrocortisone, the final
18 ratio again turns out to be between the two different
19 manufacturers, the ratio is 1.0. Again, inclined to
20 say that it could work as long as we are maintaining
21 within the same manufacturing units.

22 Next slide. Summarizing all the data for
23 hydrocortisone, the ratio turns out to be 1.0. For
24 corticosteroid, the ratio turns out to be 0.98. And
25 this is somewhat -- to what we heard earlier when one

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1 presentation found that in one particular tape the
2 ratio was around 1.15 and in the second case they
3 found the ratio to be 1.26. ± 20 percent will bring
4 the ratio to be around 1.25, between .75 to 1.25 and
5 we think that the procedure is still quite applicable
6 in those cases.

7 Next slide please. I'd like to bring out
8 the points which were initially raised in some of the
9 comments saying that we are not consistent with SUPAC-
10 SS and we are coming up with something new. No, we
11 are consistent with what is identified in the SUPAC-SS
12 guidance. SUPAC-SS stands for the scale up and post
13 approval changes for the semisolids.

14 As far as the SUPAC is concerned, it does
15 not discuss the different strengths of the dosage
16 forms. It is only discussing the changes in the
17 formulations. So when we are talking about the SUPAC,
18 the different strengths of the product should not come
19 into the picture. In one of the latest workshops we
20 had which was discussing the pros and cons of in vitro
21 release drug products, it was very clearly identified
22 that we should not make a cross comparison. By cross
23 comparisons, I mean comparing the in vitro release
24 profile from one manufacturer to the other because we
25 heard today that even though 40 manufacturers may have

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1 exactly the same ingredients, but their manufacturing
2 process might be different and end up slightly
3 different in the release profiles. Therefore, that is
4 also one of the reasons why we say that you should not
5 do the cross company comparisons and the comparisons
6 should be done within the manufacturer.

7 The procedure that we are suggesting and
8 following is trying to provide a link between the
9 bioequivalency of the highest strengths of the -- in
10 the reference product. It is also providing a link to
11 the manufacturing process and the compositions with in
12 vitro release and all this is still in accordance with
13 21 CFR 32122D2.

14 May I have the next and the last slide in
15 this area. Trying to summarize this with the slide,
16 the reference product is approved using the clinical,
17 safety and the efficacy data. The test product or the
18 generic product is approved based on the
19 bioequivalence data no matter what our bioequivalence
20 data may be. It may be the clinical studies, it may
21 be the pharmacodynamics or it may be the DPK. But
22 these two highest strengths are found to be
23 bioequivalent with one another.

24 Now, we assume -- there is only one
25 assumption that within a manufacturer the same

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1 confidence composition is being used and, therefore,
2 you go down the list, you measure the in vitro release
3 of the highest and lowest strength and find the ratio.
4 Same thing you do on the other side. And these two
5 ratios must be nearly the same. Knowing the physical
6 chemistry of the drug product, it is easy to expect as
7 to what would be the approximate ratio. If the
8 product is in suspension, it will be -- off as one
9 over S_2 . If the product is in solution, the ratio
10 will be S_1 over S_2 . So this is the scientific basis
11 and the principles how and why we are suggesting and
12 requesting the approval of the lower strength based on
13 the in vitro release after the highest strength has
14 been found to be bioequivalent.

15 Thank you. I have three more minutes for
16 questions and answers.

17 DOCTOR TAYLOR: Okay. We'll entertain
18 three more minutes of questions. If no questions, do
19 you have anything more to add? Do you have more to
20 add? You can use your time if you wish.

21 DOCTOR SHAH: I can show more data if
22 people would like to see the data on the -- and the
23 other products.

24 DOCTOR GOLDBERG: I do have a question.

25 DOCTOR TAYLOR: Yes, Doctor Goldberg.

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1 DOCTOR GOLDBERG: Do you have any release
2 rate data comparing the Hytone and the Cortisone-10
3 that we saw from Doctor Franz before?

4 DOCTOR SHAH: I don't have Cortisone-10
5 but I do have the release data on the Dermik -- I'm
6 sorry. I do have the release rate data of the
7 hydrocortisone product which is Dermik but I don't
8 have the one from Cortisone-10 and I have the release
9 rate data also product manufactured by Doctor Gordon
10 Flynn in his laboratory. Can you show that again?
11 This is the marketed product and this was the one
12 prepared by Doctor Flynn and his graduate student.

13 DOCTOR TAYLOR: Thank you.

14 The next presentation is by Doctor Wilkin
15 and involves regulatory issues.

16 DOCTOR WILKIN: Thank you, Doctor Taylor,
17 members of the two committees.

18 Also a non-subtle title for the afternoon.
19 I think one of the key points to remember from Doctor
20 Shah's excellent presentation is that the release rate
21 is anticipated to likely be different for the test
22 product, the generic, different from the reference
23 product which is the innovator. So I'm going to
24 proceed from that scenario instead of the scenario of
25 those being exactly the same.

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1 If the reference high strength and the
2 test high strength are bioequivalent and have
3 different in vitro release rates, then the vehicle
4 effects must be different. That will be one of the
5 points I want to make. Vehicle effects are clearly
6 important to this whole consideration and vehicle and
7 stratum corneum effects are not linear over a range of
8 concentrations for an individual product. Therefore,
9 the linear proportionality of in vitro release rates
10 can not be derived.

11 Again, the reference high strength and the
12 test high strength are bioequivalent. This could be
13 by a clinical test or this could be by the Stotten
14 McKenzie multi-point vasoconstrictor study. We're
15 also having the starting conditions that the reference
16 high strength and the test high strength have
17 different in vitro release rates. So they're
18 releasing in vitro different amounts over time and yet
19 they're bioequivalent. If you're going to think
20 quietly about one thing all afternoon, I would ask
21 that that be it. Why would that be the case? Why
22 would they have different in vitro release rates and
23 still be bioequivalent?

24 The answer is they have different
25 vehicles. The vehicles are interacting with the

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1 stratum corneum. They can alter the apparent
2 diffusion coefficient. The vehicle and the stratum
3 corneum comprise the partition coefficient
4 relationship. That is, the active has to partition
5 from the vehicle into the stratum corneum and so
6 different vehicles can alter the partition coefficient
7 quite dramatically.

8 So the in vitro release rate which is with
9 a membrane that does not affect the diffusion out. It
10 merely supports. It's like a hammock, if you will,
11 that has a very wide mesh. It is suspending this
12 material and it allows it to go through the active
13 from the glob of the semisolid that is sitting inside
14 of it.

15 So if the reference high strength and the
16 test high strength are bioequivalent, then they have
17 the same bioavailability. So I'm going to do a little
18 math which I think is probably at the eighth grade
19 level so it shouldn't be too complex. Basically, this
20 is the release rate from the reference high strength
21 and we know that the test high strength has the same
22 bioavailability and they're bioequivalent so what we
23 can infer from this is there is some other factor
24 that's going to cover the vehicle effect component and
25 we can call that for the high strength K_{RHS} and for the

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1 test high strength K_{THS} . The argument that Doctor Shah
2 is presenting is that we can take this ratio of the
3 $K_{RHS} K_{THS}$ and that's going to be the same as $K_{RLS} K_{TLS}$ for
4 the lower strengths.

5 So we'll look at that little detail. The
6 release rate for the higher strength again with this
7 methodology should equal the release rate of the test
8 high strength times the ratio of the factor for
9 vehicle effects of the reference high strength divided
10 by the vehicle effect factor for the test high
11 strength and likewise for the lower strengths one has
12 the same proportionalities. The same factors that
13 relate to the vehicle effects.

14 His argument is that the ratio of the high
15 strength factors that encompass vehicle effects, both
16 on partition coefficient and on apparent diffusion
17 coefficient, are going to be the same as for the lower
18 strength. And what that would then allow, if he's
19 correct, is that one could substitute. If you know
20 the release rate for the reference lower strength and
21 you know the release rate for the test lower strength,
22 you can take that. If you assume the same
23 proportionality, then one can make this assumption.

24 But we're thinking about vehicle effects
25 on the stratum corneum and vehicle effects on the

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1 partitioning of the drug into the stratum corneum.
2 Doctor Maibach is one of several authors who has
3 pointed out that there is a decreased efficiency as
4 one increases the concentrations of topically applied
5 substances. As you keep the vehicle constant and you
6 increase the concentration of the active, what happens
7 is there's this horizontal asymptote, that there is a
8 rate limiting effect of the diffusion coefficient.
9 One approach is a diffusion coefficient is maximal.
10 I mean you can't get any more drug through the stratum
11 corneum. There are just so many, if you will, pores
12 that will allow the drug to go through.

13 And so these are the data from
14 nitroglycerin. They're data for other substances.
15 What they showed was that as you increase the
16 concentration, the percent dose actually absorbed
17 drops and the total milligrams absorbed continues to
18 rise over some of the lower doses but at the higher
19 doses it would level off. So vehicle effects on the
20 drug in the stratum corneum are not linear over a
21 range of concentrations of the drug and they may not
22 be linear over the therapeutic concentrations.

23 Vehicle effects and stratum corneum
24 effects can be thought of as limit functions and the
25 concentration flux curve is not straight. It's

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1 curvilinear. So this is what my concern is. My
2 concern is that one could have -- this is the high
3 concentration and low concentration and you could have
4 flux being the same. It needs to be the same. Flux
5 is transit across the stratum corneum. Flux would
6 need to be the same if these are bioequivalent
7 products so, even though they have different release
8 rates, they're going to have the same flux at the same
9 high concentration. But because of the different
10 vehicle effects that allowed this flux rate to occur,
11 there can be a different curvilinear relationship that
12 takes them down to the lower concentration.

13 So I do not accept that one can directly
14 derive a linear proportionality. I think the linear
15 proportionality that is spoken of in Doctor Gordon
16 Flynn's work is really talking about the relationship
17 of the concentration in vitro release in vitro. It
18 has nothing to do with flux across the stratum
19 corneum. It's merely describing the behavior of these
20 substances in his, again, controlled artifact, if you
21 will which really ignores the vehicle effects on the
22 stratum corneum and also on partition coefficient.

23 So again, the argument is that if the
24 reference high strength and test high strength are
25 bioequivalent and have different in vitro release

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1 rates, then the vehicle effects must be different.
2 You can't really come to any other conclusion.
3 Vehicle and stratum corneum effects are not linear
4 over a range of concentrations for a given vehicle.
5 Because of that, linear proportionality of in vitro
6 release rates can not be derived.

7 DOCTOR MINDEL: Would anyone like to
8 refute his refutation? Thank you.

9 DOCTOR TAYLOR: That concludes the
10 presentations. I would like, however, to open the
11 floor to any additional public presentations and limit
12 them to about three minutes. I failed to do that at
13 the end of the open hearing. So if you would come to
14 the microphone and to identify yourself by name and
15 your affiliation and limit your comments to no more
16 than three minutes, if you would.

17 MS. SCHRODY: Thank you very much. My
18 name is Kathy Schrody. I come from Bristol Meyers
19 Squibb. There are three main points I'd like to bring
20 up. One, the safety of drugs that are administered
21 orally are established a priori because you're
22 administering them orally and you know how much drug
23 is in the system. When you're looking at topical
24 drugs and you're looking at skin stripping as a way of
25 assessing the drug in the stratum corneum, you have no

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1 idea about the penetration of drug into the systemic
2 circulation, and I think there is, aside from the
3 bioequivalency issue of efficacy, we need to look at
4 safety.

5 Second point. If we look at the
6 Miconazole data that was presented this morning, the
7 clinical data shows a trend of superiority of the test
8 product versus the reference listed drug. It wasn't
9 powerful enough to confirm that statistically, but
10 there was a trend. I'd like to compare that to the
11 DPK data where the comparison of reference listed drug
12 to the test article test drug showed that the test
13 drug was lower in DPK value. So you have a DPK assay
14 that shows inferiority, a clinical assay which tends
15 to show superiority. They don't correlate.

16 Finally, in vitro release for lower
17 strengths. I'd like to point out, in addition to what
18 Doctor Wilkin said very eloquently, I think we can
19 look at it from a very simple perspective. We've
20 already demonstrated and discussed to a great extent.
21 There's a significant vehicle effect with topical
22 products. It is very rational to believe that what
23 may be demonstrated bioequivalent at a high dose may
24 not necessarily be bioequivalent at a low dose because
25 of different vehicle effects.

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1 Thank you very much.

2 DOCTOR TAYLOR: Thank you.

3 Are there other individuals who would like
4 to make some public comments? Yes, would you come to
5 the microphone and identify yourself and your
6 affiliation.

7 DOCTOR GUY: Richard Guy from -- in France
8 once again. Just along the lines of the last
9 discussion concerning this high strength/low strength
10 story. There are two points which I think, Vinod, you
11 need to address in order to make everyone more
12 comfortable. First of all, I think, at least in the
13 scientific community, nobody really believes that in
14 vitro release assay using a synthetic membrane has
15 anything to do with bioavailability of the compound in
16 question.

17 And, therefore, the argument that a
18 release rate that you measure one strength which
19 admittedly has no relevance to the in vivo
20 characteristics of that material, is not going to be
21 any different when you use a lower strength. And so
22 one could dismiss the whole argument by saying that
23 measurement has no relevance to in vivo
24 bioavailability anyway. It has no relevance to any
25 concentration whatsoever. And so I think that's one

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1 important issue.

2 The second is that when the in vitro
3 experiment is done, the material, the formulation is
4 applied to the top of the plastic sheet and is left
5 there in a big sort of finite dose. There's no
6 attempt to massage that into the plastic membrane in
7 any shape or form which, of course, is how that
8 material is in fact used in vivo and how in an in vivo
9 situation, either using DPK or classic measures of
10 clinical availability, that will be assessed. And, of
11 course, when a formulation is massaged into the skin,
12 lots of things change and it's too bad Gordon Flynn
13 isn't here to specify what those are.

14 Formulation components enter the stratum
15 corneum. They can, in turn, solubilize the active
16 species within the stratum corneum. That, of course,
17 will have an effect on the availability. Certain
18 formulation constituents will evaporate and
19 valasilize. That will change the characteristic of
20 the formulation and that may be a function of how much
21 drug is in the formulation and to the extent that one
22 loses those volatile components.

23 And so once again, there are things which
24 occur in the in vivo situation which are not occurring
25 in this in vitro release assay and which, therefore,

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1 need to be thought about seriously when one suggests
2 that different concentrations can be compared in this
3 way.

4 Thank you.

5 DOCTOR TAYLOR: Would you like to respond
6 to Doctor Guy, Doctor Shah?

7 DOCTOR SHAH: I would like to go back and
8 just give the responses to some of the previous
9 questions. I'd like to bring it back to the attention
10 that we are looking at the products higher strength,
11 lower strength, made in the same manufacturing unit
12 containing exactly the same ingredients. The only
13 change is the amount of the active ingredient from .1
14 percent to .05 percent. There is absolutely no
15 difference between the two products. So if there a
16 vehicle which is going to increase the drug
17 penetrations or do anything else, the same thing would
18 be happening.

19 With respect to the bioequivalency
20 determination, this is the same slide I showed a few
21 minutes ago. We are establishing the link between the
22 two products at the highest strength, the reference
23 product and the test product. They are determined to
24 be bioequivalent. It may be a pharmacodynamic method
25 or maybe a clinical method or any other method, but

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1 they are determined to be bioequivalent. Whether they
2 contain the different vehicles or they have the
3 different propylene glycols or something, but they are
4 determined to be bioequivalent.

5 Now we are going down the parallel path
6 saying that the only change being made is the amount
7 of the active ingredient. Nothing else. And using
8 the principals of the well laid out -- equations and
9 the drug release properties, it can be predicted as to
10 what's going to be the ratio between the S1 or S2. If
11 the product is in solution, we know it is going to be
12 S1 or S2. If the product is in suspension, it is the
13 square root of S1 over S2.

14 And I can show you more data if people are
15 interested as to what at all different concentrations
16 which were studied, what are the predicted ratios,
17 what are the theoretical ratios, what are the actual
18 ratios that we have found?

19 Thank you.

20 DOCTOR TAYLOR: Yes. Thank you very much.
21 We have one additional comment.

22 MR. CAMP: Izzy Camp from Genfoam,
23 Toronto, subsidiary of -- Germany.

24 I was intrigued by the lack of correlation
25 of the DPK study with the clinical efficacy of

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1 Miconazole. Perhaps a suggestion here would be to
2 test the reference versus the reference itself in a
3 DPK study and see if that would meet those acceptance
4 criteria.

5 DOCTOR TAYLOR: Any other comments? Yes,
6 would you come to the microphone.

7 DOCTOR PARAB: I would like to make three
8 comments. Doctor Franz showed that first 10 strips
9 are contaminated because there are furrows and all the
10 references in the guidance for the DPK have taken
11 first 12 strips and then the studies. So I question
12 the validity of the studies. Maybe those are all
13 contaminated concentrations. Therefore, they're
14 getting good correlation between the concentration and
15 stratum corneum uptake.

16 Secondly, with reference to the
17 antifungals bioassay, I have question. What they have
18 done is taken the stratum corneum and extracted with
19 acetone nitrile and then they applied all the disks,
20 they operated and put on the petri dish. Stodden
21 didn't do that way. He actually took the stratum
22 corneum and put on the petri dish because when you
23 extract acetone nitrile, it does not differentiate
24 between bound drug and unbound drug.

25 Last comment on in vitro release. We say

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1 that there's no change in the formula, only change in
2 the drug substance from one percent to .1 percent.
3 At the highest concentration the drug may be in
4 suspension. At the lowest concentration it can be in
5 solution. Is it changed?

6 Thank you.

7 DOCTOR TAYLOR: Thank you.

8 Doctor Wilkin.

9 DOCTOR WILKIN: I just wanted to indicate
10 that I share Doctor Shah's conviction about the last
11 two lines. The idea of the ratio works to describe
12 what is happening in vitro with the in vitro release
13 rate. In other words, if one increases the
14 concentration in the material that's hanging in this
15 supra mattress in vitro, then you would expect the in
16 vitro release rate to change in the proportionality
17 that Doctor Shah indicates and that I think Doctor
18 Flynn and the student working in his laboratory has
19 clearly demonstrated.

20 Where I see that as not working is flux is
21 proportional to the concentration of dissolved drug in
22 the vehicle and then often we think that it's also
23 proportional to the partition coefficient and also to
24 the diffusion coefficient, and we sort of think of
25 those as linear sorts of things, but they're really

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1 not. There is an upper limit that can be governed by
2 the actual diffusion that is maximal. That's the part
3 that in vitro release rate can't really speak because
4 it's in a system that doesn't have stratum corneum and
5 doesn't have vehicle going up against stratum corneum.

6 DOCTOR TAYLOR: Can I ask you a question
7 about your comments? In considering the vehicle
8 effects on membranae, how do you know where you are on
9 that curvilinear diagram that you showed us? How do
10 you know both concentrations are not on the flat
11 portion of the curve rather than where you've said
12 they were which was at the bottom portion? How did
13 you decide the low was down at the beginning and so
14 forth? In other words, you might maximize your
15 vehicle effects at very, very low concentration.

16 DOCTOR WILKIN: That is correct, and often
17 we see topicals that are approved at a concentration
18 that really is limited because they can't get any more
19 into solution in that particular vehicle. So they
20 tend to be on the upper end of that horizontal
21 acetone.

22 DOCTOR TAYLOR: I was just curious as a
23 non-dermatologist but as a pharmacologist how you knew
24 that and, thus, it may suggest that by increasing
25 vehicle concentration you may not get any further

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1 vehicle effect on membrane.

2 DOCTOR WILKIN: That's right. Again, as
3 one typically increases the vehicle concentration, you
4 get less bang, if you will, for the buck as you keep
5 moving up the concentrations. They tend to adopt this
6 horizontal acetone in the relationship between
7 concentration versus flux which is passage across the
8 stratum corneum. That's exactly it.

9 DOCTOR TAYLOR: But the higher up you get
10 on that curve, the flat part of the curve, it refutes
11 your argument and it makes Doctor Shah's argument more
12 plausible.

13 DOCTOR WILKIN: Well, actulaly it doesn't
14 in a way and that's because Doctor Shah can't tell us
15 where we are on the curve.

16 DOCTOR TAYLOR: He can't tell me either.
17 I was going to ask him that actually.

18 Are there any other public comments? If
19 not, any other questions or comments by the committee
20 before we have Doctor Williams summarize the day's
21 activities? I'd like him to do that at this time.

22 Yes, I'm sorry. Please make your comment
23 very brief.

24 DOCTOR PARAB: You can do the -- on the
25 curvilinear portion of the curve by just doing cadaver

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1 skin permeation studies. You can understand whether
2 the flux is linearly changing. You can do that.

3 DOCTOR TAYLOR: Thank you.

4 Doctor Williams, you have the floor.

5 DOCTOR WILLIAMS: Thank you, Doctor
6 Taylor, and if Kimberly would show my first slide.
7 I've been listening very intently. I want to
8 assure all members of both committees that I've been
9 paying very close attention to the discussion. I've
10 been very interested in the opinions, but I would also
11 say I've been especially interested in the data, and
12 I'll come back to that in a little bit.

13 I'm going to commit an act of
14 schizophrenia because I'm going to argue against
15 myself in the next couple of minutes. But I've been
16 basically listening to the issues that have come up in
17 the course of the afternoon and we've talked about
18 this many times over the last several days. It's sort
19 of the therapeutic clinical approach, the
20 therapist, if you will, versus the formulator/
21 product quality/biopharmaceutical/scientist approach.
22 I've summarized those two approaches up here and sort
23 of the world of J and the world of D. It goes back to
24 the three questions I asked at the very beginning, and
25 I'm just trying to list them here, and I'd appreciate

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1 comments from both committees, but I'm going to try to
2 use this in driving some of our further work on this
3 important guidance.

4 In terms of the question, I got up and
5 said the question is release of the drug substance
6 from the drug product. That's bioavailability and
7 bioequivalence to me. But I think we heard from
8 several people -- and I'll put on the other hat --
9 that no, that's not so important us, Roger. The real
10 important thing is equivalent safety and efficacy
11 which really should be shown in comparative clinical
12 trials.

13 And then flipping back to the other hat,
14 what are we willing to rely on, and we hear a lot
15 about these exposure metrics that we talked about
16 today in the stratum corneum, and then the counter-
17 argument to those is if you're going to rely on those,
18 you have to justify it with some kind of correlation
19 to justify the surrogacy of those.

20 Then if you move into sort of the healthy
21 skin bioassay aspect where you look at this
22 dermatopharmacokinetic surrogate marker, if you will,
23 everybody would want to look at that in healthy skin.
24 You sort of ask the question, why would you ever want
25 to look at it in diseased skin which would tend to

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1 damage the barrier and make everything look the same.
2 It's sort of like doing an oral bioequivalent study in
3 people with inflammatory bowel disease. It doesn't
4 have any logic to it.

5 On the other hand, people on the other
6 side, arguing on the other side, say, Wait a minute.
7 This drug and drug product is intended to be used in
8 diseased skin or certain skin sites like the vaginal
9 epithelium or the lip and, therefore, you must do
10 comparative trials to assess the comparison. For the
11 world of J, we tend to think of the excipients as not
12 being very important and, conversely, in the world of
13 the locally acting drug product, we sort of understand
14 that excipients can be critical.

15 Separate from the issue of correlation,
16 which sort of justifies the surrogacy of whatever we
17 might be talking about, for example,
18 dermatopharmacokinetics, there's the issue of
19 validation and training of, say, a
20 dermatopharmacokinetic study, and that is, of course,
21 a very intensive question for this approach and I
22 think we all recognize that validating
23 dermatopharmacokinetics is difficult.

24 Conversely, we might say, How do you
25 validate a clinical trial? And I think Doctor Maibach

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1 began to intrude that thinking into our mind. Can we
2 show a dose response relationship in most clinical
3 trials? Have we ever really validated our reliance on
4 blood level measurements? Can anybody think of
5 studies where we've shown different blood levels that
6 correlate with different clinical responses? Those
7 studies actually aren't done very often. There are
8 certainly dose response studies in terms of PK, but
9 have we ever really validated our willingness to rely
10 on blood level studies for orally administered?

11 To the pharmaceutical science, toximetry
12 is critical but can we really say that we carefully
13 control the dosing of a topically applied product?
14 Frequently we have no control on that whatsoever, I
15 would argue, very little control, and sometimes we
16 occlude which adds another layer of uncertainty as
17 exactly what we're doing in a dosing. So why is there
18 this incredible emphasis on dosing and similarity?

19 For the world of J, we're driven by Hatch
20 Waxman which says that we shouldn't rely on clinical
21 trials. They're supposed to be avoided specifically
22 and the '77 regs say that in terms of assessing
23 bioavailability/bioequivalence clinical trials are
24 highly insensitive. So we have statutory and
25 regulatory admonitions against the use of clinical

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1 trials for J applications.

2 Certainly for the world of new drugs, the
3 world of B, we have the '38 and '62 admonition that we
4 must do safety and efficacy and rely on empirical
5 clinical trials, many times to allow market access.
6 In the world of J, we focus on the criteria, the
7 equivalence interval, and the confidence interval, and
8 we spent a lot of time yesterday talking about those
9 criteria. I'm a little uncertain about how we look at
10 these things for comparative clinical trials in terms
11 of percent cures and confidence intervals and
12 equivalence intervals.

13 There are many ways we can talk about
14 this, but I want to show some possible ways forward in
15 just a second, but before I leave all these questions
16 -- I mean these are the questions that I think I've
17 heard from around the table and from many speakers in
18 the course of the day -- I'm going to show one set of
19 data and I hope Kim Spear will excuse me because I
20 plotted his data as a good example of what I think
21 we're struggling with.

22 This is actually dose response data from
23 Kim that he showed in the course of his presentation
24 this afternoon where you're looking, I think, at an
25 acne study and a response rate that starts, I assume,

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1 at 100 although he didn't give me that data and then
2 he goes down to about a 50 percent response rate at
3 .025 and a 70 percent response rate at .1. Now, there
4 are many ways to look at these data, but I would argue
5 this points out, at least to me, some of the problems
6 that we're struggling with where we have a very small
7 dynamic range for a fourfold difference in dose. And
8 that's kind of a core issue we have to deal with here.

9 I put that dotted line over there to show
10 what we generally care about in the realm of
11 bioavailability and bioequivalence which is a 20
12 percent difference in dose delivered. Now this raises
13 -- and now I'll put on my J hat -- the question that
14 it's not so much that we're willing to rely on
15 clinical trials. I think the question is should we be
16 willing to rely on clinical trials for what we care
17 about. Differences in dose. Are we really satisfied
18 that if we showed sameness in a clinical trial that
19 the generic would be truly interchangeable under all
20 conditions of use in the marketplace?

21 Now, let me go on. I just have one other
22 thing to show just to compare the J and the B world.
23 We can ask -- and chemistry manufacturing controls a
24 lot of sameness in terms of how we regulate the
25 generic application and the B application, and we

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1 would certainly insist that both would conform to good
2 manufacturing practices in terms of their manufacture.

3 The issue, of course, that we've been
4 struggling with today is bioavailability and
5 bioequivalence. For the innovator, there is a two
6 treatment comparison study to placebo. The equivalent
7 study for the generic would be a three way clinical
8 study, test reference, and placebo. And I think we
9 sort of do endorse that, that you need that placebo
10 trial to show that you can observe a difference at
11 all.

12 And then we've been kind of struggling
13 with these additional nonclinical markers,
14 dermatopharmacokinetics and in vitro release. Now,
15 how do we think about that? Well, one way to think
16 about it is what I alluded to earlier which is we sort
17 of have a boundary in SUPAC-SS. SUPAC-SS is something
18 that deals with post-approval change and the tests and
19 filing requirements recommended for certain changes
20 for both pioneer and generic manufacturers. I t ' s
21 interesting to read that document because what that
22 consensus document said, you can make almost any
23 change you want and not do in vivo bioequivalence
24 except in two instances. The two instances were a
25 change in particle size crystalline form and the other

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1 one was when you go outside a certain range of
2 excipients. So I could argue right now that if I
3 wanted to conform to SUPAC-SS for a generic, I could
4 control the range of excipients and not do anything
5 else, and that would be consistent with SUPAC-SS. So
6 all our industries and the public at large have agreed
7 with that boundary.

8 So I think the question we're struggling
9 with is how do we control the excipients, what test do
10 we do? Would we be happy if I showed a comparative
11 clinical trial that was the same, recognizing its
12 insensitivity, and allow any change in excipients or
13 would we be happier, say, with a
14 dermatopharmacokinetic study and some control on
15 excipients? Would we be happier with an in vitro
16 release and a lot of control on excipient ranges,
17 which is what SUPAC-SS says?

18 Now, I can't pretend to have answers to
19 these questions now, but I think there will be
20 answers. I think the agency is obligated to come
21 forth with an answer. I'm very interested in what the
22 committee individually and collectively has to say to
23 us now about this. But one thing I can promise the
24 committee is I will look very carefully at all the
25 data sets we have because I think some of these data

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1 sets have clues to how we should make a regulatory
2 judgment, and I hope as we respond to the public
3 comments to this draft guidance as well as the
4 information presented here today we will come forth
5 with a document that will deal with each issue and
6 each question and respond to it.

7 I think the committee knows that sometimes
8 in the heat of battle here you don't get a full
9 thoughtful consideration of every bit of information,
10 and I will try to assure everybody that we will come
11 back to you all with that kind of document. Each
12 issue, the data associated with it, and our response
13 to it.

14 Okay. Thanks very much, Mr. Chairman.

15 DOCTOR TAYLOR: Thank you.

16 I'd like to open the committee discussion
17 up to the overall issues of the day. I want to start
18 by thanking the agency for providing a really
19 excellent overview, both pro and con, of the science
20 and issues that are important in this draft guidance.
21 From my view, I think there are a number of unsolved
22 dilemmas. I think they are all soluble and, on the
23 other hand, I think that there are some good things
24 that have been shown in the current draft guidance
25 that are worthy of further tweaking.

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1 So with that, I'd like to open it up for
2 the other members of the committee to make their
3 comments. Who wants to start? Gayle, you're drafted.

4 DOCTOR BRAZEAU: After reflecting upon
5 everything I've heard and the evidence, I would concur
6 with Doctor Taylor that I think that this is a very
7 good step in the right direction. I'm not sure
8 everything is where we want it to be at this stage,
9 but I think the FDA should be commended for its
10 activities along this way. I inherently believe this
11 is going to be an extremely valuable technique to
12 doing bioequivalence issues.

13 I think we have to address a few of the
14 critical issues. I'm not sure about vaginal. I mean
15 I'm not sure I'm convinced about that area yet, but I
16 think for topicals, I think it's got potential uses,
17 and I would recommend, I think, to go forward and try
18 to solve some of the problems we saw that were
19 discussed today. I think some good studies which show
20 the correlation between a clinical trial and this will
21 help to strengthen the data. I think we saw some
22 strong data with some other in vitro methods this
23 afternoon. I think the studies that actually will be
24 well designed will help to further strengthen this
25 method.

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1 I also think with use of this method that
2 the coefficient of variation, and as people employ it,
3 will also go down with time.

4 One more thing. And I think what makes
5 this method valuable is that it goes again back to the
6 idea of public safety and it puts the responsibility
7 on the industry to try to match the generic to try to
8 match the innovator product and to me, that seems
9 that's an ideal world.

10 DOCTOR TAYLOR: I would like to hear
11 something from the dermatology community. They're
12 uncharacteristically quiet this time. They must have
13 something to say.

14 DOCTOR DIGIOVANNA: I was not here at the
15 earlier discussions, the earlier meetings of this
16 topic, and when I first received all this information
17 a short while ago and was reading through it, I was
18 really quite enthused. My first impression was that
19 this stuff was great. It was really love at first
20 sight.

21 But for a dermatologist, eventually you
22 start seeing the moles and the warts, and the first
23 mole that I saw, I'm sorry to say Jonathan also saw
24 and it actually was on a plane, was that this really
25 wasn't dermatopharmacokinetics. What I called it was

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1 pharmacologic stratum corneo kinetics and it really
2 didn't relate to the skin but to the stratum corneum.
3 And as I began to see what some of the difficulties
4 were, I think I now see why there's such a discordance
5 between individuals that have different experiences
6 with their familiarity with this approach and
7 willingness to utilize and accept this approach and
8 why others of us don't quite feel that way.

9 In some circumstances, the skin may
10 actually be a sensitive organ in that it's more
11 sensitive than systemic administration of certain
12 drugs. By that, I mean that if you give an antibiotic
13 to someone with strep throat and you decide you're
14 going to give 250 or 500 milligrams of penicillin a
15 day, you probably have a large area where you could
16 err and still have a successful clinical outcome. If
17 I treat someone with prednisone pills and they get
18 gastric atrophy, I don't see it until they develop an
19 ulcer. However, if I treat them with too potent a
20 topical steroid or that I'm not aware is too potent
21 and they use that Temovate under the arms or in the
22 groin and develop stria or atrophy, then I may be more
23 aware of that in some circumstances.

24 So it may be that we're able to tolerate
25 less of a gradation in the difference between efficacy

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1 and toxicity. As I fully understand the inadequacies
2 of clinical trials, we're all very comfortable with
3 them because we've done them for a long time. What I
4 would like to see at the end of this, and I don't know
5 if I had added it all or can add it all to how it can
6 be accomplished, is rather a selfish motive and that
7 is that I have a conflict of interest. I write
8 prescriptions, and I want something from the FDA for
9 me and for my patients, and what I want is to know
10 that when I write that prescription they're going to
11 get what I think is going to make them better. But I
12 live in a real world, and I know that when I write
13 that prescription for Temovate they're probably not
14 going to get Temovate. They're going to get something
15 else, and how long is it going to be before I figure
16 out that they're not getting better because they're
17 not getting a product that's working as well?

18 I frequently hear dermatologists say, I
19 don't use the generic of that, it doesn't work, and
20 have very little data but anecdotal data and data that
21 arises because they speak about it amongst themselves.
22 My concern here is that if we substitute a procedure,
23 an assay, that sounds like it might work but from a
24 lot of the scientific logic doesn't seem to really get
25 to the bottom line but is much less expensive and much

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1 easier to effect, then that is going to be very
2 difficult to put back in the box. And when there are
3 products that are less effective, how does one figure
4 that out? I mean the FDA doesn't usually go around
5 and require studies again, and do we have to wait
6 until all the 7,000 dermatologists try an inadequate
7 product and then decide on their own it doesn't work?

8 So I think there's a great deal of concern
9 about this. I think that it is a public safety issue.
10 I think it's a public health issue. I think it's a
11 consumer issue, and I think that I really love the
12 dermatopharmacokinetics, but I really would like to
13 see them be more refined and validated.

14 DOCTOR TAYLOR: Any other committee
15 comments?

16 DOCTOR MCGUIRE: Roger, in case you
17 noticed I was missing, I was watching your
18 presentation from the red carpet club outside. I
19 didn't miss it.

20 The thing that concerns me is that, as an
21 investigator and as a clinician, I need something
22 better than clinical trials. They're very expensive.
23 They're imprecise and, as many people have pointed out
24 today, trying to get a dose response out of a clinical
25 trial is a very expensive game and may be a fool's

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1 game. It may not be achievable. I don't think that
2 by itself makes the DPK more attractive. It makes me
3 more needy, but it doesn't necessarily improve the
4 quality of the DPK.

5 I tend to go along with my speech writers
6 who tell me that this is an attractive artifact. I
7 think it's a very attractive artifact and I think it
8 may be a very useful artifact, but I think to confuse
9 the issue of uptake and pseudosteady state and
10 elimination from stratum corneum with something that
11 is happening in either intact or diseased skin, I
12 think that's yet to be shown, and I don't think that
13 you showed it today with the data.

14 The very best data I saw today were Doctor
15 Shrivastava's and that was, in fact, idealized data.
16 Those were not real observations. I wish they had
17 been data derived from laboratory investigation.

18 I don't know what to make of the
19 chlotrimazole. There are two observations. They're
20 both true. They're both interesting, and I'm not sure
21 they're related. I'm not sure which I would have
22 interpreted if the results had been the converse, but
23 I just don't see that that relates to the stratum
24 corneum uptake phenomenon. Don't mistake me. I don't
25 think the stratum corneum uptake and elimination

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1 models should be discarded. I think it's very
2 interesting and when I first learned of it, I thought
3 it held great promise and I think it may still hold
4 great promise, but I don't think it's approved
5 concept.

6 DOCTOR TAYLOR: Doctor Mindel.

7 DOCTOR MINDEL: There's a pressure for
8 approval of generic drugs that is very understandable
9 and I think that this really hasn't been a -- there's
10 a stacked deck. I think there's a stacked deck
11 because of that. There's a stacked deck in the
12 presentations that were made today. The number and
13 the time allotted.

14 In March the dermatology/ophthalmology
15 group heard some of the same speakers presenting the
16 same data. I don't think in six months a great deal
17 of new data has come up. I think that the act has
18 been refined better, but I have a bias that is
19 somewhat emotional, I must admit, not scientific
20 because of my perception that the agency has a
21 commitment and it's going to force a certain approach
22 no matter what the scientific merits are.

23 My final comment is that for approving a
24 drug, you have to have two masked randomized study,
25 one multi-institutional study. You have very rigid

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1 criteria or at least expensive criteria for approving
2 the drug, and we're contemplating accepting a
3 methodology of evaluating drugs that doesn't really
4 meet the same level of high quality that we expect of
5 our drug studies themselves, and I'm disturbed by
6 that.

7 I would like, as a minimum requirement, a
8 minimum requirement, that a technique be validated by
9 two peer reviewed published articles showing that that
10 class of drug has met the standards for the test
11 showing that it is a valid test method.

12 DOCTOR TAYLOR: Doctor Branch.

13 DOCTOR BRANCH: I am not a dermatologist,
14 but I do like the scientific method. It seems to me
15 that this is an area of controversy and you're using
16 an intermediate marker to try and identify an end
17 point. It also seems to me that as data is
18 accumulating -- and they did this a year ago and it
19 does seem to me there has been some progress in the
20 last year -- that there isn't a rapid of data. If
21 you're designing a trial of a new end point measure,
22 which is what this is, you should set out some a
23 priori criteria. It's not just a matter of we would
24 like to collect data and be able to do some
25 correlative comparisons. You'd like to actually place

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1 some emphasis on data.

2 From what I've heard today, the most
3 important piece of negative data that could be
4 accumulated to disprove this hypothesis is false
5 positives. Drugs that actually pass the criteria of
6 this new technique and yet the drugs are not
7 therapeutically equivalent. I would urge the agency
8 to set up criteria so that if those instances are
9 found that considerably more emphasis is given to
10 their interpretation because the reality, as I see it,
11 is you're faced with what information base do you
12 permit a generic, a new generic product to be approved
13 on and the information you're trying to find out is if
14 you do that using this one technique and simplify the
15 whole of the process of what is required for an ANDA,
16 then that is the single most important piece of
17 information for ensuring safety.

18 The false negatives are a separate issue
19 and industry has an opportunity to go the more
20 expensive, more comprehensive route of doing a
21 clinical test to say we don't believe that this test
22 is relevant. We're going to show you in a full scale
23 clinical trial that our product is capable of doing
24 what we say it's doing, and that's fine. So from a
25 safety perspective, I think it's a question of asking

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1 you to identify priorities.

2 And that sort of brings up the second
3 issue which I heard very little discussion about today
4 which is what are the numerical criteria that you're
5 going to use? You've now got a new technique that
6 actually does offer fairly precise numerical measures.
7 I'm not sure that it's a valid translation to go from
8 bioequivalency criteria that have been used for oral
9 products where your sampling site really is a well
10 distributed site to the stratum corneum, and I'm not
11 sure the 75/125 criteria or whatever the goal posts
12 are -- I think you should be prepared to look at the
13 data critically and be at least prepared to modify
14 your criteria on that based on comparison of this end
15 point measure to other end point measures.

16 DOCTOR TAYLOR: Doctor Lamborn.

17 DOCTOR LAMBORN: I guess I'd just like to
18 reiterate the concern which I've heard some of the
19 others state as part of this conclusion that we really
20 do have a need for something other than the clinical
21 trials because at the moment we do have a criteria for
22 approval of generics. That approval is at a level
23 which allows substantial differences to exist and
24 still have apparent equivalence so that if we could
25 come up with methodology, and perhaps it will be

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1 different for some of the different indications, which
2 will allow us to more precisely do that, I think that
3 it's very important that we move ahead with that
4 concept because we do have to recognize that in order
5 to allow the clinical trials to be of any kind of
6 reasonable size, the percent difference in efficacy
7 that can be there is substantial.

8 I think that's what we heard from those
9 who actually treat the patient so that at the moment
10 the way we are approving generics leaves something to
11 be desired. So I think that there is a real reason to
12 try to move forward from a public health standpoint,
13 not saying whether you're for industry, either generic
14 or the innovator, but just from a public health
15 standpoint. And so I would really express enthusiasm
16 for the effort that the agency -- whether this is
17 exactly the right one, whether it's ready yet or not,
18 I think it is an important effort to move forward
19 with.

20 DOCTOR TAYLOR: Thank you.

21 Doctor Lavin.

22 DOCTOR LAVIN: Today I think we've heard
23 a lot of things about a very obviously complex series
24 of problems. From my perception, I've seen main
25 effects as well as components of variation that are

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1 going to need to be well understood and shared openly
2 as these studies are done. I also see in this group
3 here at least 10 different sets of people that have
4 done studies of DPK, so obviously it's something
5 that's going to be studied.

6 I think what has to be done here is like
7 the new bakery, not serve the bread before it's ready
8 and fully tested. I think one of the things that you
9 should do is to set up a formal registry so you could
10 share your experiences of these people that are doing
11 the DPK studies. Share your protocols, share your
12 technicians, share your know how, let people know how
13 you do things, standardize, build toward true proper
14 validation. Look at this as if you're manufacturing
15 a car. You have a process here. There's obviously
16 something here. You don't throw out the baby with the
17 bath water.

18 And so I think build a registry, share
19 your information, come back here in six months or a
20 year with data. I heard some really excellent data
21 from some of the speakers this afternoon that, to me,
22 make one think that there are still a lot of bugs that
23 have to be worked out. So let this be a call to do
24 something perspectively and all together.

25 DOCTOR TAYLOR: Are there any additional

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1 comments from the committee or from Doctor Williams?
2 It's your last chance. Roger, would you like to make
3 some parting comments?

4 DOCTOR WILLIAMS: I do want to thank the
5 committee. I would like to say we will be committed
6 to this further evaluation and we'll figure out some
7 way to communicate the results of that evaluation to
8 the committee. I'll be honest. I'm feeling a little
9 discouraged that you would accuse us of kind of
10 stacking the deck because I think we came here with a
11 very honest commitment to say clinical trials would be
12 an easy solution. We could close up shop and save
13 ourselves a lot of time by just requiring generics to
14 do that.

15 But I think there's a real honest,
16 heartfelt commitment that those are inadequate to the
17 purpose, and I don't feel comfortable just allowing a
18 generic into the marketplace based on a comparative
19 clinical trial. I think it needs something beyond
20 that, and we've seen a lot of data today that speaks
21 to that point.

22 I do appreciate, Bob, your point about
23 what I call the canary in the mine concept. You are
24 really looking for failures where the canary doesn't
25 tell you what you're interested in, and we will

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1 certainly seek those out. But I do appreciate the
2 committee's comments, and we will take them very
3 seriously.

4 DOCTOR TAYLOR: Thank you. If there are
5 no other comments, then I'll move the meeting
6 adjourned and thank you very much for your attendance
7 and your comments.

8 (Whereupon, the meeting ended at 4:10
9 p.m.)

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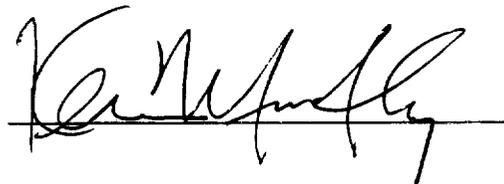
This is to certify that the foregoing transcript in the matter of: Advisory Committee for Pharmaceutical Science and Dermatologic and Ophthalmic Drugs Advisory Committee

Before: DHHS
 Food and Drug Evaluation and Research

Date: October 23, 1998

Place: Rockville, MD

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



Robert W. Smith