

FOOD AND DRUG ADMINISTRATION

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

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8:30 a.m.

Thursday, November 29, 2001

Conference Room  
5630 Fishers Lane  
Food and Drug Administration  
Rockville, Maryland 20857

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## C O N T E N T S

AGENDA ITEM	PAGE
CONFLICT OF INTEREST STATEMENT by Dr. Nancy Chamberlin	11
DERMATOPHARMACOKINETICS Introduction to the Issues by Dr. Dale Conner	15
Data Presentations by Dr. Lynn Pershing	31
by Dr. Thomas Franz	47
by Dr. Mamata Gokhale	61
Introduction to Discussion Questions by Dr. Dale Conner	71
Committee Discussion	75
OPEN PUBLIC HEARING PRESENTATIONS by Dr. K.L. Spear	109
by Dr. Chris Hendy	113
by Dr. M. Mohan Sondhi	120
by Dr. Laszlo Endrenyi	123
by Mr. Charles Bon	128
by Dr. Mario Tanguay	132
by Dr. Kamal K. Midha	135

## C O N T E N T S (Continued)

AGENDA ITEM	PAGE
INDIVIDUAL BIOEQUIVALENCE	
Introduction to the Topic and Discussion Topics by Dr. Lawrence Lesko	143
Background & Concepts of Individual Bioequivalence by Dr. Mei-Ling Chen	152
Results from Replicate Design Studies in NDAs and FDA Database by Dr. Mei-Ling Chen	162
Results from Replicate Design Studies in ANDAs by Dr. Rabi Patnaik	173
Individual Bioequivalence: Have the Opinions of the Scientific Community Changed? by Dr. Leslie Benet	185
FDA Research Plan Dr. Stella Machado	198
Discussion by Committee Members and Invited Guests	203

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

(8:30 a.m.)

DR. LEE: Good morning. I don't think you can see me, but I am Vincent Lee. I am acting chair of this committee. I'm also professor and chair at the University of Southern California.

I'd like to go around the table and have the cast introduce themselves, and please identify according to whether you are a guest or committee member or some other capacity. Bill?

DR. BARR: Bill Barr, Virginia Commonwealth University.

DR. LEE: Are you here as a guest?

DR. BARR: I'm here I guess as a special consultant.

DR. LAMBORN: Kathleen Lamborn, University of California, San Francisco. I guess I'm here as a consultant, too.

DR. MOYE: Lem Moye, University of Texas, Houston. I think I'm a prospective committee member.

DR. BYRN: Steve Byrn, Purdue. I'm an "ex-spective" -- I don't know what word we would use -- a retiring member of the committee and a special consultant.

DR. LEE: Actually Steve was the past chair, and he will step in in case I falter.

1 DR. JUSKO: William Jusko from the University  
2 at Buffalo. I'm a regular committee member.

3 DR. DOULL: John Doull, University of Kansas  
4 medical center, regular member.

5 DR. BLOOM: Joseph Bloom, University of Puerto  
6 Rico, regular member.

7 DR. ANDERSON: Gloria Anderson, Morris Brown  
8 College, Atlanta, member.

9 DR. BOEHLERT: Judy Boehlert, private  
10 consultant to the industry, member.

11 DR. KIBBE: Art Kibbe, Wilkes University school  
12 of Pharmacy, member.

13 DR. CHAMBERLIN: Nancy Chamberlin, Executive  
14 Secretary.

15 DR. VENITZ: Jurgen Venitz, Virginia  
16 Commonwealth University, regular member.

17 DR. MEYER: Marvin Meyer, emeritus professor at  
18 University of Tennessee, member.

19 DR. KING: Lloyd King, consultant, Vanderbilt  
20 dermatology.

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

23 DR. WINKLE: Helen Winkle, Office of  
24 Pharmaceutical Science, CDER.

25 DR. HUSSAIN: Ajaz Hussain, Office of

1 | Pharmaceutical Science, CDER.

2 | DR. CONNER: Dale Conner, Director of Division  
3 | of Bioequivalence, OGD, FDA. Speaker.

4 | DR. SHEK: Efraim Shek, Abbott Laboratories,  
5 | industrial representative.

6 | DR. SHARGEL: Leon Shargel, Eon Laboratories,  
7 | industrial participant.

8 | DR. FRANZ: Tom Franz, dermatologist. Here as  
9 | a speaker.

10 | DR. PERSHING: Lynn Pershing, University of  
11 | Utah, speaker.

12 | DR. LEE: Thank you. I call on Nancy  
13 | Chamberlin to read the conflict of interest.

14 | DR. CHAMBERLIN: We will have a few members  
15 | joining us by phone today. Patrick DeLuca, Nair Rodriguez-  
16 | Hornedo, Mary Berg, and this afternoon we'll have Les  
17 | Benet.

18 | The following announcement addresses the issue  
19 | of conflict of interest with respect to this meeting and is  
20 | made a part of the record to preclude even the appearance  
21 | of such at this meeting.

22 | Since the issues to be discussed at this  
23 | meeting will not have a unique impact on any particular  
24 | product or firm, but rather may have widespread  
25 | implications with respect to an entire class of products,

1 in accordance with 18 U.S.C., section 208(b)(3), all  
2 committee participants with current interests in  
3 pharmaceutical firms have been granted a general matters  
4 waiver, which permits them to participate in today's  
5 discussion.

6 A copy of these waiver statements may be  
7 obtained by submitting a written request to the agency's  
8 Freedom of Information Office, room 12A-30 of the Parklawn  
9 Building.

10 With respect to FDA's invited guests, there are  
11 reported interests which we believe should be made public  
12 to allow the participants to objectively evaluate their  
13 comments. Thomas Franz, M.D., is a stockholder in DermTech  
14 International, a contract research organization that  
15 conducts research in clinical trials for companies  
16 developing drugs and products for use on the skin. Dr.  
17 Franz also receives consulting fees from Connetics  
18 Corporation.

19 Laszlo Endrenyi, Ph.D., has consulted with  
20 several pharmaceutical companies, both brand name and  
21 generic, on an ad hoc basis.

22 Lynn Pershing, Ph.D., has consulted on  
23 dermatopharmacokinetic issues for Aesgen, Clay-Park Labs,  
24 AlphaPharma, Biomedical Development Corporation, Taro  
25 Pharmaceuticals, and DPT Labs. She also has consulted with



1 several pharmaceutical companies, for example Dermik Labs,  
2 GlaxoSmithKline, Roche, and Baker Norton Pharmaceutical, on  
3 other matters.

4 Leslie C. Benet, Ph.D., and his spouse are  
5 stockholders in Alteon, Pfizer, Watson Pharmaceuticals,  
6 Allergan, American Home Products, Elan Corporation,  
7 Schering-Plough, Amgen, Bristol-Myers Squibb, Cell Genesys,  
8 Genzyme Transgenics, Genzyme Biosurgery, GlaxoSmithKline,  
9 Eli Lilly, Merck, Pharmacia Corporation, Procter & Gamble,  
10 Quintiles, Sangstat Medical, Valentis Inc., and Walgreens.

11 Dr. Benet is also involved in contracts and  
12 grants from R.W. Johnson, CV Therapeutics, Amgen  
13 Pharmaceuticals, Daiichi Pharmaceuticals, and Fujisawa  
14 Health Care. He also serves as consultant for Avmax,  
15 Incorporated, Roche, Biosciences, Amgen, Wyeth-Ayerst,  
16 Fujisawa, AstraZeneca, Searle, R.W. Johnson, and IMPAX.

17 In addition, Dr. Benet has received  
18 compensation from Finnegan, Henderson, Farabow, Garrett &  
19 Dunner, L.L.P., for services as an expert witness on behalf  
20 of American Home Products, Wyeth-Ayerst, ESI-Lederle,  
21 Geneva, Novartis, Teva, Zeneth Goldline, Mylan, and IMPAX  
22 Laboratories.

23 Dr. Benet has also lectured for Bayer, Glaxo,  
24 Genetech, American Society of Transplantation, Merck,  
25 several universities, and the FDA.

1                   Finally, Dr. Benet is the founder and chairman  
2                   of the board of AvMax, Inc., president of Avalon, Inc., and  
3                   is co-founder of Oxon. He also serves as a member of the  
4                   corporate boards for Alteon, IMPAX Labs, InforMedix,  
5                   Institute for One World Health, Josman Labs, Molecular  
6                   Delivery Corp., Main Therapeutics, Inc., Roche Biosciences,  
7                   UMD Inc., Silico Insights, Agouron, Allergan, Alza, Amgen,  
8                   Ares-Serono International, Axys Pharmaceuticals, Biochem  
9                   Pharma, Boehringer-Ingelheim, CV Therapeutics, DuPont  
10                  Pharmaceuticals, Fujisawa Health Care, Genentech, Basis  
11                  Therapeutic Corp., Pharmacia, Procter & Gamble, R.W.  
12                  Johnson, McNeil, Ortho, and Wyeth-Ayerst.

13                         With the exception of One World Health and  
14                         Roche Biosciences, Dr. Benet has vested and unvested stock  
15                         options in these firms.

16                         We would also like to note for the record that  
17                         Leon Shargel, Ph.D., Eon Labs; Efraim Shek, Ph.D., Abbott  
18                         Laboratories; Nevine Zariffa, Ph.D., GlaxoSmithKline; and  
19                         Avi Yacobi, Ph.D., Taro Pharmaceuticals, are participating  
20                         in this meeting as industry representatives, acting on  
21                         behalf of regulated industry. As such they have not been  
22                         screened for any conflict of interest.

23                         In the event that the discussions involve any  
24                         other products or firms not already on the agenda for which  
25                         FDA participants have a financial interest, the

1 participants are aware of the need to exclude themselves  
2 from such involvement and their exclusion will be noted for  
3 the record.

4 With respect to all of the participants, we ask  
5 in the interest of fairness that they address any current  
6 or previous financial involvements with any firm whose  
7 product they may wish to comment upon.

8 DR. LEE: Thank you very much, Nancy.

9 We're going to have a busy day today. We have  
10 two important issues. This morning it will be on  
11 dermatopharmacokinetics. This afternoon it is going to be  
12 on individual bioequivalence. We have before lunch an hour  
13 for open hearing and I understand that we have six  
14 presenters.

15 Before I turn the floor over to Dale Conner,  
16 let me alert all the speakers to stay on time because I do  
17 have an electronic gavel, which I did not use yesterday,  
18 and I hope that I do not need to use it today because the  
19 committee does need the full 30 minutes to discuss three  
20 very important issues. Thank you.

21 Dale?

22 DR. CONNER: One question. Does that gavel  
23 give shocks to the speakers?

24 DR. LEE: Do you want to find out?

25 (Laughter.)

1 DR. CONNER: Sure. I'm willing to be a guinea  
2 pig.

3 My task today is to lead off this very exciting  
4 discussion, hopefully not too exciting, and to introduce  
5 you to the topic for those of you who are new committee  
6 members or perhaps not quite so familiar with the very long  
7 and illustrious and kind of controversial history of this  
8 particular technique, or proposed technique.

9 I'm going to start off with a little discussion  
10 of bioequivalence in general because it's been my  
11 observation certainly that in some of the past discussions,  
12 both committee members, the observers, as well as  
13 unfortunately some of the FDA people didn't really seem to  
14 quite understand the object of what we're trying to  
15 accomplish with bioequivalence. We at the agency use  
16 bioequivalence, obviously, to approve generic drug forms of  
17 innovator or reference products, but also the innovators  
18 use these same techniques to test or to gain approval for  
19 changes in their existing formulations. When you explain  
20 it, it doesn't seem so very complicated, but it can be very  
21 confusing.

22 I'll start out with a little bioequivalence  
23 101, or at least my version of it, and then I'm going to go  
24 into very brief, and hopefully simple, explanations of this  
25 technique, which will then be expanded upon by the later

1 | speakers, and perhaps show you somewhat of a history of  
2 | what has gone on in this topic. It's quite a long and  
3 | checkered history, I guess you could say.

4 |         To start off, I'll give a personal definition  
5 | of bioequivalence. You can think of it as we practice it,  
6 | certainly in generic drugs, as pharmaceutical equivalents  
7 | whose rate and extent of absorption are not statistically  
8 | different when administered to patients or subjects at the  
9 | same molar dose under similar experimental or clinical  
10 | conditions. It's important to remember that when we're  
11 | talking about an ANDA or perhaps a change in an existing  
12 | product for an NDA, that we're talking about pharmaceutical  
13 | equivalents. That's the first point of confusion that many  
14 | people in the outside world have.

15 |         When we talk about pharmaceutical equivalents,  
16 | we talk about the exact same drug substance. So, for  
17 | comparing two products in an equivalence, say for an ANDA,  
18 | the starting understanding is that they have the exact same  
19 | drug substance. But there are other things that need to be  
20 | the same to be called pharmaceutically equivalent. They're  
21 | the same dosage form. So, if we're looking at tablets,  
22 | we're not comparing that to a capsule or a solution. If  
23 | we're looking at an ointment for topical administration,  
24 | we're not looking at a cream or a topical solution. So,  
25 | the dosage form is the same, and the intended use and

1 | generally the labeling is the same as well.

2 |           That's the first thing that people understand.  
3 | We're not talking about therapeutic substitution, where one  
4 | substitutes or studies a totally different drug substance  
5 | or a totally different type of product. It's very, very  
6 | similar products containing the exact same drug substance.  
7 | That's point number one.

8 |           The purpose of doing this at the end is to  
9 | establish therapeutic equivalence of these products. What  
10 | a clinician wants to know is that if my patient is switched  
11 | from an existing product to the other product that I'm  
12 | going to see the same therapeutic effect, and therapeutic  
13 | effect in this case encompasses both the desirable and  
14 | undesirable characteristics. The therapeutic or efficacy  
15 | part, as well as the toxicity profile, shouldn't be  
16 | different either.

17 |           It's the FDA's position that generics or the  
18 | institution of a new dosage form of an existing NDA that's  
19 | approved can be substituted for the other product or the  
20 | reference product without any other adjustment in dose or  
21 | other additional therapeutic monitoring that wouldn't  
22 | ordinarily be done in the normal course of managing that  
23 | patient.

24 |           I put a last statement, which is very true for  
25 | oral products, is that the most efficient method of

1 | assuring therapeutic equivalence is to assure that the  
2 | formulations themselves perform in an equivalent manner.  
3 | We have a number of ways and proposed ways to try and do  
4 | that.

5 |               First off, this is my simple scheme, and since  
6 | in past discussions in the committee of DPK we often tried  
7 | to draw correlations or draw understanding from what's  
8 | happening or what's alleged to be happening with the DPK  
9 | from the oral route, and there have been statements that  
10 | it's very similar, and there have been statements that it's  
11 | not very similar at all. I thought I'd start out by taking  
12 | a simple case and discussing bioequivalence in the oral  
13 | route. My next slide or two will have a very similar  
14 | depiction of what may happen when you administer topical  
15 | products for the skin, but let's take the simple case  
16 | first.

17 |               It's important to realize that when you give an  
18 | oral product, or perhaps any pharmaceutical product, it  
19 | comes in what you might call a package or dosage form: a  
20 | tablet, capsule, cream or ointment. And a critical event  
21 | to be able to get therapeutic results from this product is  
22 | the drug substance or active drug component has to leave  
23 | the formulation and go into the patient at some point.  
24 | That's really a very, very critical step. In  
25 | bioequivalence that's really what we're trying to measure,

1 the characteristics of this dosage form that allows the  
2 drug to leave the dosage form and be available to the  
3 patient.

4           When you really think about it and you look at  
5 all the steps here, in an oral drug the drug is in solid  
6 dosage form most of the time, it goes into solution,  
7 usually in the GI tract, and it goes into solution only  
8 when it's released in solid form from the dosage form.  
9 Eventually goes through the gut wall into the blood,  
10 eventually carried to the site of activity and leads to a  
11 therapeutic effect, either desirable or undesirable.

12           There are obviously many more boxes that could  
13 be added to this, metabolism, routes and so forth. This is  
14 a very ultra-simplified view just to illustrate the course  
15 of events.

16           Fortunately for oral products, we have a more  
17 or less nice chain of events, of which we have the blood,  
18 which we can easily measure blood concentrations. We can  
19 extrapolate back and tell how this particular dosage form  
20 is performing, and by performance I mean how is it  
21 releasing the drug to the patient.

22           Also clinicians are kind of happy with this  
23 because the blood is also related to the drug appearing at  
24 the site of activity, so you can also get some information  
25 from the blood about the therapeutic effects as well, so if



1 | you'd like to look at that directly.

2 |           In this particular systemic availability of an  
3 | oral product, we have a very nice part where we can sample,  
4 | we can do essentially a single test, and we can really  
5 | answer most if not all of our questions about how the  
6 | comparable dosage units or products are performing in  
7 | relation to each other.

8 |           The blood is very nice because most of the time  
9 | it's linear in response and it's not very sensitive to the  
10 | dose you study it at for most of the products; whereas  
11 | therapeutic effects, if you assess them for this purpose,  
12 | say, by doing a comparable clinical trial, are not quite so  
13 | linear, and I'll discuss that a little later. So, that's  
14 | the simple oral case.

15 |           Now this, as you'll see, is very, very  
16 | simplified, and I have two versions of this. The first  
17 | version, for those of you who might be in favor of DPK,  
18 | this is the version you would want. I have another one  
19 | which kind of expands on this for those of you who are not  
20 | in favor of DPK. So, I don't want to act like I'm just  
21 | presenting a one-sided view of this.

22 |           My ultra-simplified scheme here has changed  
23 | somewhat. I still start out with a dosage form, of which  
24 | drug has to be released out of the dosage form and made  
25 | available to the patient or the subject in our studies.

1 Then we have that drug being released from the dosage form  
2 going into tissue, and I've got it lumped all the tissue of  
3 the skin together in one place. Again, as anyone will  
4 know, that's really kind of a leap in concept. That's  
5 about where we sample DPK. Obviously, we're sampling the  
6 stratum corneum, which isn't all the tissue or all the  
7 routes that the drug uses to get into the skin.

8 After achieving this step, it's distributed to  
9 its site of activity, which is not too far removed from  
10 where the drug is released to the tissue. It results in  
11 therapeutic effects, and at some later time possibly drug  
12 appears in the blood.

13 I don't want to really say this is an after-  
14 thought, but it happens after the part that most of us are  
15 interested in, which is site of activity therapeutic  
16 effects. Eventually that can lead in some products to some  
17 systemic effects as well.

18 So, my order of things from my first slide is  
19 changed around a bit. You'll see that the very nice way of  
20 doing things, taking a simple test from the blood, is not  
21 exactly so straightforward. Some people have proposed that  
22 you can still use blood to kind of back-extrapolate here,  
23 but that's generally not a widely accepted view.

24 Most of the time what we do right now, which  
25 I'll go into a little bit more in subsequent slides, is

1 | assess this box right here. We look at application to the  
2 | skin and we look at, say, two pharmaceutically equivalent  
3 | products under similar conditions, and we see if they give  
4 | us the same therapeutic effects. That's basically how we  
5 | approve most of the topical drugs now.

6 |         The proposed method that you're looking at  
7 | today is something that samples here, very close to the  
8 | event we're interested in, but it samples one route, one  
9 | type of tissue that that drug is entering into.

10 |         Now, here's the variation on that if you don't  
11 | like DPK. What I've done here is perhaps one step more  
12 | realistic as far as my model goes. I've separated what I  
13 | called tissue in the previous slide into separate boxes.  
14 | We have up here drug in stratum corneum, we have drug  
15 | through follicles, which is brought up constantly in this  
16 | discussion, that this does not represent drug in follicles,  
17 | and drug through other methods, however many you want to  
18 | list, in sweat glands, and various other ways to bypass the  
19 | stratum corneum.

20 |         The first slide, the DPK lovers' slide, would  
21 | say that I'm measuring only the stratum corneum, but the  
22 | stratum corneum tells me enough about the other things that  
23 | I can make inferences about all of these together, and this  
24 | is really all I need to do. I guess people who don't  
25 | believe in DPK say no, these boxes aren't the same. By

1 sampling stratum corneum, it does not tell me anything  
2 useful about this route or other routes as well.

3 So, stratum corneum is really at best a partial  
4 picture, or if this is a major route to the site of  
5 activity, then it may not tell me much useful at all.  
6 That's basically one of the negative beliefs about DPK.  
7 You really have to believe that DPK and sampling the  
8 stratum corneum tells you a lot about the whole picture.  
9 Anyone who knows the skin knows that these may or may not  
10 be the same. Probably are not.

11 Again, the rest of my scheme is the same from  
12 the previous slide.

13 As I mentioned, what we do now is generally for  
14 these products, with a few exceptions, we do a  
15 bioequivalence study with clinical endpoints, so we take  
16 real patients with the particular disease state. We apply  
17 the products, often in a parallel type of study, and study  
18 the clinical responses between the two products that are  
19 being compared. Usually if it's an ANDA, it's the  
20 reference listed drug product in the Orange Book. Quite  
21 often, that's the brand name product approved under an NDA  
22 and the ANDA product.

23 The critiques of this, although we certainly  
24 have approved many products on this basis, is that that  
25 approach is somewhat extensive. It really often requires a

1 sizeable number of patients. The variability is quite high  
2 and there is some belief that this may be insensitive to  
3 differences in formulation performance. I'll tell you the  
4 theoretical basis of that statement.

5 BE studies, for certain of the products such as  
6 corticosteroids we have alternative methods that depend on  
7 pharmacodynamic effects. For instance, with  
8 glucocorticoids they cause a blanching or lightening of the  
9 skin on a temporary basis. You can relate the potency of  
10 the steroid in the release of the drug from the product  
11 into the skin by how much of this blanching response you  
12 get. Over many years that's been developed into a  
13 technique for looking at comparative release of drug from  
14 these products. So, for topical corticosteroids very often  
15 we can use this pharmacodynamic endpoint type of study, and  
16 there is a guidance out on that.

17 There is also some data on doing in vitro drug  
18 release, although that's seldom if ever used as the primary  
19 study to get a topical product approved. Generally it's  
20 some type of in vivo study and usually in the top category.

21 Just a brief comment, and this can be  
22 generalized, I think, to any kind of clinical response type  
23 of study. As I said, blood levels usually are very nice  
24 and linear. If you study them at a slightly higher or  
25 slightly lower dose, it doesn't change the response you get

1 within variability.

2           If you remember from your pharmacology  
3 training, the responses, both clinical and pharmacodynamic  
4 responses generally fit into some kind of sigmoidal  
5 relationship, and it's sigmoidal because I'm displaying it  
6 on a log dose scale. That's important to point out. The  
7 important parts of this response versus dose are that we  
8 have a part where we give a dose that's so low that we're  
9 not getting any discernible response, and then at some  
10 point as we're increasing the dose -- and I've drawn it  
11 very steeply here, it can be somewhat flat -- it increases  
12 with small increases in dose until it finally gets to a  
13 maximum response. If you go beyond that and give more  
14 dose, you don't really get much more response.

15           Eventually in clinical practice, if you keep  
16 going out in many doses, you'll get other responses like  
17 undesirable toxic responses, but this particular continuum,  
18 if you're looking at receptors, you may have occupied all  
19 the receptors with drug and you can't occupy or stimulate  
20 more than 100 percent of the receptors, so you might get a  
21 plateau at the top.

22           When you look at comparing two products, two  
23 very, very similar products which are designed to be nearly  
24 identical in their performance, you might see from this  
25 graph that it's very important that you study it at the

1 right dosage level. If you study up here, where you're at  
2 the top of the dosage response curve, you can have a very  
3 large difference between the products at the relative dose  
4 that they deliver in relation to each other, and simply get  
5 little if any difference in the response you're measuring,  
6 whatever that clinical response is.

7 If you studied it in this dosage range, where  
8 you're on this steep part, you get actually quite good  
9 sensitivity, or potentially good sensitivity of the  
10 difference in those two products. So, that's a really  
11 critical aspect of looking at when you're doing clinical  
12 equivalence type of studies because you could end up doing  
13 a very large, every expensive, somewhat complex study and  
14 come out with virtually no sensitivity to tell the  
15 difference between products. So, something to consider  
16 when you do a type of clinical endpoint studies.

17 Just briefly -- and this will be expanded upon  
18 by the other speakers -- the theory, as I said, is that  
19 DPK, or dermatopharmacokinetics, is a pharmacokinetic  
20 approach applied to drug concentrations in stratum corneum.  
21 So, you're literally sampling the stratum corneum after  
22 drug administration and looking at the appearance and  
23 perhaps disappearance of drug from that particular tissue.

24 The method, very briefly, is that tape  
25 stripping is used. If you apply tape to the skin, it

1 strips off a layer of the stratum corneum, and by doing  
2 that successively you can kind of drill down or sample down  
3 into the stratum corneum until there's no more left, simply  
4 by taking successive tape strips, and then the  
5 investigators simply take those strips and assay them for  
6 drug. So, the uptake and elimination from the stratum  
7 corneum are determined.

8 And it's alleged the differences in formulation  
9 are determined -- the advantage is you can do this at the  
10 same time in the same individual. So, you can apply both  
11 products to the same individual at the same time, which is  
12 an advantage over even our oral products, where even though  
13 you cross the treatments over and you use the same subject,  
14 they still have to be studied at different times. So, it's  
15 kind of one of the nice features of doing some of these  
16 dermatology studies.

17 A brief history, and I won't dwell on this, but  
18 I have a couple of slides on the very long history of this  
19 particular topic. As you'll see, even I was amazed that we  
20 started back in the late 1980s, '89, and I'll just flip  
21 through these. I don't want to dwell on all of the facts.  
22 We started off with some workshops back in '89. This was a  
23 constantly discussed topic. We had a couple of advisory  
24 committees. That was the Generics Drug Advisory Committee,  
25 which I believe is what this committee used to be called.



1 Some international meetings, some more workshops, more  
2 international meetings, some trade association meetings,  
3 and more advisory committee meetings of course, and some  
4 expert panel meetings. Until finally we get to an AAPS  
5 symposium and the last joint advisory committee meeting,  
6 and that was a meeting that combined this committee with  
7 the Dermatology Advisory Committee in a joint meeting. For  
8 those of you who were here, you remember that was kind of  
9 an exciting meeting as well.

10 So, finally we get to the issues that we  
11 considered or thought about today. I listed three-year.  
12 The first is really kind of a fundamental one that  
13 underlies perhaps all of the discussion. Is the DPK method  
14 an appropriate approach for establishing bioequivalence of  
15 topical drug products? It's something that, in all those  
16 years that we've been talking about it, still hasn't been  
17 resolved. The information that will be presented today is  
18 really more information, some scientific studies and so  
19 forth that are interesting and will I think cause a lot of  
20 thought and discussion.

21 The second one is, are results and conclusions  
22 derived from the DPK method consistent within and between  
23 laboratories? Because a regulatory method, even if the  
24 first question is true and accepted, really isn't a very  
25 good method if you can't reproduce it between labs. If

1 it's very lab-dependent and one lab will get a passing  
2 grade on comparison of certain products, and two other labs  
3 that do this technique get a very different answer -- and  
4 that happens quite a lot -- it really isn't a suitable  
5 method if you can't reproduce it from lab to lab or from  
6 time to time within the same lab.

7           The last method is even if one and two are  
8 true, if only one or two laboratories can do this, and it's  
9 so difficult or expensive or arduous to set up that no one  
10 else in the world can possibly do it, it's probably not a  
11 good regulatory method either. So, even if you accept one  
12 and two, the method needs to be not too difficult to set  
13 up, not too difficult for experienced investigators in  
14 other fields to set up and get running, and it shouldn't  
15 take millions of dollars or years to set up this method.

16           You'll see that we've done some work in our FDA  
17 labs, who started out having no experience in this method,  
18 and how long it took them to get up and running and getting  
19 data where they were happy with the performance of the  
20 data. It's important that a regulatory method be  
21 reasonably easy to set up and get good results without an  
22 extraordinary effort or time.

23           That's the end of my introductory talk.

24           DR. LEE: Thank you, Dale.

25           Are there any questions from around the table

1 | for Dale?

2 | (No response.)

3 | DR. LEE: Thank you.

4 | We have three presentations by invited guests,  
5 | and I'd like the committee members to listen very carefully  
6 | because we need to have answers to those three questions.  
7 | First I'd like to invite Lynn Pershing to the podium.

8 | DR. PERSHING: Good morning. Today I'm going  
9 | to present some work about bioequivalence assessment of  
10 | three 0.025 percent tretinoin gel products, and compare the  
11 | dermatopharmacokinetic method with the clinical trial  
12 | efficacy method.

13 | I want to emphasize, before we start, that  
14 | there are many players and there are many groups of people  
15 | who influence whether a topical product gets to the market  
16 | and actually is used in patients, which is the consumer,  
17 | the ultimate individual that we're all supposed to be  
18 | focused on. Despite our individual missions, we have  
19 | physicians, the innovator industry, the health care,  
20 | insurance people who are really controlling the drug  
21 | products we use, clinical research organizations,  
22 | scientists, generic industry, and also ultimately the FDA,  
23 | who decides whether that product actually ever gets used in  
24 | the consumer. The important point here is that we all have  
25 | a common goal, and that common goal is to provide the best

1 therapeutic drug products that we can to that consumer.

2 So, let's keep that in mind as we go forward.

3 The hypothesis we're testing today is the that  
4 the dermatopharmacokinetic method will assess  
5 bioequivalence between three tretinoin gel products,  
6 similar to a clinical trial efficacy method.

7 So, the issue in bioequivalence really is, how  
8 much different can two products be and still be  
9 bioequivalent in an individual. Very important to the  
10 issue is understanding what it means to say bioequivalence  
11 in a topical drug product. First of all, they should have  
12 the same concentration of active, which is the drug in this  
13 case, and the second very important issue when you're  
14 trying to deliver a drug into the skin and looking at  
15 bioequivalence, is that they are Q1 and Q2 similar.

16 Q1 is qualitatively similar in the vehicle  
17 composition, that they have the same vehicle components.  
18 Q2 is that quantitatively they're similar, that the  
19 concentration of those vehicle components are as similar as  
20 they can be. In contrast, bioavailability is when they are  
21 Q1-Q2 different, that the vehicle composition may be  
22 composed of different vehicle components. They may have Q2  
23 differences where there's a different concentration of the  
24 active. Here we'd be looking at three different  
25 concentrations of a particular drug in a similar vehicle,

1 or that the vehicle components are actually even different.

2 In the case that we're going to talk about  
3 today, the three 0.025 percent tretinoin gel products,  
4 there were three that were decided to be studied: the  
5 innovator and two test generic products. One test product  
6 was Q1-Q2 similar to the reference product. The other was  
7 different. So, it would be termed a Q1-Q2 different  
8 product. We're going to see, then, how DPK can either  
9 differentiate these three products based on whether they're  
10 Q1 or Q2 similar.

11 I want to show you the clinical results first  
12 because that's our reference point at this stage. We're  
13 trying to compare does DPK actually predict the clinical  
14 results. And we know that it was an acne trial. Actually  
15 information is available from the FDA web site. Two  
16 parameters were compared: efficacy and safety. The  
17 products that were Q1-Q2 similar were bioequivalent for  
18 both parameters. The products that were Q1-Q2 different  
19 were not bioequivalent in efficacy and they were not  
20 bioequivalent in safety. In fact, the test product was two  
21 times safer than the innovator product, but it was less  
22 effective.

23 Important in drug delivery issues for the skin  
24 is that when you apply a topical product to the skin, that  
25 drug, as Dr. Conner has discussed, has to leave the vehicle

1 and partition into this 10- to 20-micrometer thick skin  
2 layer that controls all drug uptake into the skin. This  
3 stratum corneum layer is easily accessible. It's  
4 nonviable. It's exfoliated at one layer every day, and  
5 it's easily removed with adhesive discs.

6           Important to remember from fixed second log  
7 diffusion is that when you apply an external chemical drug  
8 in this case to the stratum corneum, you set up a  
9 concentration gradient through the skin. The highest  
10 concentration will be in the stratum corneum, and you have  
11 a concentration gradient even through the stratum corneum.  
12 If you don't get drug into that stratum corneum, you rarely  
13 get a therapeutic effect.

14           We can collect that stratum corneum. We can  
15 harvest that stratum corneum, using adhesive discs. In our  
16 study we've used D-Squame adhesive discs. They're  
17 commercially available. They come on a polymer backing, 10  
18 individual discs that can be bought in different sizes,  
19 either a 1.37 centimeter or 2.2 centimeter diameter. One  
20 of these panels of 10 discs is used for each skin site and  
21 analyzed in an individual.

22           Using this product we've noticed that the first  
23 10 skin strippings at a particular site removed about 325  
24 to 350 micrograms of stratum corneum, and this is done in  
25 12 people, four sites in each person. And the variability

1 reflects the differences between people. If we then took  
2 another series of 10 discs and tape-stripped that site,  
3 we'd see that half of the stratum corneum was removed.

4 That could be an issue when you're quantitating  
5 how much drug is in those skin strippings, how many skin  
6 strippings should you collect. What I want to show you  
7 here is if you've adequately removed residual drug and  
8 you're quantitating them, how much drug is actually in the  
9 stratum corneum, and we know that drug is in a  
10 concentration gradient through the stratum corneum, you  
11 should see that there's more drug in the -- this is percent  
12 dose applied of total retinoids -- you should see there's  
13 more drug in the first skin strippings than the second set  
14 of 10 skin strippings, and indeed we do. But that could be  
15 influenced by the amount of stratum corneum that you  
16 actually remove.

17 But you note that even if you correct the  
18 percent dose applied for the amount of skin removed, you  
19 still see a concentration gradient through the stratum  
20 corneum. That's a very important validation step in this  
21 work.

22 To be able to adequately analyze the drug in  
23 the skin strippings that you collect, you need to have a  
24 validated bioanalytical assay. What I'll share with you is  
25 we developed an assay for tretinoin and its isomer analog,

1 isotretinoin, with the recovery from these adhesive discs  
2 of greater than 87 percent for both, with no interferences  
3 from the matrix or the stratum corneum with the analytes of  
4 interest or the internal standard, with an appropriate  
5 linear regression, accuracy of greater than 85 percent, a  
6 precision less than 11, with a limit of quantification of  
7 four nanograms per ml. They were also stable to pre- and  
8 post-extraction stability.

9           The other thing you have to do is develop a  
10 reproducible method to actually dose the drug to the skin  
11 site. For this we use a 250 microliter Hamilton syringe  
12 that's aliquoted at 5-microliter intervals, and we  
13 validated that among the three products -- less than 10  
14 percent coefficient of variation -- they reproducibly  
15 deliver a 5 microliter dose.

16           The experimental design in this study was such  
17 that we wanted to capture both the uptake of tretinoin and  
18 isotretinoin, as well as total retinoids into the skin, as  
19 well as elimination. To do that, we performed a pilot  
20 study to determine the appropriate time points to capture  
21 that descriptive profile. We washed all ventral forearms  
22 of the subjects that were enrolled in the study an hour  
23 before the study. 7 minutes prior to application, we  
24 collected skin strippings from untreated control sites, and  
25 at time 0 applied the drug for either 15 minutes, 30



1 minutes, 1 hour, or 1.5 hours to the subjects, and then for  
2 the elimination phase, after one-half hour, removed the  
3 drug and looked at 3, 6, 9, and 12 hours after elimination.  
4 These are the time points that were found in our pilot  
5 study to best describe the innovator products' uptake and  
6 elimination profile into the stratum corneum.

7           The product application randomization schedule  
8 was as follows. We used both right and left forearms. We  
9 blocked all uptake time points to the right arm and all  
10 elimination time points to the left arm. The different  
11 doses in this case were randomized to four regions, 1  
12 through 4 for each subject. The elimination time points  
13 were randomized on the left arm per subject. Product A, B,  
14 and C were randomized to either site 1, 2, or 3 in each  
15 subject, and that randomization schedule was held at all  
16 regional points.

17           The demographics of the study included 49  
18 subjects, about equal numbers of males and females, with an  
19 average age of 30.7 years, representing 41 caucasians, 6  
20 Asians, and 2 Hispanics, consistent with our percentage of  
21 ethnic distribution in the state of Utah. And there was a  
22 hand preference: 45 right-handers versus 4 left-handers.

23           It's important when you're doing DPK to have  
24 surface area considerations of the treated site versus the  
25 adhesive size that you use in collection of the stratum

1 corneum. In our study we used a skin site surface area of  
2 1.2 centimeter diameter. The adhesive disc was 1.3  
3 centimeter diameter, and so when you overlap adhesive on  
4 the skin site, there was a slight overlap beyond the  
5 surface area of the treatment site.

6 So, data. Data is what we live for, right?  
7 This is the three products of tretinoin gel, 0.025 percent,  
8 the three different products. What I want to draw your  
9 attention to is that the products that are Q1 and Q2  
10 similar produce an identical tretinoin uptake and  
11 elimination profile. The product that is Q1-Q2 different  
12 from the innovator produced a profile that was 60 percent  
13 of the innovator.

14 When we analyzed the data with biostatistics,  
15 we see that the 90 percent confidence interval, which for  
16 acceptance of bioequivalence is set to be 80 to 125, that  
17 for both Cmax and the AUC 0 to the last detectable  
18 endpoint, that the two products that were Q1 and Q2  
19 different failed bioequivalence, both for Cmax and the AUC  
20 parameters. The products that were Q1 and Q2 similar,  
21 however, showed bioequivalence at both parameters, Cmax and  
22 AUC. Therefore, based on just tretinoin, this product  
23 would fail bioequivalence and that product would pass  
24 bioequivalence.

25 Tretinoin has a natural isomer, isotretinoin,

1 and so even in the product you have about 5 percent of  
2 isotretinoin, so it's important with products like this  
3 that you also measure the isomer analog, which is  
4 isotretinoin.

5 In the same skin sample, you follow the  
6 isotretinoin, and again you see the products that are Q1-Q2  
7 similar produce identical profiles of isotretinoin. The  
8 product that was Q1-Q2 different from the innovator  
9 produced a profile of about 60 percent of the innovator.  
10 Biostatistically the products that are Q1-Q2 different, it  
11 fails bioequivalence for Cmax and AUC. The product that  
12 was Q1-Q2 similar passed bioequivalence criteria.

13 Another method to look at the product that has  
14 isomers involved is to do the total concentration of all  
15 the retinoids, and so we also analyzed total retinoids.  
16 This was done again on 49 people, and you'll see the same  
17 result. The products that are Q1-Q2 similar produce  
18 identical profiles, and the product that was different  
19 produced a different profile. And again, biostatistically  
20 the products that are the same pass bioequivalence. The  
21 products that are Q1-Q2 different fail bioequivalence.

22 So, if we compare the three methods, DPK,  
23 clinical efficacy and clinical safety, we see that the  
24 products that are Q1-Q2 similar pass bioequivalence in all  
25 three methods. The product that was Q1-Q2 different failed

1 DPK bioequivalence, failed clinical efficacy  
2 bioequivalence, and failed clinical safety.

3 In summary, DPK is a good method for  
4 bioequivalence assessment of topical drug products. It's  
5 objective. It's sensitive. It's discriminating. It's  
6 precise, accurate. Most importantly, it's scientifically  
7 and clinically relevant. And it's comparable to  
8 pharmacokinetic methods used for oral solid dosage forms.

9 In conclusion, then, DPK results predict the  
10 clinical efficacy and safety results. DPK is a sensitive,  
11 reproducible, and valid method for bioequivalence  
12 assessment of topical drug products.

13 Thank you.

14 DR. LEE: Thank you, Lynn.

15 Any questions for Lynn? John?

16 DR. DOULL: You said you looked at males and  
17 females and ethnicity. Did they have any effect at all on  
18 the results?

19 DR. PERSHING: We saw no statistical difference  
20 between males and females, and no statistical difference in  
21 the ethnic groups that we evaluated.

22 DR. DOULL: Were these all similar age people?

23 DR. PERSHING: The average age is 30.7, plus or  
24 minus -- I think it's in the handout. But they were, yes.

25 Obviously important here, and this is a nice

1 aspect, as Dr. Conner has brought up, is that all the drugs  
2 are evaluated in the same person at the same time. If we  
3 had individual groups of young, middle, and old people,  
4 maybe we could see a difference. But in this case the  
5 demographics that are in your handout describe the people  
6 that we used.

7 DR. LEE: Dr. Conner?

8 DR. CONNER: I'd like to make two statements or  
9 clarifications from the FDA standpoint.

10 First off, Dr. Pershing's definitions of BA and  
11 BE are not the regulatory or FDA definitions, so it's  
12 important to point that out. Especially the way that she  
13 has defined BA is not our definition, and I actually don't  
14 even agree with it.

15 DR. PERSHING: I'll just say that's quoted  
16 directly from the draft guidance.

17 DR. CONNER: The other thing is, it's important  
18 to point out the approval criteria for these three  
19 products. The Q1 and Q2 obviously is important, but it's  
20 important to note that the two products which Dr. Pershing  
21 was referring to as Q1 and Q2 are approved as equivalent  
22 products. One is an NDA. The other is approved under the  
23 ANDA process and should be considered equivalent and  
24 switchable for the products. Officially in the Orange  
25 Book, those are substitutable products.

1           The third product, which does not show  
2       bioequivalence under DPK or even the clinical, is approved  
3       under the NDA process, so it's not considered officially  
4       switchable. It's a stand-alone NDA product, and it's  
5       important to know that when you're looking at this.

6           And obviously since it has a different NDA and  
7       it has totally different labeling. It has its own  
8       labeling, and it has its own package of information on  
9       which it was approved, of which these clinical studies were  
10      just a small portion. It has efficacy and all of the  
11      things that are needed to approve an NDA.

12           DR. LEE: Two more questions.

13           DR. KIBBE: Could we also conclude from this  
14      data that we don't need to do any bioequivalency testing if  
15      they're Q1-Q2 equivalent when we first look at them? That  
16      it predicts the outcome and why do the results?

17           For a long time with oral products we've tried  
18      to find the mystery method that would allow us to test in a  
19      laboratory, and we don't have to go into humans. I was  
20      wondering if we're at that point here.

21           DR. PERSHING: You can still be Q1 and Q2  
22      similar and, because of manufacturer processing, not be  
23      equivalent DPK because there are a lot of things that go  
24      into drug delivery of topical drug products for the skin.  
25      Particle size, and particle size still is important in

1 topical drug delivery just as it is in a solid oral dosage  
2 form. So, all the physical parameters that influence  
3 bioavailability for oral products also pertain very  
4 similarly to topicals.

5 If you only looked at physical parameters, you  
6 wouldn't know how it performed. So, this really is a  
7 performance evaluation.

8 DR. LEE: We'll take two more questions and  
9 then move on. Gloria?

10 DR. ANDERSON: What evidence do you have that  
11 the uptake mechanism and perhaps rate between the two that  
12 are the same and the one that's different are the same?

13 DR. PERSHING: As I understand the FDA issues,  
14 it's that rate and extent is important. You'll notice that  
15 the rate may not have been so different, but the extent  
16 was. That's why the Q1-Q2 different product didn't obtain  
17 the same DPK profile. The Cmax was lower and the AUCs were  
18 therefore lower. Both rate and extent are important and  
19 you have to have both of those.

20 Now, was the rate different? I didn't  
21 calculate the rate, but you can see because they overlap on  
22 the uptake part of the curve, they're quite similar, but  
23 the extent was different, so the Cmax was different.

24 DR. ANDERSON: Actually my question really is,  
25 did that affect the outcome, the results that you obtained?

1 DR. PERSHING: I see what you're saying.  
2 Actually what you're really probably referring to then is  
3 in your experimental design, what if the Q1-Q2 product just  
4 attained its Cmax? The Tmax was different. And that's a  
5 valid point. When you're doing bioequivalence testing, you  
6 have to meet the reference product profile.

7 DR. LEE: Kathleen?

8 DR. LAMBORN: Your comment that you could be  
9 Q1-Q2 the same, and yet be bio-inequivalent raises a  
10 question about the extrapolation of the results that you  
11 presented here, where you knew right off the bat that you  
12 were not Q1 and Q2 equivalent. Would you expect that the  
13 results, if they were Q1 and Q2 equivalent, would be more  
14 subtle and therefore you might, in fact, not be able to  
15 pick up the differences? In other words, you've used this  
16 where you had Q1-Q2 not similar as a justification for  
17 saying, see, we're sensitive and specific. But you don't  
18 have the Q1 and Q2 the same, so maybe you're working with a  
19 bigger difference than you would really be wanting to try  
20 to discern. If that makes sense.

21 DR. PERSHING: We've analyzed about 20  
22 different topical drug products from five different drug  
23 classes, and frankly we noticed a lot of interesting  
24 things. Usually I don't even know what the vehicle  
25 composition is, and I, frankly, didn't even know the



1 vehicle composition when I did this study. I did know they  
2 were Q1 and Q2 different. I did know that they had been  
3 evaluated in a clinical study, and that's it, when I did  
4 this work.

5 We have looked at products that were supposed  
6 to be Q1-Q2, and a lot of times they don't pass DPK. And  
7 if you further investigate as to the mechanistic basis of  
8 that, sometimes you can get back to physical parameters.

9 But what I'm trying to say is that you need a  
10 performance test. You can't just look at vehicle  
11 composition because sometimes they can be Q1 and Q2  
12 different, and they might produce a similar profile because  
13 all the parts of the product can influence drug delivery.

14 I'm just saying if you're Q1-Q2 up front, you  
15 have a much better chance of passing DPK. We can take Q1-  
16 Q2 different products. Every time I have, I see a  
17 difference in DPK. And experience just shows that.

18 DR. LAMBORN: But you have found some products  
19 which are Q1-Q2 the same which have consistently  
20 demonstrated differences using this method.

21 DR. PERSHING: I just presented some work at  
22 AAPS that showed that five different lot numbers of a  
23 particular innovator product is not always bioequivalent.  
24 So, you do need to have a performance test to evaluate for  
25 these kind of differences. Just because we manufacture, it

1 | doesn't mean it's always perfect.

2 | DR. LEE: Very well. Thank you very much.

3 | Bill?

4 | DR. JUSKO: When we study oral drug products,  
5 | we allow the full natural time course of absorption and  
6 | disposition to be followed. In this technique, uptake is  
7 | followed from 1.5 hours, so my question is, if you had  
8 | allowed the full natural time course to be examined, how  
9 | likely would you have been then to possibly see differences  
10 | between products, possibly have a different interpretation  
11 | of the entire set of results.

12 | DR. PERSHING: Excellent question.

13 | DR. LEE: Is it going to be a brief answer?

14 | DR. PERSHING: It's going to be a brief answer.

15 | Each product, each drug, each concentration may  
16 | have its own unique profile, and that's why you do a pilot  
17 | study to determine what the appropriate time points are.  
18 | For a gel product, it could be a very different time course  
19 | than it is for a semi-solid cream or ointment. In fact,  
20 | most of the studies are done over a 24-hour time point.

21 | But what we found in our pilot study is that in  
22 | Utah, in my subject population base, that if I applied and  
23 | left it on for 4 hours, the drug was already eliminating.  
24 | It starts to eliminate even before 1.5 hours. That's why  
25 | those time points have been chosen because we had done a

1 pilot study. We found what Tmax is and the half-life, and  
2 we have experimentally designed the time points of  
3 collection for a pivotal study that are pertinent to those  
4 two parameters.

5 DR. LEE: Thank you. I think it's time to move  
6 on. Dr. Franz, are you ready?

7 DR. FRANZ: Yes.

8 This study that I'm going to present, or the  
9 work I'm going to present, was conducted at DermTech under  
10 the sponsorship of Spear Pharmaceuticals, and was really  
11 done at the sort of general request that the FDA made at  
12 many of these prior meetings for other people to get  
13 involved, the industry, academics, so that there would be a  
14 wealth of data from different labs that could be used to  
15 evaluate the suitability of DPK. So, it was in that spirit  
16 that Spear Pharmaceuticals sponsored this study.

17 The work is similar in that presented by Dr.  
18 Pershing in that we examined two of the three products that  
19 she examined. We have looked at the Avita product, which  
20 is reported not to be clinically as effective, and that was  
21 compared to Retin-A, the innovator product. A lot of the  
22 details of the studies are the same, but there are a few  
23 differences.

24 In the first study that I'm going to report,  
25 this was a study in 36 subjects, 14 females, 22 males, 15

1 caucasian, 15 Hispanic -- so the demographics are a bit  
2 different than in the prior work that was presented -- 4  
3 African-Americans and 2 Asians. Mean age of 32.2 years.

4 In our study, this one and the next one I'll  
5 present, the situation is this. Two-by-two square sites  
6 are demarcated on the ventral forearms, and there's  
7 basically two rows on each forearm. Randomization of these  
8 two products is between paired sites here so that for  
9 instance, if the lateral site gets the test product then  
10 the medial site will get the reference. So, they will  
11 always applied as pairs. But they will be randomized,  
12 medial to lateral, and they will also be randomized from  
13 proximal to distal.

14 Like Lynn, we use one arm for the absorption  
15 phase, one arm for the elimination phase, and again, this  
16 is randomized. We are using 4 square centimeter site  
17 areas. We applied 20 microliters, so this is the same dose  
18 that was used in the prior work, basically 5 microliters  
19 per square centimeter. It's applied with a positive  
20 displacement pipetter and then evenly spread over the area  
21 with a smooth glass rod. We cover the forearms with a non-  
22 occlusive aluminum screen that sits up above the forearm so  
23 that there's no possibility of touching the dose sites.  
24 Then because this is a light-sensitive compound that we're  
25 working with, they're covered with a cotton sleeve to

1 minimize light exposure.

2           Based on the pilot work that we had done, we  
3 came to a similar conclusion that Lynn came to, that  
4 basically peak absorption seemed to be reached at 1.5 to 2  
5 hours. But we tend to want to leave the drug on a little  
6 bit longer than that, so our absorption phase actually goes  
7 to 4 hours with these points being the sampling points,  
8 half, 1, 2, and 4 hours. And then the elimination phase  
9 goes much longer: 8, 12, 24, and 48 hours.

10           At each one of these times in the absorption  
11 phase, the sites are blotted three times with Kimwipes.  
12 They are wiped once with a dry cotton-tipped swab, and then  
13 stripped 22 times with Transpore tape. Basically the  
14 Kimwipes and the dry cotton swab is to pick up any liquid  
15 or anything that's not quite dried that might prevent good  
16 adhesion when the tape is applied. So, this is what's done  
17 with the sites on the absorption arm.

18           The elimination phase is really initiated on  
19 the other arm at four hours, the end of the absorption  
20 phase, and at that point every site on the elimination arm  
21 will be blotted with the Kimwipes and again dried with the  
22 cotton-tipped applicator, and then stripped twice to remove  
23 unabsorbed drug. That's done on all sites. Then of course  
24 later at 8, 12, and 24 hours, paired sites will be  
25 stripped, this time only 20 times because we've already

1 taken the first two strips to remove unabsorbed drug on the  
2 surface.

3 Strips 1 and 2 in all cases are discarded, as  
4 are the Kimwipes and the cotton-tipped swab. We pool the  
5 next 10 strips. They're extracted in acetonitrile and  
6 analyzed by HPLC. Then likewise the last 10 strips are  
7 also pooled separately, extracted, and analyzed. We have a  
8 validated HPLC assay for tretinoin and its isomer, the  
9 isotretinoin.

10 All the data I will be presenting are the two  
11 isomers' sums. I won't be presenting individual data.

12 And, of course, all these procedures take place  
13 under dim yellow light to prevent as much isomerization as  
14 we can.

15 Here is the data presented first by strip sets,  
16 so I'm presenting what the first pool of 10 strips look  
17 like, and then the data deeper in the stratum corneum, the  
18 second 10 strips. You probably can't read this up here,  
19 but in fact red represents the test product, the Avita  
20 product, showing higher stratum corneum levels, both in the  
21 first 10 strips and in the second 10 strips. Then the  
22 Retin-A product, which is shown in the dark line. So, that  
23 is the first 10 strips versus the second 10 strips.

24 If we just sum all this data and present the  
25 total of what's found in 10 strips, that's presented here.

1 So, there is good separation between the two products.  
2 Clearly they're not behaving in the same manner, but in  
3 contrast to what Lynn was finding, we're finding just the  
4 reverse. We're finding higher drug levels in the stratum  
5 corneum than the Retin-A product.

6 Now, we were concerned when we got these  
7 results, and we thought obviously we had switched the tubes  
8 and we had mislabeled, so we wanted to get a quick repeat.  
9 Just a week ago we finished a second study. It's kind of a  
10 half study. It was done just in 18 subjects, and we looked  
11 only at the absorption phase because the differences that  
12 we had seen in the first study really took place in the  
13 absorption phase. Everything was basically conducted the  
14 same way, with that exception that we didn't do an  
15 elimination phase. We're still collecting at half, 1, 2,  
16 and 4 hours.

17 The other thing that was done different, we  
18 wondered about different response of the tapes. We used  
19 Transpore in the first study. So, in this study, in lieu  
20 of an elimination phase, we did one arm with D-Squame, and  
21 the other arm with Transpore to see what differences the  
22 two types might produce. Otherwise, the procedures were  
23 essentially as I reported in study number one.

24 In essence, we duplicated the work of the first  
25 study. We still found higher stratum corneum contents for

1 the two tretinoin isomers for the Avita product as compared  
2 to the Retin-A. This is using D-Squame here and Transpore  
3 here. So, what's presented are the data from the first 10  
4 tape strips for D-Squame and for Transpore. So,  
5 differences between products are found with both tapes, but  
6 we seem to get much greater recoveries of drug with  
7 D-Squame.

8 If we look at the second 10 strips, we see a  
9 similar behavior, much greater recovery with D-Squame than  
10 Transpore. Clear separation, actually broader separation  
11 in the second 10 strips between the two test and reference  
12 products. I should say that in terms of statistical  
13 analysis we did find that the test and reference products  
14 were different. So, tape stripping here has clearly been  
15 able to show that there's a difference between the two  
16 products.

17 I'm a little puzzled about why they're in  
18 different directions than what Dr. Pershing presented, but  
19 I've been assured by Dale Conner that we may have a good  
20 hypothesis coming shortly, so there may be a good  
21 explanation for this.

22 I wanted to use the rest of the time just to  
23 present work that had been alluded to, and actually I think  
24 partially presented previously at one of the prior  
25 meetings, just to suggest that as we look at techniques for



1 proving bioequivalence of topical drug products, to be  
2 aware of some of the other techniques that are and have  
3 been used, and I'll mention a couple of them specifically  
4 here.

5           There's a number of well accepted techniques  
6 available to confirm the bioequivalence of topical  
7 products, and the two I'm going to talk about is the human  
8 cadaver skin assay, the assay that's actually used very  
9 frequently by the majority of pharmaceutical companies to  
10 develop topical products. In the pre-clinical phase of  
11 development, the screening of different formulations often  
12 involve the use of cadaver skin, so it's a well grained  
13 model that is widely used and has a long history going back  
14 well over 30 years. Of course, as you would expect, when  
15 it comes to transdermal devices, this is a critical factor  
16 in the development of them. So, I'll just show some data  
17 on cadaver skin assay, and then a specific assay for  
18 retinoids.

19           I'm calling it here the transepidermal water  
20 loss assay. It's just a variation of another widely used  
21 test in the industry, the 21-day cumulative irritation  
22 assay. In probably most, if not all, NDA submissions for  
23 topical products, irritation data is submitted. It may be  
24 animal but in many cases human data is also submitted and  
25 the test most frequently used is what's called a 21-day

1 cumulative irritation assay, a subchronic assay. The  
2 variation is here we're not just looking at irritation,  
3 redness and scaling, but we're also monitoring another  
4 endpoint, which is transepidermal water loss through the  
5 skin.

6 Now, the reason I'm presenting this data is  
7 that this work was actually done for Spear Pharmaceuticals,  
8 and it is to show bioequivalence by these surrogate tests  
9 for two products that have now been shown by clinical assay  
10 to be bioequivalent. So, what we're examining here are the  
11 two generic products from Spear Pharmaceuticals, the .01  
12 and the .025 gel products, and comparing them to the same  
13 strength of the innovator gel products, and our object is  
14 to show concordance with the clinical results, which in  
15 fact did show bioequivalence.

16 The human cadaver skin assay is well known, but  
17 it's basically using dermatomed skin, and in this case  
18 we're looking at skin obtained from 8 different donors.  
19 The outer portion of the skin is exposed to ambient  
20 conditions, just like exist in this room, and dosing is at  
21 the level of 6.25 microliters per square centimeter of each  
22 of the four active gel products. We are sampling the  
23 dermal receptor solution at these times, ranging from 4 to  
24 48 hours.

25 In this case, because the amount penetrating is

1 | so low and below detection limits by HPLC, we have actually  
2 | spiked the products with radioactive tretinoin, but proven  
3 | that the tracer is actually a good tracer for the parent  
4 | drug itself by doing a rate of release test on the products  
5 | to show the concordance between the rate of release of the  
6 | isotope and the cold drug, that the specific activity  
7 | measured at the beginning of the release is the same as the  
8 | specific activity measured at the end of release. So, this  
9 | is a tracer truly behaving as a tracer and not one of the  
10 | tracers with also problems caused by yttrium exchange.

11 |           At the end of 48-hour sample, we're washing the  
12 | surface of the skin with isopropanol to remove unabsorbed  
13 | drug. We're also separating the skin at epidermis and  
14 | dermis and digesting and analyzing for radioactive content,  
15 | so it's basically a mass balance study. The primary  
16 | endpoints are AUC and maximum flux. We also look at time  
17 | of maximum flux, and we have some secondary endpoints too  
18 | that are based on dermal-epidermal content and mass  
19 | balance.

20 |           The transepidermal water loss is a much  
21 | different study. The first one is in vitro; the second one  
22 | is in vivo, using normal subjects, again using the  
23 | forearms. What happens is that small amounts, really the  
24 | same dose that was used in the tape stripping studies, are  
25 | applied to demarcated sites on the ventral forearms. A

1 daily application is made for 20 days, so every day the  
2 subjects come back, the sites are evaluated for redness and  
3 scaling and a measurement taken of transepidermal water  
4 loss with an instrument called an evaporimeter, and then  
5 after all those readings are done, the drug is reapplied.

6 In order to make the forearm skin a little bit  
7 more like the face, which is the normal site of application  
8 for retinoids, we actually apply Saran Wrap for 5 hours to  
9 enhance the absorption of these retinoids. As I mentioned,  
10 at each study visit, prior to the next dose, we're  
11 measuring transepidermal water loss and then we're grading  
12 the skins for erythema, but mostly for peeling, which has  
13 turned out to be the best endpoint.

14 So, again, we have two primary variables upon  
15 which to do our statistical assay. One is the maximum  
16 value for transepidermal water loss that's achieved, and  
17 the second one is the days to full peel. Because this was  
18 a placebo-controlled trial that only went for 21 days, we  
19 basically had to assign a value of 25 days to any sites  
20 that didn't peel by 21. So, these are the two tests,  
21 basically, that we are going to be looking at.

22 I should say in general the second test,  
23 although it's really a chronic irritation test, it's based  
24 on the fact that retinoids alter the differentiation of the  
25 skin, and when they do that, they change the barrier

1 properties of skin. The primary function of the barrier is  
2 to keep water in, so as one alters the barrier-to-water  
3 loss, we see an increase in water loss through the skin.  
4 So, that's sort of the physiology behind this  
5 pharmacodynamic assay.

6 Let's look first at transepidermal water loss.  
7 What happens is that during the first week of this  
8 subchronic application, one sees basically no change in the  
9 skin, one measures no change in transepidermal water loss,  
10 but as one gets into the second week and the third week,  
11 then one begins to see changes both in how the skin  
12 behaves, the peeling, and one also begins to see changes in  
13 transepidermal water loss.

14 So, if you look here, for instance, at the .025  
15 percent gel comparing the Spear and the Retin-A product, we  
16 find that for the value for maximum transepidermal water  
17 loss, which normally would be around 4, but because we  
18 subtracted the placebo response, it really is 0. So, we're  
19 going from 0 up here to 12. The Spear product is showing  
20 12.3, with the usual large standard deviation we see with  
21 skin studies, and the Retin-A showing 12.1, and again the  
22 large standard deviation that we normally see. But good  
23 agreement in terms of maximal transepidermal water loss.

24 Likewise, when you go to the lower strength  
25 product, you see good agreement: 7.8 versus 8.2. What you

1 | also see is dose response, that these values here are  
2 | different from these values here. So, the low-strength  
3 | product is producing less of an effect than the high-  
4 | strength product.

5 |           Likewise, when you go to days to full peel, the  
6 | high-strength gel are taking on average about 18 days.  
7 | Standard deviation is less in this case. And with the low-  
8 | strength product -- the study only goes for 21 days, so  
9 | what you're seeing is that very few sites on the low-  
10 | strength gel are actually going all the way to peeling, and  
11 | we have a lot of 25 days being added in here to give us a  
12 | value that's greater than 21. But we also see good  
13 | agreement between the two test products at that  
14 | concentration, and again we see dose response, a  
15 | differentiation between the low strength and the high  
16 | strength.

17 |           In terms of statistics, if we look at the low  
18 | strength and look at the confidence interval for the ratio  
19 | of the log transformed data, we see that they fall very  
20 | nicely within the 80 to 125 parameters, both for  
21 | transepidermal water loss and for days to full peel.  
22 | Likewise, for the high-strength product, we see the  
23 | confidence intervals fall between 80 to 125 for both of  
24 | those primary parameters. So, as another test for  
25 | consideration of testing of bioequivalence of retinoids,

1 | this certainly is one that, in this one test where we have  
2 | clinical data to compare it to, has held up rather nicely.

3 |         When we looked at the cadaver skin data, we  
4 | also found good agreement with the clinical results, and we  
5 | were able to show bioequivalence. Showing the rate data  
6 | for the low-strength product and the high-strength product,  
7 | I can't even read myself. This I believe is the test and  
8 | this the reference product for the low strength, and what  
9 | we're looking at here is rate of absorption as a function  
10 | of time. This study going out over 48 hours. Even better  
11 | agreement with the high-strength product between test and  
12 | reference. It's really difficult to tell the difference.  
13 | These here represent the standard error error bars.

14 |         We'll just look at the numbers for the  
15 | confidence intervals. Looking at the low-strength product,  
16 | the two primary parameters were AUC and here maximum flux.  
17 | And again, if we look at the confidence intervals, 97 to  
18 | 107, 92 to 115, well within the 80-125. If we look at all  
19 | the secondary parameters with the exception of the dermal  
20 | content, we also find that they fall within the 80-125.  
21 | Only the dermal content for this strength and the next  
22 | strength, if we could get the next one up, are the ones  
23 | that don't fall within the 80-125.

24 |         But if you look at the two primary parameters,  
25 | AUC and maximum flux, you see 95 to 110, 95 to 127, close

1 | enough for me. I'm sure Dale would agree with that. FDA  
2 | is very flexible in this regard.

3 | (Laughter.)

4 | DR. FRANZ: And again, only the dermal numbers  
5 | not falling within the 80-125.

6 | So, there are other tests in addition to the  
7 | tape stripping DPK method, and I think what's nice about  
8 | the skin is we do have a lot of tests that are available to  
9 | us for consideration. As we pointed out many times, one  
10 | nice thing here is that these tests and references are  
11 | compared side by side at the same time on the same subject,  
12 | so there's tremendous advantages over what the people with  
13 | oral bioequivalence have to do. And with that I will stop.

14 | DR. LEE: Thank you, Tom. I think that we are  
15 | behind a little bit. Are there any burning questions, just  
16 | one or two?

17 | DR. VENITZ: I just wanted to make sure that I  
18 | can compare the two studies. You're comparing Avita to  
19 | Retin-A. How does that compare to Dr. Pershing's A, B, and  
20 | C, because you mentioned that you get a discrepant result.

21 | DR. FRANZ: Well, the same products were  
22 | compared in both studies. We just used two of the three  
23 | that were in her study. The Avita and Retin-A were in her  
24 | study as they were in our study. Her data found the Avita  
25 | content to be lower than Retin-A. We found the Avita



1 stratum corneum content to be greater, so there's obviously  
2 some methodological differences. We both found them to be  
3 statistically different from the test product.

4 DR. LEE: We'll come back to that at the  
5 discussion period. Marv, did you want to say something?

6 DR. MEYER: Yes. Tom, you did two separate  
7 studies actually. One was smaller than the other one.

8 DR. FRANZ: Yes.

9 DR. MEYER: Did you compare, say, the area  
10 under the curve from the smaller study to the larger study  
11 over the first 4 hours?

12 DR. FRANZ: I don't have that data in my head,  
13 but looking at the y axis, in terms of what the stratum  
14 corneum drug content was, it agreed very well. The two  
15 tests agreed very well, so we were getting the same amount  
16 out when we looked at the Transpore tape. The AUCs,  
17 therefore, should be the same, but I don't recall what the  
18 data was.

19 DR. LEE: All right. I would like to invite  
20 Dr. Mamata Gokhale from the agency to present her data.

21 DR. GOKHALE: Good morning, everybody. I'm  
22 going to talk about the internal DPK study which we  
23 conducted in collaboration with the Division of Product  
24 Quality Research. I will start with a short recap.

25 Currently there are three tretinoin gel

1 products on the market, and of these, Avita and Retin-A  
2 were approved as new drugs. The formulation of Avita is  
3 different from Retin-A, while the third tretinoin gel  
4 product is a generic one by Spear, and it is qualitatively  
5 and quantitatively similar to the Retin-A. The Orange Book  
6 lists Retin-A as the reference listed drug among these  
7 three products.

8 The earlier two speakers have shown that the  
9 DPK approach can be used to determine bioequivalence or  
10 bio-inequivalence of these products, and their results  
11 correlated with the clinical studies.

12 So, the question for us is, can the DPK  
13 approach be used as a regulatory method?

14 To address this question, we focused on three  
15 issues. The first was, is the skin-stripping technique  
16 easily transferable? Are the results reproducible, and are  
17 the required time and effort reasonable?

18 With this in mind, our objective was to  
19 determine the feasibility of conducting a DPK study in a  
20 new laboratory. I want to emphasize that determination of  
21 bioequivalence was not our objective. Our agency had  
22 already sponsored a DPK study at the University of Utah,  
23 and that was successfully completed. Therefore, we decided  
24 to use Utah protocols in our study, and throughout my  
25 presentation you will see that the Utah study is used as a

1 reference point.

2           So, we divided our study in three phases. The  
3 phase 1 was conducted with Retin-A, and the purpose was to  
4 practice the skin-stripping technique in our laboratory.  
5 Phase 2 was also conducted using Retin-A, and the purpose  
6 was to determine stratum corneum profiles over time. And  
7 phase 3 was conducted using all three products, and the  
8 purpose was to compare three gels simultaneously.

9           So, I'm going to walk you through our study  
10 now. I'll address the pre-dosing part of phase 1 first,  
11 and in this phase we focused on two variables. First was  
12 the stratum corneum weights, and the second was weights of  
13 the Retin-A that was going to be applied to the skin sites.

14           I will basically describe the skin-stripping  
15 procedure, which is basically the same as used in the Utah  
16 study. Forearms of the subject were washed and dried and  
17 circular areas corresponding to adhesive tape discs were  
18 marked on the skin sites using a template, and a stack of  
19 10 adhesive discs was weighed and used to remove successive  
20 10 layers of stratum corneum. Then it was weighed again,  
21 and the difference gave us the weight of the stratum  
22 corneum layers, which were removed.

23           When we compared the results of the right arm  
24 with the left arm, you can see that there were differences  
25 between the two arms in both the studies.

1                   Intra-arm variability of stratum corneum  
2 weights was comparable in both the studies.

3                   After we had some idea about the stratum  
4 corneum which we are removing, we moved on to monitoring  
5 the weight of the dose that we were going to use in our  
6 study, and we dispensed the gel using a Hamilton syringe,  
7 and the dose was 5 microliters, which weighed around 4  
8 milligrams in our hands, which was comparable with the Utah  
9 study.

10                  So, with this data in hand we were ready for  
11 dosing. A validated HPLC method was used to quantitate  
12 tretinoin and isotretinoin, which were together expressed  
13 as total retinoids. And I want to also mention that we  
14 used internal standard in our assay as recommended by the  
15 agency's guidance for bioanalytical method development.

16                  Now, here the drug was applied and left there  
17 for 2 hours. At the end of 2 hours, residual drug was  
18 removed using cotton swabs and stratum corneum layers were  
19 harvested.

20                  You are looking at related drug disposition  
21 across stratum corneum in terms of percent of applied dose.  
22 The reason we did this was because disagreement between  
23 different investigators as to how deep down the skin  
24 stripping should be continued. So, we harvested stratum  
25 corneum layers in three sets. Strip number 1, strips 2 to

1 10, and strips 11 to 20.

2 As you can see, the first strip contains way  
3 too much excess compared to the other layers, and this told  
4 us that strip number 1 contains the residual drug product,  
5 and it made sense to discard it.

6 Now, if you look at the total retinoid  
7 concentrations in strips 2 to 10 versus strips 11 to 20,  
8 there is a gradient. And this told us that it was  
9 sufficient to harvest strips number 2 to 10 during our  
10 profile studies, and going further down really didn't have  
11 any particular advantage. I want to point out that this  
12 data correlated well with the Utah study.

13 At this stage, we were ready to look at the  
14 stratum corneum profiles of total retinoids over time.

15 I should also point out about our recoveries.  
16 You can see that if you compare recovery after total  
17 tretinoin from the right arm versus the left arm, there  
18 isn't much difference between the two arms, and that trend  
19 was seen even in the Utah study. However, I want to point  
20 out that our stratum corneum concentrations were higher.  
21 They are twice as high as those obtained in the Utah study.

22 Intra-arm variabilities were high in both the  
23 studies, and this seems to be the inherent nature of this  
24 technique.

25 I'm going to talk about the stratum corneum

1 profiles. This is a time course study. Retin-A was  
2 applied at 0 hour. The skin stripping procedure was the  
3 same as I described. We discarded the first strip,  
4 harvested only strips 2 to 10. The residual drug was  
5 removed at 1.5 hours, and sampling was continued further,  
6 up to 10.5 hours.

7           You are looking at this top curve shown in red.  
8 That shows our initial effort. You can see that the total  
9 retinoid levels were higher than those obtained in the Utah  
10 study. Also, we did not obtain a good elimination phase.

11           However, with practice we got better and after  
12 using about 5 subjects in our study, we were able to obtain  
13 stratum corneum profiles which were superimposable with the  
14 Utah study.

15           What I want to point out is, from red to dark  
16 blue shows the progression of our learning curve. We got  
17 better with practice and with more experience. We also got  
18 more comfortable with the skin stripping technique.

19           So, at this stage we are ready to move on to  
20 phase three, which involved comparison of three different  
21 products simultaneously. How did we do?

22           Again, each drug was applied at 0 hour.  
23 Sampling was started. Residual drug was removed at 1.5  
24 hours and sampling was continued up to 10.5 hours for each  
25 drug. Now, note that here we had to triple our effort

1 | because we needed skin site corresponding to each of these  
2 | products at each sampling point, which meant accommodating  
3 | about 27 sites on both arms.

4 |               So, we had only 2 subjects in our study. In  
5 | our hands concentrations of Avita were lower compared to  
6 | Retin-A and Spear products, and the question is, how did we  
7 | compare with Utah?

8 |               This is the Utah study which you saw earlier.  
9 | They had 49 subjects in their study. Their profiles were  
10 | well defined. Differences or similarities were clear, and  
11 | concentrations of Avita were lower than Retin-A and Spear  
12 | products.

13 |               Now, I want to emphasize again the purpose of  
14 | Utah study was determination of bioequivalence or  
15 | inequivalence, while the purpose of our study was to  
16 | determine the feasibility of conducting a DPK study in a  
17 | new laboratory. I think even with two subjects we were  
18 | able to achieve that goal.

19 |               So, when we compared the DPK parameters, you  
20 | can see that with respect to Cmax there were some  
21 | differences for each product between the two studies. Tmax  
22 | for Avita was delayed compared to the two products in our  
23 | study. And the AUC was lower compared to Retin-A and Spear  
24 | in our study, which compared very well with the results  
25 | seen in the Utah study.

1           Can we draw any inference with this limited  
2   number of subjects? Yes. We did see a trend in our study  
3   that was similar to the Utah study. You can see that at 1  
4   hour stratum corneum concentrations of Retin-A and Spear  
5   products were higher than those of Avita, and the same was  
6   the case for AUCs where they are higher for Retin-A and  
7   Spear compared to Avita. And this correlated again well  
8   with the Utah study. So, you can see here that differences  
9   or similarities in the formulations can relate with the DPK  
10   parameter such as AUC.

11           I also want to touch upon the time line. It  
12   took us about 1 month to go from phase 1 to phase 2, and  
13   another month to go from phase 2 to phase 3. I want to  
14   point out that at phase 1 we were totally inexperienced.  
15   We were uncomfortable with the skin stripping technique.  
16   However, with practice we gained more experience, and at  
17   this point we were comfortable with the skin stripping  
18   technique. We were confident about our results.

19           So, to conclude, the DPK approach has the  
20   potential to detect formulation differences in topical  
21   products. The skin stripping methodology can be easily  
22   transferred, and results are reproducible, and finally, the  
23   time and resources needed for the transfer of skin  
24   stripping methodology and the DPK follow-up are reasonable.

25           I want to end with acknowledgments. The team



1 from the Office of Testing and Research. Robbe Lyon was  
2 responsible for the protocols. Everett Jefferson and Bob  
3 Hunt were responsible for the HPLC analysis. Everett also  
4 helped me with the skin stripping, and he was pretty good  
5 at it. Tapash Ghosh from OCPB also helped us in skin  
6 stripping. And I want to acknowledge Dale Conner and  
7 Barbara Davit for their support while I was working on this  
8 project. Last but not the least, I also want to thank Dr.  
9 Pershing for useful discussions, and finally, thank you all  
10 for your attention.

11 DR. LEE: Thank you, Mamata. We have time  
12 maybe for a couple of questions.

13 DR. MEYER: I noticed on your phase 1 post-  
14 dose, was this early on while you were just learning?  
15 Because your variability is tremendous, certainly compared  
16 to Utah. You have CVs of 100 percent, 50 percent, whereas  
17 Utah is down below 10 percent for stripping 2 through 10,  
18 for example, and you're bearing all that variability in a  
19 single number that comes out as a subject value. So, you  
20 hide a lot of the variability when you take the sum of all  
21 nine strips. Was this an early-on study?

22 DR. GOKHALE: Yes. In fact, the very reason I  
23 put it up was to show how did we do, even in the beginning.

24 DR. MEYER: How did you do at the end in terms  
25 of variability?

1 DR. GOKHALE: How did I do at the end? Okay.

2 DR. MEYER: I mean, in terms of variability.

3 If you compared Utah.

4 DR. GOKHALE: Well, our variability was  
5 reduced. It was manageable. I didn't have enough time to  
6 put all the numbers, but I can say that we had a better  
7 control over the variability.

8 DR. MEYER: But as good as Utah?

9 DR. GOKHALE: Yes. Within 20 percent.

10 DR. LEE: Are you satisfied, Marv?

11 DR. MEYER: No.

12 (Laughter.)

13 DR. MEYER: But I received the answer I wanted.

14 DR. LEE: Mamata, I just want to get a sense  
15 for the timing of these experiments. Did you do yours  
16 after the results of the two studies were made available to  
17 you?

18 DR. GOKHALE: No. Actually we started after  
19 Dr. Pershing's study was completed, and I think Dr. Franz's  
20 study was ongoing at the time.

21 DR. LEE: Thank you. Okay, thank you very  
22 much.

23 Dale?

24 We have two committee members who are supposed  
25 to be calling in but they are not here yet.

1 DR. CONNER: I'm just going to show a few  
2 slides to start off the discussion period.

3 As you've seen from a previous couple of  
4 studies, we've had two very experienced investigators in  
5 laboratories come in and present data, as well as our own  
6 attempts to get one of the versions of this method up in  
7 our lab. When I saw the results from at least the two  
8 expert laboratories, I was, to say the least, a little  
9 perplexed. Perhaps even alarmed would be a closer  
10 description because although the results of both studies  
11 showed what we expected, the two NDA products, which we  
12 knew from previous clinical work were not clinically  
13 equivalent, they showed them different, the results went in  
14 different directions. The fact that they showed a  
15 difference didn't comfort me in the fact that they got such  
16 different directions.

17 Dr. Pershing's Utah data seemed to go in the  
18 direction we expected from the clinical results, and Dr.  
19 Franz's didn't. They went in the opposite direction. So,  
20 I was a little concerned. Of course, the group in the FDA  
21 was scratching our heads as to what could have possibly  
22 caused this. We've had some discussions with Dr. Franz and  
23 Dr. Pershing about what could possibly have accounted for  
24 these such dramatic differences.

25 It's important to note or to go over what has

1 | already been pointed out, and this is our hypothesis. And  
2 | we did a little quick and dirty experiment that may  
3 | illustrate this.

4 |           We think that a very, very important factor in  
5 | explaining this is the actual stripping technique that both  
6 | of these investigators used, because as they both  
7 | described, it's somewhat different. The Utah study tends  
8 | to strip pretty much the exact area of application. They  
9 | don't go outside that area to any great degree. Dr. Franz,  
10 | on the other hand, has chosen to apply to a somewhat larger  
11 | area, but also strip a considerably larger area around the  
12 | area. How could this possibly affect the results?

13 |           Now, first off, before I show this kind of  
14 | quick and dirty experiment, whenever I name specific  
15 | products and seem to be relating their characteristics, I  
16 | always get angry calls from manufacturers saying I've  
17 | somehow maligned their product or something, and I want to  
18 | add a disclaimer that the following results or illustration  
19 | is in no way a comment on the quality or appropriateness of  
20 | any product that we happen to mention. This is simply an  
21 | illustration of different properties, and I'm not saying  
22 | whether those are good or bad properties in clinical sense.  
23 | So, I'm not trying to malign anyone's product.

24 |           The laboratory, the OTR folks, did a little  
25 | experiment that goes as follows. They took filter paper

1 and they put 10 microliters of each of these three  
2 products, Avita, Retin-A and tretinoin.

3 And I'd like to point out that Avita and Retin-  
4 A are separate NDA approved products through our previous  
5 work, and what you've heard today, you realize that they  
6 are not considered bioequivalent based on clinical grounds,  
7 and each of them was approved under its own NDA with its  
8 own labeling. The third, the tretinoin gel from Spear is  
9 an ANDA approved product that was approved on the basis of  
10 equivalence to the Retin-A reference product. So, that's  
11 important to point out.

12 Our expectation going into this, from all the  
13 data we have as far as clinical data, was that the Retin-A  
14 and the Spear tretinoin would come out equivalent, and we  
15 did not expect the Avita to come out equivalent.

16 But how could differences in these products  
17 actually be affected by differences in stripping  
18 methodology? Now, the hypothesis is that as has been  
19 stated, the Retin-A and Spear are Q1 and Q2, where the  
20 Avita is not. Perhaps they had some different properties  
21 that would account for why you got more drug in Dr. Franz's  
22 technique of stripping and not in the Utah study.

23 This is a very, very crude illustration of  
24 different properties. As I said, it's not supposed to  
25 malign anyone's product or say one is superior or inferior.

1                   But the lab in OTR in FDA just put out 10  
2   microliters on filter paper. As you can see, these are the  
3   two circles of the Spear and Retin-A products and this is  
4   the Avita. Now, first off, time points. They took  
5   pictures of these with a scale down below -- and this was  
6   drawn by the person that took the pictures -- to try and  
7   say, do these have different physical properties that would  
8   account for differences that would be picked up by the two  
9   methods. As you see, the comment of the person who did  
10   this was that the air in the lab at the time was very dry  
11   and of course you're putting out filter paper, which isn't  
12   really skin. So, that's why this is very crude.

13                   But already the Retin-A and Spear, which are  
14   the equivalent products and Q1 and Q2, seem to be a little  
15   dried out. They seem to be staying in the same place,  
16   whereas the Avita is starting to spread around the edges.

17                   We look at it at 15 minutes. These look pretty  
18   darned dry to me, and still within their original  
19   application period. They haven't spread out. Yet, the  
20   Avita is still spreading. If you paid attention to the  
21   scale, the circle is now a little bit bigger than it was at  
22   2 minutes. If we went to 30 minutes, again it gets a  
23   little fuzzy around the edges, but it's larger yet in its  
24   circumference. These are still the same. Kind of  
25   thoroughly dried by now. And finally again, even harder to

1 | see, it isn't picked up well by the camera, but even the  
2 | spot is spread a little bit further.

3 |           This is obviously filter paper. On the skin it  
4 | may spread more or less, but it shows a difference in  
5 | physical properties of these two non-Q and Q products.  
6 | Think, if you will, the hypothesis might be that because  
7 | the Avita spreads out into the surrounding area beyond the  
8 | application point, that Dr. Franz's stripping method of  
9 | taking extra area around may actually pick up more drug  
10 | than the method that's performed at Utah, which simply  
11 | strips the actual application area. So, that may account  
12 | for why the exposure of drug and the eventual absorption  
13 | into that stratum corneum that's harvested is different for  
14 | the two methods. Just something to think about, when  
15 | you're trying to figure this out as we did, why two  
16 | investigators with somewhat different techniques got  
17 | different results, you may want to take this into account.

18 |           DR. LEE: I don't know whether it would be  
19 | appropriate to ask you this question. What is the action  
20 | item?

21 |           DR. CONNER: This is an update on available  
22 | data. We've had previous advisory committee meetings on  
23 | this. Trying to get some kind of read by the committee now  
24 | with the updated data about where we should go with this  
25 | technique. When I look at the various results from

1 different very expert laboratories, I'm inclined to say  
2 that there may be some doubts in committee members' minds  
3 about whether we should continue with this. We have a  
4 draft guidance out. Should we continue that draft guidance  
5 or should we pull back and perhaps reassess where we're  
6 going with this technique, and perhaps look at some of the  
7 other techniques, of which Dr. Franz just mentioned a few,  
8 perhaps in place of this.

9           The committees in the past -- and you saw from  
10 my slides we've had a number of committee meetings on this  
11 -- have come up with some feeling based on existing data  
12 about whether we should continue, whether we should pull  
13 back or whether we should just totally abandon this and try  
14 to develop some other techniques to potentially replace it,  
15 or to perhaps do better than we are doing with just  
16 clinical equivalence trials. Or perhaps to say the  
17 clinical equivalence trials are probably the best that we  
18 could do.

19           DR. LEE: It seems we are kind of doing a skin  
20 stripping experiment in this committee. Never mind.

21           (Laughter.)

22           DR. LEE: Anyway, there are three issues before  
23 the committee. Yes?

24           DR. WILKIN: I think just to amplify from the  
25 agency's perspective Dr. Conner's comments, at the last



1 joint meeting of the two committees, the Pharmaceutical  
2 Sciences Advisory Committee and the other committee that is  
3 very much interested in this, the Dermatologic and  
4 Ophthalmic Drugs Advisory Committee, that Dr. Hussain  
5 mentioned at the last meeting, and Helen Winkle confirmed  
6 in a discussion while the meeting was going on, that  
7 ultimately before actually moving ahead with DPK and sort  
8 of confirming it as the method, that we would want to have  
9 a joint committee meeting with all of the data. I know  
10 that the standard for all of the data means that you would  
11 have more than you had this time, which were just a couple  
12 of abstracts.

13 I think really the intent here is to get a read  
14 on whether this really is where we need to go with it. I  
15 think Dr. Franz very eloquently pointed out that we may  
16 have been overlooking some opportunity costs in not really  
17 considering alternative methodologies. Dr. Conner pointed  
18 out that we have been with this from 1989. I didn't  
19 realize it was 1989. It's painful to hear that it was even  
20 earlier than what I thought.

21 DR. CONNER: Makes you feel kind of old,  
22 doesn't it?

23 DR. WILKIN: It makes me definitely feel old.

24 You know, I think it's really whether we want  
25 to devote the resources to having the really full, complete

1 joint committee meeting that has all of the data, and we go  
2 through this, or whether you think this is the time to pull  
3 the plug and move on to other methodologies.

4 DR. HUSSAIN: I agree with what Jonathan just  
5 mentioned. At the joint committee we had -- and many of  
6 you were there -- a very negative reaction to this method  
7 from the Derm Committee members, and the phrase "You're  
8 beating a dead horse" was used, and it's in the minutes.

9 One of the objectives here is to have this  
10 committee discussion and see whether it's worth even going  
11 to the next step of a joint committee meeting. I don't  
12 want to keep going to that committee and getting those type  
13 of comments back.

14 DR. LEE: That's why I said that we have the  
15 experience of a skin stripping experiment. We're down to  
16 the 10th stripping.

17 DR. WILKIN: Maybe a clarification. I think  
18 the message that came out of that last joint advisory  
19 committee was a very negative message, but I don't think it  
20 came solely from the dermatologists. I recall Dr. Venitz  
21 and I actually looked up rapidly here where he indicates  
22 that I think in the final analysis, and probably going to  
23 agree with those clinicians -- I think there were other  
24 members of the PSAC that were seeing the same sort of  
25 thing. I don't really think this is a dermatologic

1 clinical viewpoint versus a more data-driven kind of  
2 clinical pharmacology kind of view.

3 I don't feel any schizophrenia. It works both  
4 in dermatology and clinical pharmacology, and I have to say  
5 that I think this all fits together. I think I hear both  
6 committees essentially saying the same sort of thing.

7 DR. LEE: Very well. Now the stage is set for  
8 the discussion. We have until 10:45 to come to some kind  
9 of a solution. I think the agency does look to this  
10 committee for some guidance, and there are three issues. I  
11 invited Dr. Doull to, more or less, lead the discussion.

12 DR. DOULL: Mr. Chairman, let me start off by  
13 asking Dr. Pershing. You had in one of your figures a  
14 biphasic curve where you were talking about the absorption,  
15 topical drug delivery it's entitled. You were talking  
16 about the absorption through the stratum corneum and down  
17 through the other layers. That first thin layer there, for  
18 this particular drug how many strips do you think that  
19 would be?

20 DR. PERSHING: You always get a concentration  
21 gradient through the skin with any drug, in any vehicle.  
22 It's just the steepness of that concentration gradient.  
23 One of the important aspects in DPK is to make sure you've  
24 adequately removed residual drugs so you're actually  
25 capturing that concentration gradient.

1                   What was the other question about that?

2                   DR. DOULL: As I read through this guidance, it  
3                   seems to me there are a number of questions which are  
4                   difficult for me to answer. One of them is the predictive  
5                   value of this whole procedure in predicting the clinical  
6                   effect, say, of an antifungal or whatever. They're not  
7                   really dealt with a lot in the guidance. You need some  
8                   kind of assurance in there that this procedure, if you do  
9                   it, will in fact give you the right answer.

10                  I looked back at what we said in the July  
11                  meeting and I don't find a lot of assurance there either.  
12                  I guess what concerns me is how do you really know, when  
13                  you go from drug to drug and person to person, and if you  
14                  did this on the back or if you did it in a child -- and we  
15                  talked last night about diseased skin. How do you really  
16                  know that this system is really giving you the right  
17                  answer?

18                  DR. PERSHING: Over the years, the different  
19                  advisory committees have consistently challenged the FDA on  
20                  the guidance in that take specific examples where there are  
21                  clinical efficacy trials done and do DPK, show us where you  
22                  fail a clinical study and show us what DPK with those  
23                  products do. I think this came from Dr. Wilkin actually  
24                  who was one of the proponents of this even within the FDA.  
25                  And take one where the clinical studies pass but DPK fails,

1 and keep going back and forth.

2 We have done those, and in every successive  
3 advisory committee we've shown that data. We've shown it  
4 in five different drug classes, and now this is the final  
5 coup de grace, so to speak, because the FDA had a very  
6 specific example where similar and dissimilar products,  
7 approved by ANDA versus NDA methods, where DPK could be  
8 evaluated. According to Dr. Lamborn's comment, I think  
9 it's very appropriate that it should be evaluated in  
10 products that have been evaluated in a clinical study, and  
11 we've done that.

12 I've also done it in diseased skin. I've also  
13 done it in a psoriasis study, where if you compare one  
14 elbow to the other with a generic versus a reference  
15 product and you follow the clinical efficacy, would it  
16 agree? And the answer is yes. I've done it in tinea  
17 pedis. Does it work? Yes, even in diseased skin.

18 DR. DOULL: If you did it on the upper forearm  
19 or on the back?

20 DR. PERSHING: Well, in tinea pedis, of course,  
21 we used the plantar surface of the foot to collect DPK from  
22 the diseased site. In psoriasis, we used the elbows. So,  
23 it does work, in diseased skin, in healthy skin.

24 I would caution you about diseased skin.  
25 Diseased skin is not an effective barrier, and it will

1 diminish differences between drug products where healthy  
2 skin will not. When you have an active, ongoing disease,  
3 you do not have a discriminating barrier.

4 Second point. There are many drug classes for  
5 which there are no pharmacodynamic surrogate markers.  
6 Antivirals are a case in point. The clinicians can't even  
7 agree what the clinical endpoints should be. What do you  
8 do in those cases? You have a self-resolving disease,  
9 herpes simplex virus disease. They're self-resolving in  
10 cold sores in two weeks. What are you going to do there?  
11 They're difficult, difficult studies to perform.

12 Do you want to do a 21-day study? If you think  
13 1 day has variability, imagine 21. Those are issues that  
14 have to be considered, I think, and it's a cost/benefit  
15 ratio.

16 DR. DOULL: The other thing. In your studies  
17 you compared area under the curve and Cmax and Tmax and so  
18 on. I would think for an antifungal, for example, if it's  
19 a threshold phenomenon and you don't get above the  
20 threshold you're not going to kill those. It's not going  
21 to work, no matter how big the AUC is.

22 I was looking at your data as whether Cmax or  
23 area under the curve or Tmax, whatever is most predictive  
24 in this system, and I'm not sure I can sort that out from  
25 your data.

1 DR. PERSHING: Both turn out to be important,  
2 which is why the FDA still uses both parameters to make  
3 their assessment. That's what I've concluded. Extent is  
4 very important, and extent will dictate the shape of the  
5 curve.

6 DR. LEE: I'd like to remind us that we are  
7 addressing these three issues on the screen.

8 I understand there's a member on the phone.  
9 Who's that? Somebody called in but is not hearing us.

10 Bill?

11 DR. BARR: It seems to me, as we were  
12 evaluating these data, this is very much like we do in any  
13 bioequivalence study in the sense that we're looking at  
14 blood levels and whether the area under the curve has some  
15 clinical relevance may depend upon the drug. What we're  
16 really looking at is some measure of how it's getting to  
17 the biophase in some way that we can evaluate it  
18 comparatively.

19 What I saw today I thought was two remarkably  
20 reproducible within the study site pieces of data, which is  
21 as good as we get from most blood level studies, I think.  
22 We're looking for some method in which we at least can  
23 compare things in a reproducible way.

24 My question is that the FDA did a very quick  
25 study with a very limited number of subjects in order to

1 | evaluate the other two studies. It seems to me that the  
2 | real key in this is just how good you are at this. How  
3 | long did it take you in order to be able to get  
4 | reproducible data? Is that a major factor in whether we  
5 | ought to use this as a means between different  
6 | laboratories?

7 |           It's a little bit like when we, for example, do  
8 | CACO II cells. We find out whenever you look at one  
9 | laboratory and compare it to another, the results can be  
10 | three or four-fold different. But if you standardize it  
11 | within a laboratory then it becomes reproducible. Is that  
12 | what we're dealing with here?

13 |           DR. PERSHING: I've taught people to perform  
14 | stratum corneum harvesting or skin stripping in two days.

15 |           The important thing here is that you have an  
16 | immediate feedback system that helps you. In other words,  
17 | I make them weigh the skin strippings on a sensitive  
18 | balance, and you'd be amazed at when they're doing this how  
19 | they learn to do it reproducibly when they weigh it and  
20 | find out what the immediate result is.

21 |           The weight in and of itself is a great way to  
22 | learn how to collect the stratum corneum harvesting in a  
23 | very consistent manner. It doesn't require any special  
24 | tools other than the same person collects every single time  
25 | point from the same subject in the study. That's very



1 critical. If you're going to have multiple investigators  
2 collecting the stratum corneum with these adhesive discs  
3 that they have to be validated to be reproducible between  
4 themselves as well as within themselves.

5 I kind of fashion that after collecting blood  
6 samples. When phlebotomists first start, they don't have  
7 very good quality blood samples either. So, practice  
8 always makes perfect. You have to be trained and you have  
9 to validate and document that you can do it well.

10 DR. BARR: It's also a little bit like even the  
11 variability we had within in vitro dissolution, which is as  
12 about as simple as you can do, but still it was necessary  
13 to have some kind of external comparator that we could use  
14 to compare laboratories and get results. It seems to me  
15 that maybe that's the way that we have to go in something  
16 like this, is to find some kind of a comparator that you  
17 can use between labs and maybe within the lab with  
18 different investigators.

19 DR. LEE: Yes, I want to give the microphone to  
20 Steve and then I want to go around the committee and see  
21 what does each member think.

22 DR. BYRN: Dr. Pershing, do you have -- and  
23 maybe this is for everybody, and I know we're kind of out  
24 of order -- do you have the slides from Dr. Spear, a set of  
25 slides from him? Because he's stating things that are

1 quite a bit -- if you look on page four of those. And I  
2 know Dr. Spear is going to speak later, I guess. But what  
3 you're saying seems quite a bit different from what he's  
4 saying. Maybe you could just explain to us the difference.

5 For example, he's saying that two top DPK  
6 research sites got contradictory results, and we can't  
7 comment on other classes of dermatologic drugs. And SS is not  
8 rugged.

9 Then in the next slide he's saying, comparative  
10 these clinical trials is difficult to perform, highly  
11 variable and insensitive. Spear Pharm has performed four  
12 400-patient clinical trials. Skin stripping is as hard as  
13 clinical trials. And then he says clinical trials are the  
14 only confirmatory studies with drugs that act below the  
15 stratum corneum.

16 So, I don't know whether you can comment on  
17 all those, but there seems to be quite a bit of difference  
18 between what you're saying and what he's saying.

19 DR. PERSHING: First and foremost, I think it's  
20 important that both study sites found that the Bertek and  
21 the Ortho product were bio-inequivalent. It's very  
22 important.

23 Secondly, about the 400-patient clinical trial.  
24 In patient clinical trials we never know what the  
25 intrasubject variability is. You can't document precision

1 or accuracy. And an objective method like DPK you can.  
2 You know what your intrasubject variability is, and that  
3 dictates how many people you have to evaluate to achieve  
4 any statistical significance. That's a great benefit.

5 DR. BYRN: Well, what about the contradictory  
6 part? Do you agree that it is contradictory?

7 DR. PERSHING: I think the key there, to be  
8 quite honest, is that it would have been most beneficial in  
9 comparing these two studies if all three products had been  
10 evaluated. I think what was important is that when your Q1  
11 and Q2 are different, we both saw in these products that  
12 they were bio-inequivalent. It would have been very  
13 interesting to know how the Spear product performed in Dr.  
14 Franz's lab in comparison to the other two products as  
15 well.

16 DR. BYRN: So, you're thinking that we need to  
17 do more work, some additional series of studies to answer  
18 whether they're truly contradictory or not.

19 DR. PERSHING: I think that in any study that's  
20 done, it would be very beneficial to have two products that  
21 have been shown to be similar in a clinical trial and look  
22 at DPK. I think it's also interesting to have the opposite  
23 view, where they failed a clinical trial and they showed  
24 DPK results in the same trend.

25 I think that was a very important step that Dr.

1 Wilkin encouraged us to do. And I think it proves the  
2 point that DPK can discriminate between products that are  
3 physically, chemically, or clinically bioequivalent, or  
4 aren't equivalent. That's the true test.

5 How many studies do you need to do that? We've  
6 done an antifungal study, an antiviral study, an  
7 antibacterial study, and now a retinoid study. What they  
8 generally show is that you can pass a clinical study and  
9 you might fail DPK. But in this case DPK and clinical  
10 trials agree.

11 Why is that so? It's because clinical  
12 endpoints are not always good indicators of bioequivalence.  
13 What we have found in our own research is that with topical  
14 drugs we generally deliver lots more drug than we actually  
15 need to get the effect we desire, and that by delivering  
16 too much drug you're on that plateau of response. So,  
17 clinical and biological markers often don't differentiate  
18 between products.

19 DR. LEE: I see that Dr. Franz wants to make a  
20 point.

21 DR. FRANZ: Yes. Just one comment. I think it  
22 would be important to look at the clinical data on the  
23 comparison of Avita to Retin-A because, as I read the  
24 summary basis of approval, the statistical section was a  
25 nightmare. The results depended on which studies were

1 | thrown out. There was a problem. It was a multicenter  
2 | study but there was one investigator common to two  
3 | multicenter studies. And for regulatory reasons, not as I  
4 | understand it scientific reasons, the study was thrown out.  
5 | Whether the two drugs gave the same answer or different  
6 | answers depended on which was thrown out.

7 | I think we need to look closely at this gold  
8 | standard we're using for comparison with DPK. I was hoping  
9 | perhaps someone here would review the basis upon which  
10 | we're saying that the Avita is inequivalent.

11 | DR. LEE: I would like to ask the committee  
12 | members if there are any questions for these three  
13 | speakers. Also we have accessible to us Dr. King and Dr.  
14 | Wilkin to provide some advice so we can address these  
15 | issues in the next 15 minutes. Bill?

16 | DR. JUSKO: When one is doing traditional  
17 | bioequivalence studies measuring plasma or blood  
18 | concentrations, the sample that is taken is homogeneous and  
19 | reasonably representative of all the blood that's  
20 | circulating. My big concern with what I've seen this  
21 | morning is the fact that the sampling is so susceptible to  
22 | not artifacts per se, but all sorts of variation.

23 | I would find more credibility in the sampling  
24 | technique that takes a larger portion of the tissue. It  
25 | seems like if you're only focusing on a lesser piece of the

1 | tissue and not recovering as much of the drug that was  
2 | administered, the results shouldn't be as representative of  
3 | what is really being absorbed.

4 | I think the jury is out on this whole  
5 | technique. More evaluation needs to be done in regard to  
6 | sampling issues.

7 | DR. LEE: Art?

8 | DR. KIBBE: I'd like to go back to what Steve  
9 | first went after, and I still can't let go of, and that's  
10 | when we do an evaluation of two things. And if I say that  
11 | Manute Boll is taller than Bugsy Moggs, and you turn around  
12 | and tell me that Bugsy is taller than Manute, and we both  
13 | agree they're a different height, I still don't like that  
14 | outcome. I think there ought to be at least rank order. I  
15 | would have even been happier if the two studies, one had  
16 | said they're different and the other had said they're the  
17 | same but they were in the same rank order, then I would  
18 | say, okay, what kind of sensitivity problems have we got.

19 | But when the techniques can be used in two  
20 | different labs doing quite reputable, representative work  
21 | and come up with absolutely opposite responses, I agree  
22 | with Bill. The jury is still out in my mind. I don't think  
23 | we've got a robust test.

24 | I don't necessarily think that because our  
25 | clinical endpoints are not robust we should go to something

1 else that is also not robust. When we're looking for a  
2 product that cures a condition and that's really the  
3 ultimate goal, we have to stick with that until we've got  
4 something that's very predictive of the product's ability  
5 to work in a clinic.

6 DR. LEE: Kathleen?

7 DR. LAMBORN: I'm not sure I disagree with the  
8 conclusion, but I do think, in making the decision, you  
9 need to remember that we're just trying to talk about are  
10 they equivalent or are they not equivalent. If you measure  
11 two different things, the fact that you get that they  
12 disagree, but in one case it goes higher and in one case it  
13 goes lower -- in other words, if the results that were  
14 shown relative to that filter paper turns out to be the  
15 rationale for this difference, then if someone tells me  
16 that one product spreads out and ultimately it gets just as  
17 much to the site as the other one does, then they may be  
18 equivalent in efficacy but by the technical definition of  
19 bioequivalence they aren't equivalent because they aren't  
20 behaving in exactly the same fashion. So, the fact that  
21 the small measure tells me it's less and the bigger measure  
22 tells me it's more, I don't think necessarily disqualifies  
23 the technique.

24 Then if we get to some of these other issues,  
25 like, well, what if the primary site of action is

1 different, and what's happening here doesn't represent  
2 what's happening some place else, then I get a little bit  
3 less comfortable.

4 I think one of the things I was very interested  
5 in was the comment that using normal skin would be more  
6 sensitive detecting differences than diseased skin, because  
7 that's certainly been one of the issues that's come up many  
8 times in the past. I'd have to defer to others as to  
9 whether they're comfortable that that in fact is a robust  
10 statement.

11 I guess the other thing is that I'd like a  
12 clarification. The draft guidance, if it were to be  
13 proceeded with, would mean that this would be one of the  
14 methods available, stated as a preferred method, and why is  
15 it that we haven't been looking at some of these other  
16 methods that were mentioned this morning. I'd like to pose  
17 that as a question.

18 DR. LEE: Are you soliciting an answer?

19 DR. LAMBORN: I think from the agency.

20 DR. CONNER: The guidance is out as a draft and  
21 has been out as a draft for quite a while. Perhaps one of  
22 the things that we would look for from the committee is  
23 what should be the future of that guidance.

24 What I've heard a couple of times today, which  
25 I at least in part agree with, is that when you look at the



1 results of these two labs, I'm not comforted at all by the  
2 fact that the overall answer was that they were not  
3 equivalent. I too was disturbed by the fact that they went  
4 in different directions. I think we have a hypothesis why,  
5 and I suppose you could take that hypothesis and confirm it  
6 and say, okay, well, either Dr. Franz or Dr. Pershing  
7 should really alter the way they do things to get more  
8 realistic or true data. But then again the question has  
9 been brought up, what is the gold standard that we're  
10 comparing it to.

11 I guess one of the things the committee should  
12 decide, and I heard some doubts about this, what I'm  
13 interpreting is that DPK, this technique is not there yet.  
14 But the question is, do you see any potential to be ever  
15 there, ever acceptable. Or is it something that we should  
16 just take a step back and look at other things that might  
17 be much more suitable to perform to achieve our goals in  
18 this. Is this truly, as a previous committee said, beating  
19 a dead horse, and that even if we got a lot more work in on  
20 this, we probably never would be much further than we are  
21 now?

22 Should we, say for example, withdraw the  
23 guidance? Should we go back into research mode, look at  
24 this and everything else and try and bring something  
25 forward and develop something that might be a bit more

1 suitable, both from a cost-effective standpoint and being  
2 equal to or superior to what we're doing now.

3 DR. LEE: Ajaz?

4 DR. HUSSAIN: I just wanted to give some  
5 information for Dr. Lamborn's question in terms of will  
6 this be the only method or is this one of several methods.

7 Traditionally in the bioequivalence, world we  
8 tend to define one preferred method and stick to that.  
9 There are many reasons for that. That has been the  
10 traditional approach. At the joint committee meeting, I  
11 had proposed the possibility of alternate methods, but in  
12 the bioequivalence world, for legal reasons we prefer to  
13 have just one method.

14 DR. LEE: Dr. Wilkin?

15 DR. WILKIN: I really hadn't heard the proposed  
16 difference between the Franz-Pershing methodologies, the  
17 explanation for that, until now or the filter paper study.

18 One attractive hypothesis is the spreadability,  
19 but an alternative hypothesis would be that the two that we  
20 saw on the right had more volatile components, that those  
21 volatiles went off fairly rapidly, and that the active  
22 ingredient went out of solution. We have to remember that  
23 the active has to be in solution before it's going to be in  
24 that thermodynamic gradient that is going to move it across  
25 the barrier. I think actually if the volatiles are the

1 key, then maybe the Franz method is showing what really  
2 happens.

3 If I could just follow up with a very brief  
4 thing. I think validating a new method actually has three  
5 stages, and the first stage is, can you get reproducibility  
6 within one laboratory. I think we've seen that in the two  
7 laboratories they can reproduce their own method.

8 The second level of validation is, can someone  
9 else in another laboratory, maybe talking with another  
10 investigator, follow a recipe and come up with essentially  
11 the same kind of output. I think potentially that's what  
12 the FDA has shown, that using the exact same protocol that  
13 was used in Utah, that you can come up with very similar  
14 kinds of results. It's a small n, and there's some  
15 question about the variation in the outcome, but I think  
16 potentially it's achievable.

17 The third stage is the part that several of the  
18 members of the committee I think have been calling into  
19 question, that really hasn't been focused on, and that is,  
20 what in the end does it mean? I think in the end you can  
21 get through those first two levels of validation, and that  
22 only gives you a controlled artifact. You've got something  
23 that's kind of reproducible. Everyone can kind of get the  
24 same set of numbers. I think that they can get to that  
25 stage. The question is, what does the answer mean in the

1 end.

2 Dr. Conner gave sort of the pro and con. In  
3 the past he's been kind of on the supportive side, I think,  
4 for DPK. It's nice to see there's enough evolution toward  
5 neutrality that he can give both the pro and con sides of  
6 this.

7 I think it was Dr. Jusko raised the point about  
8 how well does the stratum corneum conform to our notion of  
9 a compartment. One aspect of the oral model, looking at  
10 blood AUCs, that just makes it an incredibly powerful  
11 predictive model is that it is a well mixed compartment.  
12 The stratum corneum is not mixed at all. The second piece  
13 that I didn't hear you say but I think you were alluding  
14 to, is that the blood is in equilibrium with the target  
15 organ, the concentration. That has enormous predictive  
16 potential, that model.

17 In this particular circumstance, we really  
18 don't know that there is an equilibrium between what is  
19 found in the stratum corneum, which in most of these  
20 disease states, as pointed out by Dr. Pershing, doesn't  
21 even really exist in diseased skin, the stratum corneum.

22 So, I think it's that third step. In the end  
23 you can get a number. It's probably going to be  
24 reproducible from lab A to lab B, but at the end of the day  
25 the real question is, does this conform to the grand

1 analogy? Does it really conform to the solid, oral dosage  
2 products and the AUC in blood? I think that's still a key  
3 unanswered piece.

4 DR. LEE: Thank you.

5 Marv?

6 DR. MEYER: It's very difficult, I think, at  
7 least for me, to make a judgment here because I hear  
8 different results but I hear different techniques. I think  
9 in order for this thing to work we'll have to have three  
10 labs perhaps. We have three now: Tom's, Lynn's, and the  
11 FDA lab. And the FDA lab would have to do more than two  
12 subjects. I'm not convinced that they've shown comparison  
13 to Lynn's or Tom's data.

14 And I think we need more drugs. Lynn says  
15 she's done additional drugs but I haven't seen the data  
16 personally. I'm sure she's published it and I was too lazy  
17 to look it up.

18 DR. PERSHING: And presented here.

19 DR. LEE: Anyway. Because the guidance, as I  
20 read it, says this guidance applies to antifungal,  
21 antiviral, antiacne, antibiotic, corticosteroid, and  
22 vaginally applied drugs. All I've heard about is one drug.  
23 So, I think it's difficult to say whether this guidance  
24 will work.

25 Maybe one of you could answer. Has someone

1 |     tried this technique with comparing a 20 percent lower  
2 |     dose? Can you detect a 20 percent difference?

3 |             DR. FRANZ: Yes.

4 |             DR. LEE: You can. Is it bioequivalent if you  
5 |     have just a --

6 |             DR. FRANZ: I think the data that I showed on  
7 |     the transdermal water loss had the two strengths of  
8 |     Retin-A, .01 and .025. We've done similar work with tape  
9 |     stripping. It's easy to differentiate doses.

10 |            DR. LEE: 20 percent, though.

11 |            DR. FRANZ: I've not gone that low, no.

12 |            DR. PERSHING: I've done plus or minus 25  
13 |     percent. In fact, the guidance request that you  
14 |     demonstrate dose responsiveness of the products you're  
15 |     interested in evaluating, specific to the drug, and  
16 |     actually we do plus or minus 25 percent. Depending upon  
17 |     the drug and depending upon the vehicle, you can either  
18 |     achieve plus or minus 25 percent, or plus or minus 50. It  
19 |     depends on the drug and the vehicle.

20 |            DR. MEYER: Does that mean you can tell the  
21 |     difference between plus 25 and minus 25?

22 |            DR. PERSHING: Yes.

23 |            DR. MEYER: But not 100 percent and 80 percent.

24 |            DR. PERSHING: Yes. It depends on the drug and  
25 |     the vehicle. And I'll say some drugs you can tell a

1 difference of plus or minus 25 percent of the marketed  
2 formulation. It's dose-responsive.

3 Some other drugs, however, you can only detect  
4 differences between plus or minus 50 percent, and that's  
5 because the marketed concentration is already pretty maxed  
6 out for what will go on the skin.

7 In general, DPK is dose-responsive, and I just  
8 published an article on triamcinolone acetonide, a  
9 corticosteroid, that showed .025, .1, and .5 percent, that  
10 DPK is dose-responsive and actually so is the  
11 vasoconstriction response.

12 DR. LEE: Last question.

13 DR. MEYER: One quick question for the chair.  
14 We have a couple of presentations on this topic at 11:00.  
15 Are we going to vote before we hear?

16 DR. LEE: Yes, we are. We're going to express  
17 an opinion.

18 Dale?

19 DR. CONNER: Just one point. In a way we were  
20 fortunate with tretinoin in that we had two NDA products  
21 where we actually had some comparative clinical data  
22 between them. Most of the products, even when they're  
23 multiple NDAs, it's not a question of whether they are or  
24 aren't equivalent. It's a question of whether anyone has  
25 ever actually studied that. So, one of the reasons why we

1 | went to tretinoin in these particular products was because  
2 | we already had data. Even though it's been criticized  
3 | here, we actually had some data that set up this clinical  
4 | gold standard.

5 |           A lot of the other topical products, even if  
6 | they exist as different NDAs, we just don't have the actual  
7 | data to connect them, either as equivalent or non-  
8 | equivalent. So, in a way we kind of lucked out with this  
9 | one in that we had the data.

10 |           DR. LEE: Okay. From my perspective the draft  
11 | guidance was drafted in 1995. So, the context upon which  
12 | this has been drafted has evolved. I just ask the  
13 | committee whether or not you are ready to address these  
14 | three issues. I think that we have to provide some  
15 | guidance to the agency on what to do with this. John?

16 |           DR. DOULL: Well, I think we're a lot closer to  
17 | being able to answer these three questions than we were in  
18 | July. I thought we might have a tentative yes for the last  
19 | question. Even though it's only two people, it's in the  
20 | right direction.

21 |           Clearly this is not sufficiently solid in order  
22 | to move ahead, I think. Dr. Conner has said we're going to  
23 | look at an alternate methodology and so on. I guess that  
24 | means it's an ongoing project and that as we get more  
25 | information about alternative methods and we develop more