

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF
THE ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

8:42 a.m.

Thursday, December 11, 1997

Maryland Room
Quality Hotel
8727 Colesville Road
Silver Spring, Maryland 20910

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P R O C E E D I N G S

(8:42 a.m.)

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2
3 DR. ZIMMERMAN: Good morning, ladies and
4 gentlemen. We'll get started. I'm Cheryl Zimmerman from
5 the University of Minnesota. It has been indicated to me
6 that I'm Acting Chair of this group today, so I'd like to
7 welcome you all here to the Advisory Committee for
8 Pharmaceutical Science.

9 Before we go any farther, Kimberly Topper will
10 read the conflict of interest statement.

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

15 Since the issues to be discussed by the
16 committee will not have a unique impact on any particular
17 firm or product, but rather may have widespread
18 implications with respect to entire classes of products, in
19 accordance with 18 U.S.C. 208, waivers have been granted to
20 each member and consultant participating in the committee
21 meeting. A copy of these waiver statements may be obtained
22 from the agency's Freedom of Information Office, Room 12A-
23 30 of the Parklawn Building.

24 In the event that the discussions involve any

1 other products or firms not already on the agenda for which
2 an FDA participant has a financial interest, the
3 participants are aware of the need to exclude themselves
4 from such involvement and their exclusion will be noted for
5 the record.

6 With respect to all other participants, we ask
7 in the interest of fairness that they address any current
8 or previous financial involvement with any firm whose
9 products they may wish to comment upon.

10 Thank you.

11 DR. ZIMMERMAN: With that, we'll start by
12 introducing ourselves around the table. We will start with
13 Dr. Williams.

14 DR. WILLIAMS: I'm Roger Williams. I'm Deputy
15 Center Director for Pharmaceutical Science in the Center
16 for Drug Evaluation and Research.

17 DR. O'CONNELL: I'm Kathryn O'Connell. I'm
18 substituting for Jonathan Wilkin who's the Division
19 Director of Dermatologic and Dental Drug Products in the
20 Center for Drug Evaluation and Research. I'm a medical
21 officer.

22 DR. STEWART: I'm Jim Stewart from the
23 University of Georgia and the College of Pharmacy. I
24 specialize in pharmaceutical analysis.

1 DR. MAYERSOHN: Good morning. Michael
2 Mayersohn, the College of Pharmacy, the University of
3 Arizona.

4 DR. GOLDBERG: Arthur Goldberg. I'm an
5 independent consultant to the Pharmaceutical Development.

6 DR. BRAZEAU: Good morning. I'm Gayle Brazeau.
7 I'm from the Department of Pharmaceutics at the College of
8 Pharmacy, University of Florida.

9 DR. BRANCH: I'm Bob Branch from the Center for
10 Clinical Pharmacology, the University of Pittsburgh.

11 DR. McGUIRE: Joe McGuire. I'm Chairman of the
12 Dermatologic Advisory Committee, FDA.

13 DR. ZIMMERMAN: Thank you.

14 Well, we'll start with an overview by Dr.
15 Williams.

16 DR. WILLIAMS: Okay. Thank you very much, Dr.
17 Zimmerman. I'd like to add my note of welcome to both the
18 committee, as well as a very nice attendance from the
19 audience who will help us in next two days on discussion
20 and consideration of a number of topics in the area of
21 pharmaceutical science.

22 The topic of pharmaceutical science I would say
23 is a very interesting and challenging set of topics for the
24 Center and for the agency and considers certain disciplines

1 such as medicinal chemistry, pharmaceuticals or
2 biopharmaceuticals, microbiology, and clinical pharmacology.

3 Now, to help me keep things clear, I tend to
4 divide those topics into topics of what I call safety and
5 efficacy of the drug substance versus product quality which
6 relates to the quality of the drug substance in the drug
7 product. You'll hear me allude to that distinction several
8 times in the course of my presentation, and you will also
9 see it explicitly stated in the course of the agenda.

10 Now, I will not review for the committee the
11 details of the agenda, but I will just point out that the
12 first topic, Biopharmaceutical Classification System, I put
13 in the category of product quality, as well as the second
14 one, locally acting drug products, dermatologic drug
15 products.

16 And then also narrow therapeutic index drugs,
17 and I might regard this as an important distinction, that
18 when we discuss this topic before this committee, we are
19 generally focusing on it from the standpoint of product
20 quality and not from the standpoint of safety and efficacy
21 of the active moiety, and I will allude to that again when
22 I talk.

23 Now then, if you look at the final pages of the
24 agenda beginning tomorrow, you will see a series of

1 clinical pharmacology topics which I put in the category of
2 safety and efficacy of the drug substance.

3 Now, with that very rapid overview of the
4 program, I will stop and not talk anymore about the program
5 specifically, leaving it up to the committee and the Chair
6 to move us through that.

7 I would like to turn now to our structure and
8 some of our processes in the Center very briefly. This is
9 the Center for Drug Evaluation and Research which is one of
10 three human product review centers of the agency, the other
11 being the Center for Biologics Evaluation and Research, and
12 the third being the Center for Devices and Radiologic
13 Health.

14 I would say many of the most critical drugs
15 available in the American marketplace and classes of drugs,
16 new drugs, OTC, generics come out of the Center for Drug
17 Evaluation and Research. It's a large center with
18 approximately 1,700 staff, and as you can see, it has three
19 main blocks of organization.

20 Over on the left, you see the Office of Review
21 Management, which is headed by Dr. Murray Lumpkin, and
22 which focuses on the new drug approval process, and I might
23 say specifically the safety and efficacy of the active
24 moiety working in the 15 Office of Review Management

1 divisions which function under the 5 offices of Drug
2 Evaluation.

3 Supporting that group and also supporting OPS
4 as well is the Office of Epidemiology and Biometrics.

5 Now, in the center is a group of offices that I
6 won't touch on in the course of this conversation, but they
7 provide very needed, important support to the Center's
8 mission.

9 And finally, over on the right you see the
10 Office of Pharmaceutical Science which comprises about 500
11 of the 1,700 FTEs in the Center. In that office you will
12 see the Office of Generic Drugs, the Office of Clinical
13 Pharmacology and Biopharmaceutics, the Office of New Drug
14 Chemistry, and the Office of Testing and Research.

15 In the next overhead, you will see a
16 magnification enlargement of the Office of Pharmaceutical
17 Science, and I will just touch briefly on its mission. You
18 can see the mission is color coded, and we're highly
19 sophisticated in terms of our graphics in OPS. These
20 colors represent the colors of the application jackets.
21 So, when you think red, you should think of chemistry.

22 The chemists, in the office in terms of their
23 function, appear in red, and you can see that there are
24 large collections of them in the Office of New Drug

1 Chemistry, as well as the Office of Generic Drugs.

2 You will see a blue color for clinical
3 pharmacology, kind of a pink color for biopharmaceutics,
4 and there's also an Office of Testing and Research which
5 focuses on pharmacology and toxicology research, as well as
6 several product quality issues.

7 Now, you might say that the Office of
8 Pharmaceutical Science focuses on product quality, and you
9 would certainly be right in that regard. I would say for
10 the first time the Center has brought together under one
11 management roof all product quality aspects of what the
12 Center regulates and that covers chemistry,
13 biopharmaceutics, microbiology. But it also has some other
14 very critically important functions to what the Center
15 does, and I certainly include in that pharmacology and
16 toxicology and clinical pharmacology as well.

17 Now, I will allude to this structure in the
18 course of the meeting. It's a structure that has been in
19 place for over two years now in the Center, and I would say
20 for the most part it was created at the direction of our
21 Center Director, Dr. Janet Woodcock. There are many
22 aspects of this picture we could talk about, but I think in
23 the interest of time I'll move on.

24 Now, here's another view, I might say, of what

1 I think the Office of Pharmaceutical Science does in part,
2 and it relates to a paradigm that we talk about frequently
3 in the office which relates to research to policy to
4 review. I would say a very strong commitment on the part
5 of the Center and the Office of Pharmaceutical Science is
6 the concept that good, publicly available scientific
7 information is the basis for our public policy, and that's
8 what's represented by research there. Our public policy is
9 represented primarily by guidances now that we offer to
10 regulated industry to help them get appropriate information
11 to us in the form of applications. And I'll be talking
12 about both the research and policy aspects of OPS in more
13 detail.

14 Obviously the most critical part of what we do
15 in the Center and in OPS is the assessment function, and
16 you'll see over on the right a series of disciplines that
17 contribute to the assessment of a new drug application or a
18 generic drug application in the United States for products
19 regulated by CDER.

20 Now, there are many other aspects of this
21 picture as well that we could talk about and you can see
22 there are strong links between what OPS does to the Center
23 itself, as well as to the agency, as well as to regulated
24 industry, as well as to the professional societies and

1 scientific disciplines that we work with extramurally, and
2 finally to other regulatory agencies and harmonization
3 activities in the world.

4 Now, as you saw in the prior slide, one of the
5 ways the Center has established over the last several years
6 to develop cross-cutting consistency in policy is via these
7 committees that we call coordinating committees. You can
8 see in my Center now that there are several of them, and I
9 won't go into all of them but the four that are colored
10 relate to what I call the scientific disciplines connected
11 with our mission. You can see that there's a Medical
12 Policy Coordinating Committee, a Chemistry, Manufacturing,
13 and Controls Coordinating Committee, a Biopharmaceutics
14 Coordinating Committee, and a Pharmacology/Toxicology
15 Coordinating Committee. I will focus on three of those,
16 excluding the Pharmacology and Toxicology Coordinating
17 Committee.

18 But the advisory committee should think about
19 each of these committees working intensively now on a
20 series of guidance documents that are designed to help
21 regulated industry come in with high quality, readily
22 reviewable applications.

23 I might argue that this advisory committee I've
24 looked to playing a strong role as we develop and finalize

1 these policy guidances. So, you will hear me allude to
2 them frequently in the course of my presentation and they
3 will also be alluded to in many of the subsequent
4 discussions over the next two days.

5 Now, this is a quick glimpse at the
6 Biopharmaceutics Coordinating Committee, and you might
7 think of this particular overhead as indicating its work
8 plan. The committee will certainly recognize that many of
9 these topics have been touched on before. Each one of
10 these little boxes and areas of focus should be thought of
11 as leading to a guidance, if it hasn't already happened. I
12 might point in certain cases, thanks to some prior
13 deliberations before this committee, we have already
14 created guidances that are finalized and out being used
15 hopefully in a very productive, valuable way by industry to
16 develop submissions for us. I might point out IVD-IR, In
17 Vitro Dissolution Immediate Release, and In Vitro
18 Dissolution Modified Release guidances that are now final,
19 out on the Internet, and are based in part on a discussion
20 that occurred before this committee when it was known as
21 the Generic Drugs Advisory Committee.

22 Now, biopharmaceutics, as you know, in terms of
23 our regulatory function focuses on bioavailability,
24 bioequivalence, and dissolution. You can see that there

1 are many topics in here of importance in those areas and
2 some will be talked about today and tomorrow. You will
3 hear Dr. Shah lead a discussion on locally acting drug
4 products for topicals, and there will also be a discussion
5 on population and individual bioequivalence.

6 This is the work plan for the Chemistry,
7 Manufacturing, and Controls Coordinating Committee. I'm
8 delighted to say that the membership of the advisory
9 committee is chosen to have disciplines on its membership
10 who can help us with our topics. For that reason, we have
11 chemistry represented here today. I'm delighted to see our
12 new member on the committee in that regard, and although we
13 are not talking particularly about chemistry topics today,
14 I certainly envision that happening in some of the
15 subsequent meetings.

16 I might point out to the committee that this is
17 a very broad-based work plan. It covers both preapproval
18 guidances, guidances that help in the generation of the IND
19 process and NDA and ANDA applications, and it also focuses
20 on the post-approval period, the period that we call the
21 PAC, in terms of generating information and supplements to
22 approved applications.

23 Now, the committee may see in this work plan
24 certain documents that I call the Q documents. Those Q

1 documents refer to guidance and policy documents that are
2 being harmonized in the International Conference on
3 Harmonization. This is a very important effort in the
4 three regions of ICH, namely the United States, Japan, and
5 Europe, to come to harmonized policies for application
6 submissions.

7 Again, I would regard assistance from the
8 advisory committee in this matter as very important to us
9 as this country considers its participation in ICH. The
10 committee may recall that in a prior meeting we did discuss
11 Q1A and Q3A, the stability and impurities document of ICH,
12 and that was a very helpful discussion as the agency came
13 to its conclusion about its position in the harmonization
14 process.

15 Now, you notice I've talked so far about the
16 two coordinating committees that focus on product quality,
17 Chemistry, Manufacturing, and Controls and
18 Biopharmaceutics, and I don't want to neglect microbiology
19 in that mixture. Microbiologists exist in the Office of
20 Pharmaceutical Science. They have a very important mission
21 relative to sterility assurance of certain products, and
22 they are part of the Chemistry, Manufacturing, and Controls
23 Coordinating Committee.

24 Turning now to safety and efficacy, I will say

1 this is somewhat the work plan of the Medical Policy
2 Coordinating Committee. You'll notice that we've created a
3 clinical pharmacology section of that committee that
4 focuses on topics pertinent to the discipline of clinical
5 pharmacology. I won't say anything more about this work
6 plan because you'll hear a great deal more about it from
7 Dr. Lesko, who's head of the Office of Clinical
8 Pharmacology and Biopharmaceutics in OPS, during the
9 deliberations on those clinical pharmacology topics in the
10 course of the next two days.

11 Now, leaving the world a little bit of science
12 and technical matters, which of course is where this
13 committee focuses, I will say that there's a process now of
14 guidance development in OPS and the Center and also
15 guidance implementation. I might argue that this is
16 becoming an increasingly important part of our business in
17 OPS and the Center, and that importance was magnified I
18 would say by the recently enacted FDA modernization
19 legislation. There's a terrific emphasis in that
20 legislation on the agency communicating to industry via
21 guidances on what is important and needed to know in an
22 application or supplement.

23 Now, OPS is trying to develop a very explicit,
24 value-added, useful approach to both guidance development

1 and guidance implementation. You've seen the guidance
2 development process for the three coordinating committees
3 where OPS has a primary role: CMC CC, BCC, and the
4 Clinical Pharmacology Section of MPCC.

5 There's also a guidance implementation process
6 which is quite critical to the way we work and it involves,
7 I would say, participation both from regulated industry, as
8 well as the review staff, which you see down at the bottom
9 with those two lateral arrows coming into the side, that
10 help us as we implement a finalized guidance.

11 Now, the reality of a guidance is it's a lot of
12 work to get it out and into the public eye, but it's
13 probably even more work to work with it with regulated
14 industry and the review staff. It takes a lot of training,
15 a lot of questions, and finally it takes updating. I will
16 show you later on a process of updating of these guidances
17 that I think will be critical to their success over a
18 multi-year period. Again, I would look to this advisory
19 committee as a way of helping us in the updating process.

20 Now, speaking specifically to that, this is a
21 paradigm for how this might work. Over on the left, I have
22 chosen as an example the work plan of the Chemistry,
23 Manufacturing, and Controls Coordinating Committee. After
24 these create finalized guidances, which can be a very long,

1 cumbersome process, the guidances come to the review staff
2 and to regulated industry to implement. There's a training
3 part of implementation. There's a management part of
4 implementation. There's a capturing of questions and
5 concerns about a guidance in the implementation process.

6 That in turn leads to an updating, and you can
7 see I have lessons learned about a guidance which I might
8 say are the lessons learned about its use over a multi-year
9 period.

10 Then down at the bottom, you see come strange
11 initials called CDDI and PQRI. CDDI stands for the
12 Collaboration on Drug Development Improvement, and PQRI
13 stands for the Product Quality Research Initiative. These
14 are a novel approach that OPS and the Center and others in
15 the agency are building to help the Center and regulated
16 industry build good information to support its public
17 policy.

18 Now, I'll talk a little bit more about the
19 collaborations in just a second, but the concept here in
20 terms of updating is that new scientific information will
21 be generated in these collaborations and elsewhere that
22 will help us as we update these guidances. Now, these are
23 not hypothetical collaborations. We are moving forward on
24 them, hopefully with due diligence and speed given resource

1 constraints, but the idea is to work in a collaborative way
2 to generate publicly available information to support our
3 public policy.

4 Again, in the areas of focus for the Office of
5 Pharmaceutical Science, I would look to this advisory
6 committee to be a key link in this updating process so that
7 as new information is generated to change perhaps a
8 guidance approach, it will be discussed before the advisory
9 committee and hopefully receive good public discussion and
10 input from the committee.

11 Is that the last one? Okay. I'm delighted.

12 I think you got a good picture of it. I might
13 mention that you will hear in the course of the talk,
14 further discussions about both CDDI and PQRI, perhaps with
15 a focus on PQRI, and there will be a public meeting of PQRI
16 in February of 1998 where we talk publicly, hopefully to a
17 broad range of stakeholders and constituencies, about the
18 missions, goals, and objectives of PQRI. There will be
19 further discussions perhaps later on in the year about
20 CDDI, and I look forward to discussing both of those
21 programs and projects with the advisory committee.

22 Now, I think I've stayed roughly within my time
23 frame, Dr. Zimmerman, and I apologize for going over a
24 little bit, but once again let me emphasize how delighted I

1 am to have you all here and to help us as we struggle with
2 I think some very challenging and exciting science and
3 technical issues.

4 Thank you.

5 DR. ZIMMERMAN: Thank you.

6 Well, we'll move to our first topic for the
7 morning and that is the Biopharmaceutics Classification
8 System. The moderator for this section will be Dr. Ajaz
9 Hussain. He's going to speak to us in the beginning here
10 on the Biopharmaceutics Classification System, guidance
11 development, and he's going to talk about general issues.

12 DR. HUSSAIN: Thank you, Dr. Zimmerman, members
13 of the advisory committee.

14 Lydia Kaus could not be here today, so I'm
15 going to speak for her also, so I've combined her
16 presentation with mine.

17 What I would like to present to you is our
18 thought processes that we have on the development of this
19 guidance of a Biopharm Classification System. I have
20 provided to you all the slides that I have used. Over the
21 course of this presentation, I will not be using all those
22 slides in my presentation, but I think the sequence is
23 there. If you have questions on data or information on
24 some of those slides, we can go back and discuss those.

1 I'm speaking here on behalf of the working
2 group, and I just want to acknowledge the contribution of
3 the core working group and members and others who have
4 contributed to this process.

5 When we started developing this guidance, we
6 kept in mind two things. This is an example of a research
7 to policy to review process, and research is used here to
8 establish causal links, understand mechanisms, and create a
9 framework for rational decision making. The policy that we
10 are trying to develop has to use this research and identify
11 areas of agreement between the links and our regulatory
12 decisions.

13 The hope here is to improve the way we regulate
14 and essentially improve the effectiveness and efficiency of
15 the review process by allowing reviews to focus on more
16 problem areas, and where we have agreement, we really would
17 not have to worry about it. In a sense, this becomes a
18 tool for industry, as well as the agency, to improve the
19 drug development process.

20 The process for BCS has been quite extensive,
21 and I just wanted to summarize the research contribution
22 and the public debate that have occurred with this.

23 Research was started with the University of
24 Maryland, Michigan, and Uppsala quite some time ago,

1 actually in 1991, along with collaboration with the Medical
2 Product Agency of Sweden. Public debates have been in the
3 form of the AAPS/FDA workshop in 1991, advisory committee
4 presentation, Capsugel Symposium in 1995 which led to
5 adoption of this Biopharm Classification System in the
6 SUPAC-IR Guidance, and the research continued with
7 collaboration with Uppsala and the Medical Product Agency
8 and within the FDA. We have presented some of our findings
9 to you in 1996-1997. We're doing it again at this point.
10 Capsugel Symposium, AAPS/FDA workshop, and the Fourth
11 International Drug Absorption in Scotland, and we also had
12 an expert panel meeting.

13 When we initiated this process, the opinions
14 were quite diverse within the group and outside in the
15 community. To summarize, in a sense opinions ranged from
16 for highly soluble/highly permeable drugs, why do we even
17 need a dissolution, we should regulate these on the basis
18 of disintegration to, on the other hand, we really need
19 clinical testing for bioequivalence assessment. And the
20 Biopharm Classification System turns out to be actually a
21 tool to really address some of these issues.

22 At the risk of getting fired from FDA, I
23 thought I'll just show this. What we are doing is still
24 under construction and please pardon our dust. I think we

1 have tried to do this policy development in public, and
2 some of our errors may be quite apparent.

3 The tasks assigned to the working group were to
4 do two things: one, recommend methods to permit
5 classification according to dosage form dissolution and
6 solubility and permeability characteristics of the drug,
7 and then further examined, we recommended a class of
8 immediate release dosage forms for which we could move to
9 an in vitro standard for bioequivalence.

10 In the background packet that I sent to you, I
11 tried to emphasize the focus of biopharm classification is
12 assessing bioequivalence and not bioavailability. I think
13 one of the issues that happens is issues come up and people
14 start thinking of bioavailability when really the issue is
15 bioequivalence.

16 I also described to you the current situation
17 of biowaivers. In a sense, current regulations use
18 dissolution as the primary factor for bioequivalence, and
19 excipients are important and there's a mechanism to
20 consider the impact of excipients.

21 The role of dissolution before and after SUPAC.
22 In a sense SUPAC-IR allows use of dissolution in absence of
23 a traditional in vitro/in vitro correlation, and the
24 Biopharm Classification System really explains on the basis

1 of mechanisms when to expect and when not to expect
2 correlations. So, from that perspective, it is a very
3 useful tool which is based on solubility, permeability, and
4 dissolution characteristics for identifying when to expect
5 IVIVC and to recommend when bioequivalence may be assessed
6 on the basis of in vitro.

7 I just wanted to define high solubility and get
8 it out of the way and move on to dissolution and
9 permeability. A drug is classified as high solubility when
10 the volume of water or buffer required to dissolve the
11 highest strength is less than or equal to 250 ml.

12 The recommendation coming out of the working
13 group at this point is you would really like to see a
14 complete pH-solubility profile for a pH range of 1 to 8
15 preferably at 37 degrees Centigrade and also that solution
16 stability under different pH conditions would need to be
17 documented, using a validated HPLC or other analytical
18 technique.

19 The permeability definition in SUPAC-IR started
20 out stating permeability is defined as the effective human
21 jejunal wall permeability of a drug, but in a sense the
22 rest of the definition is based on the outcome. High
23 permeability drugs are generally those with an extent of
24 absorption greater than 90 percent in the absence of or

1 when they're not unstable in the GI tract. And that's the
2 key feature. The Biopharm Classification System excludes
3 drugs which are generally considered unstable in the GI
4 tract.

5 The definition will be modified somewhat, and
6 two aspects that probably would be introduced in the
7 definition is -- and this is based on our expert panel
8 meeting -- high permeability drugs are generally those
9 which can be classified or considered to be rapidly and
10 completely absorbed. The definition on the basis of
11 outcome really does not address how rapidly a drug gets
12 absorbed.

13 The other recommendation was that 90 percent
14 may be too strict a criteria. If you are 95 percent
15 confident that extent of absorption is greater than 80
16 percent, that may be sufficient.

17 Defining permeability and the rule of
18 permeability in a sense is based on the relationship --
19 this slide is not in your handout, but I'll provide you a
20 copy of this -- is this relationship. Effective human
21 jejunal permeability is related to fraction of dose
22 absorbed. In the Biopharm Classification System and
23 especially in SUPAC-IR, the dissolution requirements are
24 based on the fact that the slope of this curve is quite

1 steep. You reach a point when you are about 80 percent and
2 it's a flat line. It's almost like a threshold logic
3 function, yes or no, either the drug is high permeable or
4 low permeable.

5 Permeability and concentration at the
6 absorption surface are the key parameters that determine
7 the rate of absorption. So, if we are uncertain with
8 dissolution and the concentration at the intestinal
9 membrane surface is not really being maintained, you're
10 likely to see major failures for a low permeability drug
11 and not for a high permeability drug. That's the reason
12 why permeability is in this classification system.

13 I think soon we would come up with an approach
14 of defining permeability on the basis of the jejunal
15 permeability value itself, and it appears to be an
16 effective permeability of greater than 2 might be what
17 would be considered as high permeability.

18 So, the task at hand right now is to, in some
19 ways, think of the process as going beyond SUPAC. If you
20 recall, in SUPAC-IR we have classified drugs as highly
21 soluble, highly permeable, and so forth, and we have
22 identified the critical processes. For rapidly dissolving
23 drugs, highly soluble and highly permeable drugs, I think
24 there is good assurance that gastric emptying is the rate

1 limiting factor, and a single point dissolution comparison
2 and .1 normal HCl was sufficient for level 2 changes.
3 These are very narrowly defined changes.

4 The working group selected this group for
5 further examination and said, can we go beyond SUPAC-IR and
6 allow any major change to occur in these formulations and
7 still be certain whether we are going to be bioequivalent?
8 The answer is yes. The working group has reached the
9 conclusion highly soluble/highly permeable drugs should be
10 regulated on the basis of in vitro dissolution.

11 There are minor differences of opinion here,
12 and I'll explain. The differences of opinion simply come
13 from the fact should one point be sufficient or should we
14 look at the full profile, and that's about it.

15 Also, the differences of opinion we have
16 internally or outside, should we even extend it to high
17 solubility/low permeability drugs? Because in a sense
18 rapid dissolution -- if a drug is highly soluble, gastric
19 emptying is going to be rate controlling even if
20 permeability is low. So, I think this appears to be
21 conservative, and it's possible to proceed on to the other
22 classes. But I think at this point our decision is to go
23 step-wise and just recommend one class for which in vitro
24 would be acceptable.

1 Just to summarize why this class has a very low
2 potential for bioequivalence problems, absorption is
3 generally rapid and complete when given as a rapidly
4 dissolving product or a solution.

5 Gastric emptying is the primary factor which
6 controls rate of absorption.

7 High solubility plus high permeability
8 essentially ensures extent of absorption. These drugs are
9 good candidates for controlled release and you can actually
10 slow down the release to 100 percent release in 12 to 16
11 hours and yet you can see 100 percent absorption.

12 And dissolution tests are used simply to
13 protect C_{max} .

14 In practice, how do we think BCS will be
15 applied in drug development? The colors didn't come out
16 right, but in a sense we hope that the classification could
17 be initiated in preclinical drug development. Essentially
18 when during clinical trials you have confirmed what your
19 maximum strength is and you also have some PK data on the
20 drug, you can confirm what your class membership is.

21 If you have designed your product to meet
22 certain specifications with respect to dissolution and
23 those specifications are applicable throughout the
24 stability profile or shelf-life experimentation, you can

1 use BCS to waive bioequivalence requirements when you go
2 from a clinical trial -- to-be-marketed product -- when
3 there are changes in process, site, and so forth. Again,
4 you could use it for major changes at level 3 after
5 approval and for generic approval of products. Essentially
6 the expert panel agreed that we have to stick to science
7 and the science should be applied equally on both sides.

8 The types of changes that really occur for what
9 you would consider as level 3 changes in SUPAC-IR would be
10 anything that is beyond current level 2. An example is a
11 change greater than plus or minus .5 percent in Mg-stearate
12 would be considered level 3 at this point. Any qualitative
13 change in composition -- you're substituting one excipient
14 to the other excipient -- is a major change. Change in
15 type of manufacturing process, going from wet to dry, is a
16 major change.

17 Also, some changes which are not considered
18 under SUPAC are changes in drug particle size, capsule to
19 tablet, but these are relevant changes that occur in the
20 drug development process and we have to apply BCS to even
21 these changes.

22 So, looking at the magnitude of changes, I
23 think we agreed that this really is a big step forward and
24 we have to be conservative and stick to the most safest

1 class of drugs, that is, highly soluble/highly permeable
2 drugs which dissolve rapidly.

3 In a sense the hypothesis could be stated
4 differently. We really are saying immediate release drug
5 products of highly soluble and highly permeable class of
6 drugs manufactured in accordance with cGMP's to meet
7 optimal predefined specification for rapid dissolution are
8 likely to be bioequivalent, and therefore bioavailable is
9 allowed.

10 The underlying understanding here is we have
11 acceptable standard operating procedures, in-process
12 controls, other specifications, stability, and all
13 processes are validated. The manufacturing techniques,
14 processes are fully validated.

15 The hypothesis we started with was to use the
16 SUPAC-IR case A dissolution as a boundary for our rapid
17 dissolution class. That is, dissolution of not less than
18 85 percent in 15 minutes in 900 ml or less of water, or .1
19 normal HCl, at 37 degrees when tested in the USP 1 and 2 at
20 the usual rates of 100 and 50 rpm respectively.

21 The 15 minutes simply came from the in vivo
22 gastric emptying time it takes to empty 50 percent of 200
23 to 250 ml of water under fasting conditions. So, this was
24 a hypothesis.

1 Our evaluation procedure was based on
2 FDA/University of Maryland research data where we looked at
3 two drugs, metoprolol and propranolol, which belong to the
4 high solubility/high permeability class, but we also looked
5 at other classes of drugs, ranitidine and naproxen,
6 piroxicam, and so forth. In a sense that database confirms
7 that dissolution is a very sensitive measure of differences
8 in products, and in fact it's probably too sensitive and we
9 have to allow major differences in dissolution to occur.

10 We also completed a survey of the literature.
11 We looked at in-house data, and we also performed some
12 simulation studies to support what we were getting at.

13 In a sense from a historical perspective, we
14 have built the Biopharm Classification System on two
15 foundations. One was our prior history of approving drugs
16 on the basis of dissolution which was 21 CFR 320.33 which
17 essentially had a classification system which is based on
18 clinical, physicochemical, and pharmacokinetics -- I talked
19 to you about this in my first presentation to you -- and
20 then based on the USP experience which really indicates
21 that dissolution is quite sensitive. But we feel that we
22 really needed to tighten some requirements to maintain the
23 current standards of bioequivalence, and that's where BCS
24 comes in. We have looked at exceptions and failures in

1 this class.

2 The snapshot data you have already seen but in
3 a different form. Here is the model drug we chose at the
4 University of Maryland and the dissolution profile of the
5 reference compound, but tested at different laboratories,
6 at generic laboratories and at the University of Maryland.
7 So, in a sense the data looks quite tight, and this would
8 meet our requirements of high solubility/high permeability
9 and rapid dissolution.

10 But if you look at the multisource and the
11 research formulations that we prepared to challenge this,
12 we found that dissolution could be much slower and yet
13 these products would be bioequivalent. The slowest product
14 that was prepared at the University of Maryland was
15 designed to fail the current requirement and it does.

16 This slow formulation happens to be
17 bioequivalent to the reference, but there is a significant
18 trend of lower Cmax and so forth. So, we know this is
19 already gastric emptying. You've gone beyond gastric
20 emptying and dissolution has a significant influence there.

21 So, the current situation would look like this.
22 This is the USP requirement of product release
23 specification. That's where biopharm classification, 85
24 percent in 15 minutes, would come.

1 And the relationship that we expect between
2 bioequivalence and dissolution here is the ratio of percent
3 drug dissolved, test versus reference, at time, 10 minutes.
4 The only reason for selecting 10 minutes was because
5 samples were not collected at 15 minutes in many places and
6 the results would not be really different.

7 And here AUC and Cmax test ratios. In a sense
8 that's the slowest formulation, and these all fall under
9 the current goal posts. We included dissolution for
10 comparison there. So, you essentially have an anchor on
11 your right-hand side, dissolution, and so you cannot go
12 beyond dissolution generally. So, this would be a safe
13 range to work under.

14 The simulation study also confirmed this.
15 Lydia is the key individual who did the simulation, but
16 Bill Gillespie, myself, and Gordon Amidon contributed to
17 some extent. What it also says is if you look at -- I'm
18 just going to look at the bottom half here -- if gastric
19 emptying is rapid, say 6 minutes, in vivo dissolution can
20 take about 1 hour or more for 85 percent to dissolve in
21 vivo and yet you won't see major differences between a
22 tablet and a solution. But if you go beyond that, you
23 started to see a difference. The boundary was 80 percent
24 difference between a solution versus tablet.

1 The other experiments we are doing with the
2 simulation is changing the intestinal transit time. High
3 permeability drugs are less prone to problems when
4 excipients affect intestinal transit time like sorbitol or
5 mannitol.

6 The need for early sampling was quite evident
7 from a number of examples that we had internally, as well
8 as the research at the University of Tennessee which said
9 that 85 percent or looking at dissolution beyond 30 minutes
10 was really not sensitive enough in many cases. Here is one
11 example of propantheline bromide which was a AA drug
12 approved on the basis of dissolution, meets the USP
13 specification of 75 percent in 45 minutes, but yet we have
14 data suggesting that these are bioinequivalent products.

15 The blood level profile that I have provided is
16 only truncated. It's only the early time points.

17 We also kept on looking for failures in the
18 literature, in-house, and so forth. We essentially felt
19 that we could categorize dissolution failures as
20 inappropriate specification, inappropriate test conditions,
21 or the product is highly variable.

22 The literature examples really didn't give us
23 enough complete information to really do mechanistic
24 analysis and so forth. For example, propoxyphene

1 hydrochloride has been reported as a rapidly dissolving
2 product. The test product dissolves 96 percent in 10
3 minutes as compared to reference of 89 percent in 10
4 minutes, was not bioequivalent, but 21 subjects studied.
5 But we don't have any other information beyond that. So,
6 it is difficult to explain that.

7 But if you look at -- we took propoxyphene and
8 did a pH/solubility profile, it's highly soluble at pH 1 to
9 4, and actually this is an underestimate. We just couldn't
10 measure the solubility. It was so high. But as pH
11 changes, solubility drops off quite rapidly. At 8.17,
12 which happens to be the last point, solubility would be 0.1
13 milligram per ml. With the current boundary definition for
14 high solubility, that will require 650 ml of water to
15 dissolve and that pH would be low soluble.

16 But I just want to point out, if you just move
17 on to here -- this is not a log scale -- the solubility is
18 1 milligram per ml. It could fall under high solubility.
19 That was a bit of a concern that we had.

20 We also surveyed in-house data. We focused on
21 one class of drugs, CNS drugs, and selected for the last
22 three years all drugs that dissolve rapidly between, say,
23 30 minutes, 80 percent in 30 minutes, and looked at what
24 sort of information we are getting from this, and tried to

1 classify these drugs, found one which probably would be the
2 borderline low solubility, and looked at relative
3 bioavailability, food effects, metabolism, and the relative
4 isozymes that have been involved, and in a sense found that
5 80 percent in 30 minutes really gives you a good indicator
6 of rapid dissolution. The solution and tablets are not
7 very different.

8 Food effect was simply sort of a comfort
9 situation because if food effect is not that dramatic, how
10 can excipients, which are generally GRAS, have an effect
11 too? That was simply a comfort zone we had.

12 We also looked at biofailures, what changes
13 were made, and analyzed some of these biofailures and found
14 that in one case, going from wet granulation to direct
15 compression, changing particle size, really resulted in a
16 worse relationship between dissolution and bioequivalence
17 only with respect to Cmax. We did not see any failure with
18 respect to AUC in all these studies that we have done.
19 Cmax failures are few but are generally explainable on the
20 basis of dissolution except for one case where we had an
21 inverse relationship.

22 These are three failures from that survey.
23 This is the boundary drugs which probably could fall under
24 high solubility, and the dose strength used was small.

1 Again, there was an inverse relationship. Just to give you
2 an example, a larger particle size to-be-marketed product
3 was directly compressed, dissolved rapidly. The clinical
4 trial material was a smaller particle size but did not
5 disintegrate. Disintegration differences overshadowed
6 dissolution differences in vivo.

7 Here is one example where we have a high
8 solubility/high permeability drug which meets the current
9 specification. There were a total of 11 bioequivalence
10 studies done for this drug. One failed in terms of Cmax,
11 just the confidence interval, in a multiple dose setting in
12 patients. Actually that study was repeated and found to be
13 bioequivalent.

14 So, you can see the impact BCS could have.
15 Eleven bioequivalence studies would have been eliminated in
16 this case.

17 Just one example. There was one case reported
18 for a pro-drug. This probably would not fit in the BCS.
19 It's a pro-drug which required a 5-minute dissolution
20 specification. The change was going from capsule to
21 tablet. Again, a very sensitive drug to pH. It was
22 classified as low solubility definitely because of the high
23 dose, but you can see how bioequivalence is related to
24 dissolution in this case. You had definite failure of

1 bioequivalence with respect to AUC and Cmax when
2 dissolution was very poor for the tablet, 10 percent in 5
3 minutes and 47 percent in 15 minutes. But early
4 dissolution or rapid dissolution or gastric dissolution was
5 critical for this pro-drug for it to maintain Cmax.

6 So, just the summary on dissolution.

7 Dissolution in vitro of 85 percent in 15 minutes may be too
8 conservative, but I think we haven't made any decision on
9 that yet. And some concern regarding high solubility drugs
10 which would be the borderline drugs which show rapid
11 decline in pH with respect -- solubility with respect to
12 pH.

13 Essentially the requirement proposed by some
14 members of the group is let's look at two or three pH
15 conditions in this case before we -- these are members of
16 this class, and we're not concerned with biofailure but
17 just want to look at some more data for such drugs.

18 Let me just give you a brief summary of
19 clinical methods for permeability before I move on to
20 excipient effects.

21 What we feel is the gold standard for
22 permeability would be the clinical methods, whether direct
23 or indirect, where you establish permeability class based
24 on PK data or jejunal perfusion techniques also, but

1 preclinical methods would be acceptable as long as they are
2 done properly and validated.

3 The selection criteria or issues for
4 discussion, there would be -- any method that does not
5 directly estimate the extent of absorption in humans would
6 need to be justified and ability to predict extent of drug
7 absorption in humans demonstrated.

8 Impact of absorption mechanism and pre-systemic
9 metabolism need to be considered. And Donna will talk to
10 you about CACO-2, using that as an example of how we need
11 to address this.

12 Let me just go on to excipients now. We
13 realize excipients play a significant role in
14 bioavailability. Excipient-drug interactions that are
15 detectable in vitro are chemical and physical interactions.
16 However, excipients can have a profound effect on GI
17 physiology. They can change the GI motility or even change
18 the permeability of the membrane. They can interfere with
19 metabolism. And we need to have some assessment of what
20 impact commonly used excipients have that are used in
21 tablets and capsules.

22 Examples of possible mechanisms reported in the
23 literature. Sodium pyrophosphate is a cathartic laxative,
24 had a significant effect on ranitidine and bioavailability.

1 It reduced it by half and essentially this study also
2 measured small intestinal transit time. Reduction in small
3 intestinal transit time leads to reduced bioavailability
4 for low permeability drugs like ranitidine, cimetidine,
5 mannitol, sorbitol.

6 For theophylline, for example, I have included
7 a study here. This is an old study from Dr. Riegelman's
8 group -- and Dr. Shah is a co-author on this -- where they
9 administered a 300 and 500 milligram dose of a sorbitol
10 solution of theophylline. The amount of sorbitol that is
11 used in this is about from 22 grams for the 300 milligram
12 dose to 500 milligrams, about 50 grams or so. So, the
13 amount of sorbitol administered is humongous and they see
14 slight differences in Cmax and Tmax. So, theophylline,
15 being a high permeability drug, would be protected. It is
16 not sensitive to such changes like a low permeability drug
17 like ranitidine would be.

18 Myristic acid can change gastric emptying time.

19 Polysorbate 80, cremophor, and other
20 surfactants are inhibitors of Pgp. Again, these have been
21 demonstrated in vitro and in vivo -- after IV
22 administration and in vitro in the cultures, CACO-2
23 cultures.

24 Oleic acid-bile salts can change the absorption

1 mechanism of propranolol.

2 And these are all fine but these are not the
3 excipients which are widely used, except for maybe
4 polysorbate 80.

5 We have gone through and did a survey of
6 excipients that are commonly used in tablets. What we find
7 is about 50 excipients are the ones which keep being
8 repeated again and again, and these are the most widely
9 used excipients. Magnesium stearate is number one. It has
10 been used in about 2,240 submissions.

11 As you see here, what I would like to point out
12 is concerns would come from surfactants. Polysorbate 80 is
13 a Pgp substrate or it inhibits Pgp and potentially can
14 change metabolism and a few others. But the rest, lactose
15 and so forth, are really not considered problematic.

16 We are looking at data sets comparing different
17 products on the market. Again, this information is
18 publicly available. We've compiled this list from the
19 Physician Desk Reference and other sources which are
20 publicly available.

21 Here if you look at verapamil products --
22 verapamil, by the way, is a highly permeable drug. We have
23 measured that. So, if you have a surfactant like
24 polysorbate 80 which inhibits Pgp, you will not likely see

1 an increase in absorption because these are all highly
2 permeable drugs. That probably would be more of a concern
3 for low permeability drugs, if they can increase the
4 absorption of those drugs.

5 But it has been used in some products and not
6 in all. The quantity of polysorbate used in tablets is
7 generally 4 to 15 milligrams. What is it used for? It is
8 used for a wetting agent and it is used as a plasticizer
9 for film coating. We believe such amounts are really not
10 problematic, and we have mechanisms in place to evaluate
11 such excipient effects.

12 Here's another example of potential impact of
13 excipients, propranolol. This is our University of
14 Maryland formulation, the slow release one. All fall under
15 our bioequivalence, except we had three studies in house
16 which looked at liquid formulations. Two formulations of
17 liquid preparations were bioequal to the tablet, but one
18 pediatric formulation failed. It had higher Cmax and AUC.
19 What I believe at least, this is due to some other effects
20 on metabolism. In a sense it may be possible that you're
21 inducing some physiological changes with flavors and sugars
22 and so forth that you may use in fed state -- in a non-fed
23 situation with some oral preparations.

24 So, the summary on inactive ingredients is

1 this. Conventional solid oral products are not intended to
2 alter GI motility and metabolism. If you include an
3 excipient which is designed to do that, obviously we have
4 to regulate it that way.

5 Disintegration, distribution, and dilution
6 effects that are seen in the GI tract reduce the likelihood
7 of excipient interactions.

8 Excipients in conventional solid oral products
9 are actually likely to be more inert compared to current
10 liquid products such as elixirs and syrups.

11 New excipients and/or unusually large
12 quantities in products would have to be definitely
13 evaluated. So, we would build that in.

14 So, the final analysis is in applying BCS for
15 giving biowaivers, we would need rapid dissolution, high,
16 solubility, high permeability. Other studies that are
17 supportive -- this is not done in isolation in drug
18 development. You have dose proportionality and absolute or
19 relative bioavailability studies that will support this.

20 The use of the dose proportionality study comes
21 from the fact that high permeability determinations may not
22 be done at the highest dose. If that's not, then you need
23 to rely on this to confirm high permeability.

24 Then finally, the therapeutic index or other

1 therapeutic concerns would come in. We have not worked on
2 this but we are recommending that it be applied to wide
3 therapeutic index drugs. This is a separate group defining
4 what narrow and wide is, so we are waiting for them to give
5 us that definition.

6 So, this would be the sequence.

7 During all these meetings that we have
8 presented outside, we have received several comments, and
9 the major criticism that we have received is permeability.
10 There's high variability. Fick's Law may not really apply.
11 But I feel that those issues are not directly impacting on
12 the way we have approached the guidance, and we addressed
13 some of these at an expert panel. The membership is shown
14 here.

15 I think I'll stop here and address other
16 questions that you have later on.

17 DR. ZIMMERMAN: We will now hear from Dr. Donna
18 Volpe who will talk to use about permeability determination
19 in vitro.

20 DR. VOLPE: Good morning, everyone. Thank you
21 for inviting us out here to give a talk on some of our
22 research data that is supporting a section of the
23 Biopharmaceutics Classification System. I'll be talking
24 about an introduction to the system and how it relates to

1 the guidance, and then Dr. Pat Faustino will be discussing
2 some of our most recent data of a project that we just
3 undertook approximately two months ago.

4 First I'd like to describe briefly the cell
5 culture method with the CACO-2 cell line. The CACO-2's
6 provide us with an in vitro method to evaluate blood
7 permeability after oral administration.

8 Now, the CACO-2 cell line -- I don't know if
9 many are familiar with it -- is a human colon
10 adenocarcinoma cell line that undergoes a spontaneous
11 structural and functional differentiation to an enterocytic
12 like cell. It is the only colon cell line or intestinal
13 cell line that does this for humans.

14 The CACO-2 cells form confluent monolayers on
15 filter membranes with an enterocytic morphology that are
16 typical of villus cells, and these cells have very tight
17 junctions, have brush border enzymes, and have a number of
18 active transporter systems.

19 There is a literature base that shows that the
20 CACO-2 permeability values correlate well with the extent
21 of absorption for humans, especially for the passively
22 absorbed drugs.

23 Now, just an idea of what the CACO-2 cell
24 culture system looks like. In a normal -- something like a

1 6-well plate, a 24-well plate, or even a 96-well plate in
2 some cases -- the CACO-2 cells are suspended in sort of a
3 cup-like apparatus that has the filter membrane on the
4 bottom. The CACO-2 cells, as they're growing, will form a
5 basolateral to apical type of a system where we have an
6 apical chamber up here and a basolateral chamber here, and
7 they form a nice monolayer on the filter membrane.

8 The studies can be conducted where you add a
9 drug to the apical chamber, and over time you would sample
10 drug that appears in the basolateral chamber and you can
11 look at drug permeability in this direction, apical to
12 basolateral.

13 Alternatively you can add drug to the
14 basolateral chamber and see if drug flows in the opposite
15 direction.

16 Just an idea of some of the in vitro/in vivo
17 correlations that have been presented in the literature.
18 Artursson and Karlsson provided us with a good correlation
19 between oral absorption in humans and the results in the
20 CACO-2 cell model of approximately 20 drugs. They compared
21 it to bioavailability. If the bioavailability was 100
22 percent, they had a P_{eff} value of greater than 1 times 10
23 to the minus 6th centimeters per second. However, if the
24 bioavailability was less than 100 percent, down to 1

1 percent, the bioavailability values ranged from .1 to 1
2 times 10 to the 6th centimeters per second. Then if the
3 bioavailability was less than 1, the Peff values were much
4 less than 1 times 10 to the 7th centimeters per second.

5 In a more recent publication by Yee of 34
6 drugs, they classified things again with the
7 bioavailability and again saw a relationship of -- a
8 bioavailability of approximately 70 to 100 percent, they
9 would see an in vitro Peff value of greater than 10 times
10 10 to the minus 6th centimeters per second. And then the
11 next category they had were 20 to 70 percent and the Peff
12 values were 1 to 10. Then if bioavailability was 0 to 20
13 percent, the Peff value was much less than 1.

14 Keep these values in mind for the drugs that we
15 have tested, three drugs of ranitidine, naproxen, and
16 metoprolol. Their bioavailabilities and our subsequent in
17 vitro Peff values fall very well within these Yee values
18 that are reported.

19 In a publication by Hans Lennernas, he found
20 that the CACO-2 cells were very good in predicting passive
21 drug transport in humans. However, the prediction of
22 carrier-mediated transport may require a scaling factor due
23 to low expression of the carrier mechanisms in the CACO-2
24 cell line.

1 In the working group, we have discussed one
2 application of the CACO-2 cell line and it's using an
3 internal standard for doing our permeability studies and
4 for determining high and low permeability drugs. We'd like
5 to classify these test compounds based on the comparison to
6 a high and/or low permeable internal standard or standards.

7 The selection of the internal standard would be
8 based on its well-known permeability values. We wanted to
9 know how it will react in the humans and how it reacts in
10 the CACO-2 cell system. We wanted to have a known
11 absorption mechanism, preferably a passive absorption
12 mechanism. The test compound must be physically and
13 chemically compatible with the internal standard. We
14 cannot have things as complex formation, and we would like
15 to know if they have a metabolic or an efflux protein
16 compatibility.

17 The working group has come up with at least
18 four potential standards that can be discussed or used in
19 the system of naproxen, atenolol, metoprolol, ranitidine.

20 The internal standard will be built into the
21 test system, and it will be able to demonstrate that the
22 membrane has integrity and stability of the system within
23 the laboratory over time so that the internal standard
24 serves two purpose.

1 As Ajaz had alluded to, we had an expert panel
2 meeting earlier this year, and we discussed the CACO-2 cell
3 line and we got some feedback from this expert panel
4 meeting and what can we build into our guidance. They were
5 very much in favor of a standard methodology in the
6 guidance document but not a very detailed experimental
7 procedure where you have to use a certain media, a certain
8 serum concentration, et cetera.

9 They are very much in favor of the inclusion of
10 an internal standard in the permeability studies, and what
11 they'd like to see the guidance to show is a definition of
12 the high and low permeability drugs within the culture
13 system. The guidance should also have acceptance criteria
14 for data submission.

15 The CACO-2 cell studies should only be
16 submitted in conjunction with other in vivo or in vitro
17 permeability studies. The CACO-2 cell system will not be a
18 standalone test to determine permeability.

19 The exclusion that they would like to see is
20 that the CACO-2 system is only used for passively absorbed
21 drugs due to complications of active transporters and
22 efflux mechanisms which occur in the CACO-2 cell line but
23 not always at the same level of expression as you would see
24 in the intestine.

1 Now Dr. Faustino will discuss some of our
2 current studies that are undergoing in our laboratories.

3 DR. FAUSTINO: Good morning. I'm Pat Faustino
4 from the Division of Product Quality Research in the Office
5 of Pharmaceutical Science, and I'd like to discuss the OTR
6 CACO-2 permeability study that's currently going on in FDA
7 intramural laboratories.

8 First is the use of an internal standard with
9 test compounds. One of the concerns for us is complex
10 formation between compounds, high permeability/low
11 permeability compounds, and the internal standard,
12 permeability of test compounds with or without the internal
13 standard, chemical parameters, binding drugs to plate,
14 filter, media components, monolayer integrity of the
15 system. And that would be done by TEER measurements or
16 resistant measurements, Lucifer yellow, which is a
17 pericellular marker, effect of stirring on drug
18 permeability, collagen-coated versus uncoated membrane
19 filters since there's a whole series of different types of
20 membranes out there, polycarbonate, nitrocellulose, teflon,
21 and permeability of P-glycoprotein substrates.

22 This is an example of some initial data. As
23 Donna said, we looked at three different drugs:
24 ranitidine, a low permeability drug; naproxen, a high

1 permeability drug; metoprolol, a drug that is classified as
2 high permeability but is at the boundary. These are some
3 of our initial studies.

4 These concentration bracket the literature. We
5 did 10 micromolar, 25 micromolar, and 250 micromolar
6 ranitidine, and the same for naproxen. We did these
7 samplings at 15 minutes through 240 minutes. You can see
8 there's very quick correlation. This is function of three
9 trans wells versus time, and you can see the percentage of
10 absorbed or the effective permeability is 1 percent, 1
11 percent, and 1 percent over the concentration ranges. We
12 see the same thing for naproxen. We have very good
13 correlation as a function of time.

14 The in vitro permeability values are calculated
15 as a function of this equation: the volume of the receiver
16 divided by the area of the membrane times the initial
17 concentration times the slope of the change in the
18 concentration as a function of time.

19 The permeabilities that we got for naproxen
20 were 3.1×10^{-4} centimeters per second;
21 metoprolol, 0.38; and ranitidine, 0.64. Naproxen in in
22 vivo -- we have very good correlation -- is 8×10^{-4}
23 the minus 4th.

24 This is the ratio of the permeability values as

1 a function of the internal standard. You can see that we
2 get very good correlation at all three concentrations of
3 the permeability value of the drug divided by the
4 permeability value of the internal standard for ranitidine.
5 We also get it for naproxen, and there is reasonably good
6 correlation between the in vivo values and our in vitro
7 values.

8 Our conclusions from our pilot or initial study
9 are the internal standard can be used when evaluating in
10 vitro drug permeability.

11 Permeability data shows in vitro/in vivo
12 correlation to human data.

13 The ratio of the permeability values for the
14 drug versus the internal standard normalizes the data and
15 should help to bring together better inter-laboratory
16 variation that's currently existing in the in vitro
17 literature.

18 Future studies that will be ongoing in the
19 intramural laboratories are the effect of stirring on the
20 water boundary layers, effect of the efflux pump on
21 permeability with P-glycoprotein substrates, effect of
22 direction of drug permeability, and the evaluation
23 potential for metabolic effects in the CACO-2 cell line.

24 Thank you.

1 DR. ZIMMERMAN: Thank you.

2 Now it's time for the committee discussion of
3 these issues, and we've been asked to direct our questions
4 to the panel here: Dr. Amidon, Dr. Hussain, and Dr. Volpe.
5 Are there any questions? Dr. Mayersohn?

6 DR. MAYERSOHN: Ajaz, thank you very much for a
7 nice presentation.

8 I'm going to ask a question I asked of Gordon
9 actually at a dissolution and bioavailability meeting of
10 the USP, but I just wanted to get it on the record and see
11 if, Gordon, you've thought anymore about this, and that is
12 the question about measurement of intrinsic dissolution
13 rate, especially in early preclinical studies before any
14 dosage form has developed. Have you given any more thought
15 to that?

16 DR. AMIDON: The intrinsic dissolution rate I
17 think is something that could be characterized and
18 calculated just from CMC type data. We did debate and I
19 think we're still debating whether that should be required
20 as part of the guidance -- that is, what would be the
21 expected dissolution rate of the drug -- and then have that
22 as kind of your reference relative to your formulation
23 dissolution rate.

24 I think we're still currently at the decision

1 that that might be nice to know, but it's not a
2 requirement, not a need-to-know thing. I think we're still
3 in that region. Maybe Ajaz can elaborate on it. But it's
4 something that I would want to do as part of development,
5 something I want to know how my formulation is doing
6 relative to what the drug properties would predict it
7 should be doing, but I don't think we want to require it.

8 DR. MAYERSOHN: My thinking, Gordon, was it
9 clearly can't obviate the need for a dosage form
10 dissolution. You still have to do that. But I thought it
11 might give you an indication real early on whether you're
12 headed for trouble and early on how you would classify the
13 compound into which of the categories.

14 DR. AMIDON: Yes. It could be simply
15 calculated, estimated very easily. It's something that
16 should be done. Whether it's required as part of a
17 submission to request a waiver from in vivo bioequivalence
18 trials, I would certainly put it in. It should be part of
19 your CMC data analysis as to how this compound will
20 perform. I personally would like to see it in because I
21 think it's something that's easy. It's a characteristic of
22 the drug that's a very important pharmaceutical property,
23 but I'm not sure we could require it.

24 DR. MAYERSOHN: Thank you.

1 DR. ZIMMERMAN: I'd just like to point out that
2 our committee has now been joined by Dr. Steven Byrn from
3 Purdue University who I think is just about the ask a
4 question.

5 DR. BYRN: Yes. I just wanted to go on on the
6 intrinsic dissolution. We found that it's difficult in
7 some cases to do accurate reproducible intrinsic
8 dissolution studies, and we almost always combine intrinsic
9 dissolution studies with direct powder dissolution studies
10 which, of course, are more difficult because you're dealing
11 with particle size then. So, it may not be easy to
12 determine intrinsic dissolution of all drug substances just
13 because of the technical problems of pressing them into
14 pellets and so on.

15 DR. ZIMMERMAN: Dr. Brazeau?

16 DR. BRAZEAU: I have one question for Dr.
17 Hussain. With respect to your example of level 3 changes,
18 I'm wondering, your first bullet was there that you'd have
19 a greater than 0.5 percent change for magnesium stearate.
20 I'm wondering if you need to maybe expand that and look at
21 some of the effects of some of the binders and adhesives
22 which could have an effect in this.

23 DR. HUSSAIN: That was just an example.
24 There's a whole list of excipients. That example came out

1 of SUPAC-IR. That's the current guidance that is out
2 there, and that's only one definition. So, it lists other
3 examples.

4 But for applying this in the level 3, we felt
5 that the system needs to be robust enough that we shouldn't
6 be concerned on defining what the change is, leave the
7 change up to in this. As long as you make your product
8 whatever way you can, validate the procedures, and if you
9 meet the dissolution requirement, that's sufficient. That
10 was the approach we tried to take on this and not go back
11 and define what are the changes or levels of changes.

12 DR. BRAZEAU: I have two questions for Dr.
13 Volpe. I think an area that you're going to have to be
14 very conscious about using CACO-2 cell lines is the passage
15 number. I think some of the recent literature suggests
16 that there can be real large changes in the TEER values.
17 So, I think you're going to have to be specific and specify
18 where you're going to be with the passage cell line. I
19 think there's some literature that came out from Pat
20 Sinko's lab in Pharmaceutical Research a while back that
21 really showed dramatic changes in the TEER value as a
22 function of how many passages you've done of that cell
23 line.

24 A second issue I think you need to raise is I

1 think a two-point standard will always be better than a
2 one-point standard, one that documents both a high and a
3 low value, because the change I'm seeing you're saying is
4 only a power of 10. So, in order to make sure that the
5 system is running smoothly, you're going to have to be able
6 to provide and show that that range is approximately the
7 same value.

8 So, those would be my concerns with some of the
9 CACO-2 cell lines.

10 DR. VOLPE: Yes. I've always been cognizant of
11 the passage number just doing a literature search, and we
12 have just not built it in. These studies have only begun
13 in the past two months, but it is something that we are
14 really looking into and not just TEER values, but maybe
15 something like Lucifer yellow that would also tell you the
16 permeability effect over time when you passage these cells
17 continuously.

18 And, yes, we just started doing it with one
19 internal standard, but we've also discussed, well, let's
20 look at maybe a high permeability drug and a low
21 permeability drug as our standards and build that in. It's
22 just these are initial experiments, and yes, that's
23 something we would like to consider down the road.

24 DR. GOLDBERG: I would like to comment on the

1 intrinsic dissolution. I think the intrinsic dissolution
2 is directly proportional to the solubility, and I think
3 that it has less experimental variation in determining that
4 than in measuring intrinsic dissolution. So, I would
5 certainly want to see solubility data in any submission as
6 opposed to necessarily intrinsic dissolution. That's just
7 a comment.

8 I have questions on in vitro dissolution. I
9 think that you are willing to go along with the dissolution
10 specification for HS/HP drugs, high solubility/high
11 permeability drugs, and my question is, shouldn't that also
12 apply to high solubility/low permeability drugs? And why
13 are you differentiating? Or is it just because you're
14 going very slowly?

15 DR. HUSSAIN: No. That continues to be an
16 issue of debate in the working group itself, the need for
17 permeability, why do you need permeability. If a substance
18 or a product is rapidly dissolving and highly soluble, why
19 does permeability come into play?

20 The concerns have been with respect to
21 dissolution, how reliable it is. For example, there are
22 changes that can occur in particle size, and if these
23 changes go along with a change to a wet to dry process
24 where you use a water insoluble type of a filler,

1 dissolution results could be in the opposite direction in
2 the sense the system does not protect. So, I think we are
3 overly cautious at this point and that issue is debatable.

4 The graph that I showed you where permeability
5 versus f has a sharp slope, and the feeling was if we make
6 a mistake in allowing a product which really, really
7 doesn't dissolve rapidly in vivo but it appears in rapid
8 dissolution in vitro, that product would be drastically
9 affected not only in C_{max} but also in AUC. So, wide
10 therapeutic index drugs, high solubility, the permeability
11 protects against that. That's the logic right now.

12 DR. ZIMMERMAN: Dr. Amidon?

13 DR. AMIDON: I think the short answer to your
14 question, Art, is it does if you set your dissolution
15 standard right. In other words, you probably for a low
16 permeability drug, which in our experience like your
17 cimetidine, ranitidine, atenolol, is position-dependent
18 permeability. So, duodenum, jejunum, ileum may have
19 different permeabilities. You probably need a tighter
20 dissolution specification for a low permeability drug. So,
21 it must dissolve instantly in the stomach and it behaves
22 like a solution; whereas with a high permeability drug, by
23 definition it's well absorbed. And so you could probably
24 slow down, as Ajaz showed with the data on metoprolol and

1 propranolol, but certainly metoprolol. You could slow down
2 the dissolution rate to a 30-minute specification and still
3 meet bioequivalence criteria. That's probably not the case
4 for a high solubility/low permeability drug.

5 So, the answer is yes. I think if you set your
6 dissolution specification tight enough, short enough, then
7 it would pertain to both. With the current standard of
8 dissolution of 85 percent in 15 minutes, I think it would
9 apply to both, but a dissolution in 30 or 45 minutes
10 probably would have to be applied just to high permeability
11 drugs. That's our thinking as to where permeability will
12 become discriminating, and we're just taking the most
13 conservative position now.

14 DR. GOLDBERG: Okay. A comment on measurement
15 of dissolution is that you have showed data at 30 minutes
16 and at 15 minutes of some drugs. You had to go to 5
17 minutes. We're using time as the x axis instead of having
18 something like the time to dissolve 10 percent of the drug.
19 So, when we do a profile by time, we often see at the early
20 time point 80 percent of the drug dissolved, and it's very
21 difficult to discriminate between 80 percent and 90
22 percent.

23 But if you look at the time to dissolve, let's
24 say, 10 percent of the drug or 25 percent of the drug and

1 get a profile that way, you see a real difference in times
2 I think, and I think that may be a much more sensitive
3 measure for comparing dissolution profiles.

4 A question for Donna Volpe. Donna, thank you
5 very much for the presentation. But I wonder whether these
6 same correlations that you've shown for permeabilities to
7 fraction of drug absorbed have been done with partition
8 coefficients and what kind of correlation coefficients
9 you've seen.

10 DR. VOLPE: There are a number of papers out
11 there in the literature that look at the Peff values in
12 vitro with the CACO-2 cell lines that do correlate with the
13 partition values. I just didn't have the values here, but
14 there are a number of papers out there that you can find
15 that on where they look not just at percent bioavailability
16 but they also look at the partition values and then the in
17 vitro values. There is correlation between the CACO-2 cell
18 lines and the partition values.

19 DR. GOLDBERG: As I look at the correlation
20 coefficients that you've shown for the correlation between
21 the permeability and the fraction absorbed --

22 DR. VOLPE: Right.

23 DR. GOLDBERG: -- and we're seeing correlation
24 coefficients ranging on the data you showed from .63 to

1 .78.

2 DR. VOLPE: Right.

3 DR. GOLDBERG: I was wondering what those
4 correlation coefficients would be if you did the same
5 correlations with partition as opposed to permeability.

6 DR. VOLPE: I can't say. I have not gone back
7 in the literature and done that, but that would be an
8 interesting thing to look at, yes.

9 DR. GOLDBERG: Thank you.

10 DR. MAYERSOHN: I think Dr. Goldberg is making
11 a case for low tech.

12 DR. GOLDBERG: In a sense, yes.

13 DR. AMIDON: I just wanted to comment on what
14 Art and Steve said. I agree with you, Art, you can
15 estimate intrinsic dissolution quite easily. All you need
16 to do is estimate or determine your diffusivity. And
17 that's something that I think should be done, not
18 necessarily required if I were a development person doing
19 it.

20 But I agree with Steve. Experimentally
21 measuring intrinsic dissolution has some experimental
22 difficulties that in some cases it's very difficult to get
23 an experimental intrinsic dissolution rate. But I think it
24 should be estimated. In fact, I think it's a type of

1 experiment to prove that you can do an experiment because
2 you know what the intrinsic dissolution rate is and if you
3 don't get that, you have a problem with the experiment.

4 DR. ZIMMERMAN: Dr. Mayersohn?

5 DR. MAYERSOHN: With regard to the permeability
6 issue, it's actually a comment that I'd like to leave with
7 Roger, and that is I'd like to see the agency pursue animal
8 models, whole, living live animal models, for assessing in
9 vivo absorption which you're using in the same terms as
10 permeability. There have been efforts over the years. I
11 don't think they have been as thorough and complete as they
12 could be. You may want to give some thought to the
13 possibility of developing an appropriate animal model for a
14 screen, at least for a screen.

15 DR. ZIMMERMAN: Dr. Mayersohn, are you talking
16 whole animal and not the intestinal --

17 DR. MAYERSOHN: That's correct. Whole animal.
18 Yes, in the permeability breakdown that Donna presented,
19 there were some in vivo perfusion studies that were
20 suggested and that's fine. You still need to select an
21 animal, but the whole animal in terms of dosing might be
22 very useful.

23 DR. HUSSAIN: At the expert panel, Professor
24 Win Chiou presented data regarding absorption in rats

1 compared to absorption in humans, and I think he's pursuing
2 that and he'll be submitting his complete analysis.

3 At least our intention is to keep the guidance
4 as open as possible. If an animal model is found suitable,
5 sure, the guidance would allow that.

6 DR. ZIMMERMAN: But what do you mean by "found
7 suitable"?

8 DR. HUSSAIN: I think we are looking for
9 predictive value. We would like to be certain that, say,
10 90 percent absorption predicted in the rat would also -- or
11 the prediction in humans would be a reliable prediction
12 because the whole animal leads to different metabolic
13 pathways, different metabolism, and the techniques might be
14 more difficult and we may not have enough hard data to
15 accept that.

16 DR. MAYERSOHN: Well, the techniques are
17 unquestionably more difficult. I was really suggesting as
18 an initiative for the agency of the Pharmaceutical Sciences
19 group.

20 The other thing I guess that comes to mind --
21 and you're going to have tell me where I'm going wrong here
22 in my thinking -- is the difference between permeability
23 and absorbability. I know, Gordon, you've shown a
24 relationship between the two.

1 Permeability it seems to me can be correlated
2 among virtually all membranes in any mammalian species. In
3 fact, you can probably use latex membranes, and that will
4 work too. Partition coefficients might work as well.
5 Whereas, absorbability is a very different issue. There is
6 likely not to be a correlation in absorbability of dosage
7 forms, rat versus human.

8 DR. ZIMMERMAN: How are you defining
9 absorbability?

10 DR. MAYERSOHN: The completeness of absorption
11 is absorbability, whereas permeability is a measurement of
12 rate per distance.

13 Do you make that distinction in your mind?

14 DR. AMIDON: Well, I think permeability
15 technically is a mass transfer coefficient, so you
16 typically measure it in only one segment like in typically
17 the jejunum. Permeability can vary along the GI tract
18 because it's highly differentiated.

19 So, the ability to predict absorption just
20 based on the jejunum rests on the assumption that that
21 permeability is applicable over the rest of the GI, and
22 that may not be true. In fact, we know it's not true for
23 some drugs, particularly carrier-mediated drugs, but drugs
24 that also might be pH-dependent where the pH in the lumen

1 varies along the GI tract.

2 So, I think the absorbability and permeability
3 are well predicted when the jejunal permeability is a good
4 estimate of overall permeability along the GI tract, but
5 when there are more specialized considerations, it's not,
6 and you have to include then your position-dependent
7 permeability.

8 DR. ZIMMERMAN: Dr. Branch?

9 DR. BRANCH: I like the approach of trying to
10 get at underlying mechanisms, but I'm a little confused as
11 to how you're taking in active transport and metabolism in
12 the whole equation of permeability. I guess my major
13 concern there is the much greater inter-subject variability
14 that you're going to get if this mechanism is involved.

15 So, my questions relate in terms of the overall
16 policy. When you're trying to define permeability, you
17 have listed either direct mechanisms of looking at
18 permeability or total AUC which is hard to know which
19 mechanisms are involved. So, how are you separating out
20 this and are you taking into account drug metabolism?

21 Then in the CACO model particularly, I wonder
22 if you have a model that you know is under-expressed in
23 terms of transport mechanisms and probably drug
24 metabolizing enzyme capability whether if you identify any

1 metabolism or any transport, then that model should
2 probably be considered inappropriate for addressing that
3 particular drug issue.

4 Is there any consideration given to where the
5 model should not be used?

6 DR. HUSSAIN: Extent of absorption that is used
7 in the definition of permeability is total amount absorbed.
8 It includes drug that was converted to a metabolite in the
9 gut wall or hepatic metabolism.

10 The view we have is I think variability is high
11 for highly metabolized drug, but that variability is
12 associated with bioavailability.

13 The focus that we have kept is on
14 bioequivalence. Two products of the same drug, if they
15 provide the same concentration/time profile at the
16 intestinal membrane surface, are likely to be bioequivalent
17 unless there's an excipient which would affect metabolism.

18 From that perspective what the group has
19 suggested is if dissolution is rapid enough, then gastric
20 emptying and the rest of intestinal motility defines that
21 concentration profile, not the product. So, that's not a
22 product quality issue which is bioequivalence. That's a
23 major issue for bioavailability determination.

24 So, metabolism is a concern from the point of

1 view of excipients that are used only in this.

2 I hope I've addressed that and extent of
3 absorption is the total amount absorbed. So, you could
4 simply look at the urinary excretion of total drug, say, a
5 radiolabeled drug, to get that.

6 Donna?

7 DR. VOLPE: In terms of the CACO-2 cultures,
8 right now what the guidance will focus on is passively
9 absorbed drugs that do not involve active transporters or
10 efflux membranes. That is also coming to us from the
11 expert panel meeting.

12 There are new cell lines being developed, or I
13 should say new strains of CACO-2 cell lines that will
14 overly express an active transporter or under-express it,
15 and especially like the P-glycoprotein, you'll see cell
16 lines out there that they've developed that either over-
17 express it for things. But right now what we'll focus on
18 is just passively absorbed drugs, but it's something that
19 we have been considering and it's always been in the back
20 of our minds in terms of active transport mechanisms.

21 DR. ZIMMERMAN: Dr. McGuire?

22 DR. MCGUIRE: The CACO-2 model is interesting
23 in that it's of colonic origin and it has brush borders and
24 tight junctions. The question is whether all of those

1 things are necessary. In other words, if you had another
2 epithelial cell line that didn't have that apical and
3 basolateral differentiation, if you would find the same
4 characteristics of transport. Is there something specific
5 about this cell line that makes it more applicable to
6 intestinal absorption?

7 DR. VOLPE: I think we focus on the CACO-2 cell
8 simply because of the body of literature that backs it up.
9 I have seen studies using the HT29 cell line. The only
10 problem with that is you have to change the media
11 components, and then you will get an enterocytic
12 differentiation in the cell line. But I have not seen any
13 studies with just other colonic cells lines or just even
14 intestinal cell lines. The system seems to be well worked
15 out and the database is behind it in terms of literature.
16 But that is an interesting factor.

17 There are some things that I've done with
18 epithelial cells looking at transport, such as a kidney
19 cell line, but the CACO-2 cell line comes to us with a lot
20 of literature base and a lot of usage in the academics.

21 DR. ZIMMERMAN: Dr. Brazeau?

22 DR. BRAZEAU: With respect to that, I think you
23 are going to be very conscious of having the individual
24 characterize where their cell line with respect to P-

1 glycoprotein. When I think about what we do sometimes
2 renal cells -- you know, you do marker enzymes for
3 activity. If you're going to have different transport
4 processes as a function of different passages, you're going
5 to have to be able to give some guidance as far as what
6 you'd expect for the various expression of some of these
7 transporters or P-glycoprotein. Otherwise, the data is
8 going to be all over the place. You're not necessarily
9 going to be able to interpret it.

10 DR. VOLPE: As you can see it in the things
11 that we like to do, we do have in-house expertise in terms
12 of P-glycoprotein problems, albeit in human cancer cells,
13 and there's a series of studies we'd like to look at
14 looking at drugs that are transported by the P-glycoprotein
15 and then look at blockers at the same time. In conjunction
16 with those experiments, we'll be looking at the expression
17 of P-glycoproteins on our cells that we have in house and
18 look at the expression over time in terms of passage
19 number.

20 DR. BRAZEAU: This is where I'd like to
21 disagree respectfully with my colleague, Dr. Mayersohn. I
22 think that these CACO-2 cell lines can be a really useful
23 tool to do some initial screening. While I value animal
24 models, I'm not sure what the value added is going to be of

1 that. If you've got certain drugs that show that there
2 isn't going to be any problems, I'm not sure that you
3 necessarily need to do the animal models. So, I think it's
4 kind of a TEER approach.

5 DR. ZIMMERMAN: Dr. Amidon had a question.

6 DR. AMIDON: Yes, a couple of comments. I
7 think one, Gayle, of course the animal model has everything
8 expressed at levels that allow the organism to live, and so
9 the balancing -- and as I think Donna is saying, once you
10 start manipulating CACO-2 cells, there's a whole lot of
11 things you can do. So, the characterization becomes very
12 important.

13 I think that's one reason for in the guidance
14 not wanting to get too detailed but kind of put the
15 challenge to the company saying you convince us that you
16 have a good system and we'll listen. I think that's
17 probably where we have to be.

18 And I absolutely agree with you. Screening-
19 wise you would want to use these systems and that's the way
20 to go. When you want to actually determine in vivo what
21 might happen, I think some in vivo experiment is necessary
22 just to be sure you didn't miss something.

23 DR. BRAZEAU: I think you could do those sort
24 of in a step-wise approach.

1 DR. AMIDON: Yes.

2 DR. BRAZEAU: You could use the CACO-2 cells to
3 screen a variety of things, choose your best compounds, and
4 be more efficient when you go to the animals because
5 animals take time and money.

6 DR. AMIDON: Yes.

7 I think a comment just to Dr. McGuire. I think
8 one reason the CACO-2 cells have become so popular is that
9 they do form confluent monolayers that are fairly tight
10 junctions and are not leaky. So, you can do a transport
11 experiment. You can put something on the donor side. You
12 can find it on the receiver side. You don't have to grind
13 the cells up. You don't need to have a particularly
14 sophisticated assay. I think a cell line that you could do
15 a transport experiment in would probably correlate at least
16 for parallel passive absorption. So, I think the CACO-2
17 cells become useful because they're technically easier in
18 many ways to do a transport experiment.

19 DR. ZIMMERMAN: Dr. Byrn?

20 DR. BYRN: Is there a way in the CACO-2 cell
21 system to reduce the errors? It looked to me like some of
22 the numbers, the errors were relatively large. And then
23 when you use an internal standard, you're ratioing two
24 numbers with large errors. So, depending on what method

1 you use, you're getting even larger errors, and maybe
2 within a laboratory, is there a way to reduce those errors?
3 I understand we're working in a system that's difficult to
4 work in because it seems to me that if we split the numbers
5 -- you know, if it's greater than .4 or whatever -- we're
6 dealing with quite a large error there sometimes.

7 DR. ZIMMERMAN: Dr. Hussain?

8 DR. HUSSAIN: Two points. One was with our
9 CACO-2, the highest coefficient of variation we found was
10 26 percent with high permeability naproxen. From a
11 biological experiment, I think that's pretty tight.

12 Also, the use of the internal standard is quite
13 actually desirable because we feel that metoprolol is
14 probably at the boundary of high and low. So, if you
15 simply demonstrate the ratio is higher than 1, if
16 metoprolol is the internal standard, that drug is
17 definitely high permeability. That's how we are trying to
18 use the internal standard concept.

19 I agree. I mean, you're putting two drugs
20 together for the ratio and variability would go high for
21 the ratio. At least when we looked at some of the data,
22 that doesn't appear to be the case in all, but that's
23 possible.

24 DR. ZIMMERMAN: Dr. Mayersohn?

1 DR. MAYERSOHN: Let me, Gayle, try to defend my
2 position with whole animals. I think you'll understand
3 what I'm saying.

4 We seem to ask the industry to do more and more
5 and more and there's no end to it. On the other hand, this
6 classification system which introduces sound scientific
7 principles early on in the development process is going to
8 go a long way to reducing costs ultimately.

9 My comment about whole animals was more geared
10 to the following way. If you can have an inexpensive
11 animal model, not a human, which allows you to screen
12 different dosage forms purposely created to have different
13 dissolution properties and you can crate your in vitro/in
14 vivo correlation, now you have potentially an animal model
15 that will let you do all the screenings and even
16 potentially submit in vivo data to the agency for
17 bioequivalence acceptability. That's a long way off. I
18 don't know if an animal model like that exists.

19 I will just throw out to you we have an
20 interest in looking at swine for this purpose, and the
21 literature suggests that may be an interesting animal model
22 to use. But that's where my thinking was.

23 DR. ZIMMERMAN: We're getting to the point
24 where we probably should take a break unless there are

1 other burning questions. Dr. Williams?

2 DR. WILLIAMS: Well, Dr. Zimmerman, I'd just
3 like to remind the committee -- and I'm sure they're all
4 quite well aware of this -- that I think this is probably
5 one of the most important topics that we're going to
6 discuss before this committee.

7 Just to review the regulatory history a little
8 bit, which I'm sure all of you know at least as well as I
9 do, I would start with that Office of Technology Assessment
10 report of the early 1970's which had a very distinguished
11 panel of membership, people who you all know quite well.
12 It was a very significant contribution to our thinking in
13 the United States about bioavailability and bioequivalence
14 and I think formed in some ways the underpinnings for the
15 1977 regulations that the agency promulgated.

16 Those of you who go back and read that will see
17 very clearly articulated the principle that not all drugs
18 and drug products needed in vivo bioequivalence studies and
19 bioavailability studies.

20 Now, with that in mind, the further evolution
21 in the history of the agency's use of that information and
22 other information was that in the 1977 approach we did talk
23 about bioproblem drugs and non-bioproblem drugs. I'm sure
24 you all remember that approach. It was applied in the

1 United States to pre-1962 drugs in such a way that we had
2 the AA category. If it was a non-bioprobem drug, we could
3 waive in vivo bioequivalence for drugs approved prior to
4 1962.

5 Then after 1962 and with the advent of Hatch-
6 Waxman, there was a general agency conclusion, although it
7 was not a fixed irrevocable conclusion, that all post-1962
8 drugs would need in vivo studies.

9 Now, obviously what we're talking about here is
10 backing away from that post-1962 decision, and it's saying
11 for certain drugs you will not need in vivo studies.

12 So, I think I agree with Dr. Mayersohn quite
13 clearly. This has tremendous impact on regulated industry
14 who submit abbreviated applications.

15 I'm also pleased to say that I think it has
16 tremendous impact on innovator pioneer manufacturers in the
17 sense that we can excuse them perhaps from many
18 bioequivalence studies during the preapproval period of an
19 NDA.

20 And then I'm finally delighted to say that I
21 think if it all works out, we can reduce regulatory burden
22 associated with post-approval change, the SUPAC concept,
23 for both pioneer and generic manufacturers.

24 So, I again I want to emphasize what Dr.

1 Mayersohn said. This is a very far-reaching policy that
2 we're building here.

3 I might argue that we're also working with the
4 world community in understanding the science of what we're
5 talking about here.

6 Now, of course, when we talk about this kind of
7 major change, there is the true desire to reduce burden to
8 industry to reduce unnecessary clinical testing, and then
9 it's the rock and the hard place. On the other side of the
10 coin, you get into the public health risk of letting
11 products into the marketplace that aren't equivalent.

12 I'm delighted to see the attention to that
13 concern that Dr. Hussain brought to the discussion.
14 Obviously we're searching far and wide both in our own
15 databases and in the literature for examples of failure,
16 and when we see those examples, they raise a special
17 concern to me because ultimately I think the Office and the
18 Center will have to justify to the public and the various
19 constituencies involved that we are promulgating a rational
20 public health policy.

21 Just to give you some sense of the further
22 steps involved here, we will try to put out -- I believe
23 the guidance is a level 1 guidance. You all had our Good
24 Guidance Practice document in your backgrounder. So, that

1 level 1 guidance will solicit public input, and then we
2 will create what hopefully is a final draft guidance.

3 Then I think we have a responsibility to
4 communicate to the various constituencies -- I might start
5 there with the public and the patient, the health care
6 community, the legislature and our government, the medical
7 community within the Center, the agency -- that we are
8 doing something that's rational and scientifically
9 defensible. And I would argue that this endorsement of
10 this committee at the right moment will be very important
11 to us.

12 Now, I don't think we're ready to ask that
13 particular question of the committee right now. I think we
14 have to do some further work and maybe come back to the
15 committee at the right moment with the final draft document
16 so that you can see how we carried forth your discussion,
17 which I thought was excellent today, and all the other
18 efforts that we're doing here to make sure that we have a
19 defensible, rational, scientifically defensible approach.

20 So, I want to thank the committee and then give
21 them that suggestion as to what the further steps might be.

22 DR. ZIMMERMAN: Thank you.

23 We'll conclude our discussion of the
24 Biopharmaceutics Classification System. I think that the

1 discussion centered a lot around standardization of some of
2 the permeability methods, particularly with regard to the
3 CACO-2 system that you're working on. There were some
4 questions of whether we should be looking at intrinsic
5 dissolution measurements rather than solubility, and I
6 think we reached consensus that the solubility measurements
7 are probably the most practical.

8 With that, I think we'll take a break for 10
9 minutes till 10:30 and then reconvene here. Thank you.

10 (Recess.)

11 DR. ZIMMERMAN: If I could get my committee
12 back, we're going to get started. Well, we're already
13 behind time, so we're going to get started here. Please
14 come in and take your seats.

15 The second part of this morning's program will
16 be on locally acting drug products with an emphasis on
17 dermatological drug products. Our moderator for this
18 section of the program is Dr. Vinod Shah, and he's going to
19 start by talking about guidance development, overviews and
20 issues.

21 DR. SHAH: Thank you, Dr. Zimmerman.

22 I'd like to change the gears now. In the
23 morning we talked about the oral drug administration when
24 we can give the waivers, but now I would like to shift the

1 gears to the topical drug products or we call it the
2 locally acting drug products, topical dermatological drug
3 products. These are the products which you know are
4 applied topically for the topical action. They're applied
5 on the skin or on the affected part of the body for having
6 the local action and not a systemic action.

7 In this section we'll discuss the guidance
8 developments and overview and the issues. That's the first
9 part of the presentation.

10 Following that, we'll have some clinical
11 considerations which will be presented by Professor Howard
12 Maibach.

13 After that, we'll have the dermatological
14 perspectives which will be presented by Dr. Joe McGuire,
15 who is also the Chairman of the Derm Advisory Committee.

16 Then we'll have some presentations on the
17 dermatopharmacokinetic approaches from Professor Hans
18 Schaefer of France, and we'd also like to discuss the lower
19 strengths.

20 Now, going back to my first point, which is the
21 guidance development, overview and the issues, what are we
22 talking about in this case? I'm trying to develop a
23 guidance, a guidance for the bioequivalency studies, in
24 which case we'll define or at least indicate how the

1 bioequivalency studies should be compiled.

2 Bioequivalency for what? This is the
3 bioequivalency for the same type of dosage form; that is,
4 to take two creams from the innovator company and the
5 generic company and make a comparison. So, it will be
6 against the same cream versus cream, same ointment versus
7 ointment, and the same active ingredient and the same
8 strength. We need to keep this in mind because it is
9 primarily focusing on the bioequivalency of the similar
10 type of the dosage forms.

11 What are the different ways how the
12 bioequivalency could be determined? Well, at least there
13 are four ways that we can think about, one being the
14 clinical way of determining the bioequivalency which is
15 doing the clinical studies, making the comparison between
16 the test and the reference products. In general, our
17 feeling is that clinical studies are difficult to perform.
18 They're expensive and a lot of times they are insensitive
19 to some of the findings that you want to look into. Dr.
20 Howard Maibach will go into the details about the pros and
21 cons of the clinical studies when he'll be discussing that.

22 The second aspect is the pharmacodynamic
23 studies. That's where we will be seeing some of the
24 pharmacodynamic endpoints like in the case of the

1 glucocorticoids, which is the only example where we have
2 done such studies, where it develops a blanching after the
3 topical applications and we did discuss that.

4 Today we will not be discussing on the
5 pharmacodynamic aspects and the blanching of the
6 glucocorticoids because that was discussed in the presence
7 of the previous committees here, which was known as the
8 Generic Drug Advisory Committee, several times, and with
9 the input from the committee, we had come forward with the
10 guidance which is in existence.

11 We would like to discuss today the
12 dermatopharmacokinetic aspects about the bioequivalency.
13 In general, we feel that that approach is feasible. It is
14 logical because the drugs are applied topically and what we
15 are measuring, what we are looking at are the drug
16 concentrations in the skin with the
17 dermatopharmacokinetics, pharmacokinetics applied to the
18 blood concentrations in the skin.

19 There are simple methods, simple ways how that
20 could be done, and that will be presented. So, we feel
21 it's a logical way, if we can do that determination, and
22 also it is generally applicable. It may not be universally
23 applicable at times, but we feel that it is generally
24 applicable for almost all the types of topical

1 dermatological drug products.

2 With respect to the in vitro release methods,
3 it is also universally applicable, but today we feel that
4 it cannot be used as a single method to document the
5 bioequivalency. But the value of the in vitro release
6 method is it is can signal inequivalency in the topical
7 dermatological drug products.

8 What type of products are we looking at? Well,
9 with respect to the topical drug products, we are looking
10 at the glucocorticoids, and as I indicated, we already have
11 a guidance on that which was made available on June 2,
12 1995. For the antifungals, this was a clinical study
13 guidance and we had only a draft which was published in
14 1990. We don't have any final guidances available either
15 on the antifungals, antivirals, antiacne like the
16 retinoids, or the antibacterials. We feel that maybe the
17 new principles that we are looking at might be useful to
18 provide us the way how to do the bioequivalency for the
19 topical dermatological drug products.

20 So, I would refer this advisory committee
21 people to give us an input on the two different issues, the
22 first one being can dermatopharmacokinetic, or the DPK,
23 methodology be used for bioequivalency determination for
24 all dermatological drug products which includes the

1 antiacne or the retinoids, antivirals, antifungals,
2 antibacterials, and the glucocorticoids? If not, then for
3 what classes can it be used?

4 I would like to indicate here that there has
5 been some concern that maybe for certain types of drug
6 products it may not be applicable from one side of the
7 coin. The other side of the coin indicates that no, it can
8 be applicable because it does provide sufficient
9 information, especially when you want to compare the two
10 products, the test product and the reference product. If
11 they give both the similar profiles in
12 dermatopharmacokinetic analysis, then it should be
13 acceptable. So, there are two sides of this coin, and I
14 hope that the discussions at the committee would really
15 give us the proper direction as to for those types of
16 products whether it would be applicable or not.

17 Then the second question I would like to
18 discuss and that I'll come back later on in my presentation
19 is can in vitro drug release be used for granting
20 biowaivers for lower strengths.

21 In the handout or the background information, I
22 have provided a summary of the workshop report. We had a
23 workshop in 1996 where about 250 pharmaceutical scientists
24 were present, nationally as well as internationally known

1 people who participated in it. A summary of the workshop
2 has now been submitted to Pharmaceutical Research for
3 publication, and hopefully that will be out either in the
4 February or March issue of Pharmaceutical Research.

5 Some of the important things that came out from
6 the workshop are that the DPK is a viable method for
7 bioequivalency evaluation of topical dermatological drug
8 products.

9 Skin stripping is a specific DPK method that
10 assesses the drug concentration in the stratum corneum as a
11 function of time, like when we are talking about the
12 pharmacokinetic principles, we are always interested to see
13 what is the rate of absorption, when does it reach the
14 maximum level, and how rapidly it disappears or gets
15 eliminated from the body. The same principles could be
16 applied to determine the drug concentrations in the skin,
17 and that is as a function of time.

18 And the drug uptake and elimination phases of
19 the DPK profile should be always evaluated.

20 These are some of the conclusions that came out
21 from this workshop.

22 In order to help me in developing the guidance,
23 as you also saw from the previous presentations of Dr. Ajaz
24 Hussain, there are always groups of members who start

1 working together and who develop that. Now, in this
2 particular guidance, we have several groups, which I call
3 subgroups, which are discussing on the areas of the
4 comparative clinical trials and the systemic absorption
5 because we also need to worry about the safety issues if
6 the formulations are different; the dermatopharmacokinetic
7 aspects; the pharmacodynamic aspects; the CMC, standing for
8 the chemistry, manufacturing, control, and the in vitro
9 release aspects; and the comparability of the inactive
10 ingredients. These are the different sections of my
11 guidance.

12 I have the members from the different
13 disciplines which are included in this particular
14 development of the guidance.

15 So, with this as a background and overall
16 objectives of this meeting, I would like now to move to the
17 other aspects of the clinical considerations for
18 determining the bioequivalency of these products, and I
19 would request Professor Howard Maibach to come and make his
20 presentation. Thank you.

21 DR. MAIBACH: It takes enormous arrogance for
22 an academician to begin to try to cover all of the field of
23 clinical trials in 14 and a half minutes, but as most of
24 you know, both physicians and academicians are arrogant, so

1 I will try.

2 (Laughter.)

3 DR. MAIBACH: The issue really is not one
4 system, namely the stripping system, against clinical
5 trials. The issue is what are the weaknesses and strengths
6 of the stripping method, which you'll hear about
7 subsequently, and what are the strengths and limitations of
8 clinical examination in standard efficacy studies.

9 Everybody in this room knows it is not a matter
10 of debate. It is not sub judice. Everybody knows that the
11 clinical trials are awkward and time consuming and energy
12 consuming.

13 The issues, therefore, then are what can we,
14 who do clinical assays who are involved in this type of
15 biology, do to improve the metrics. There are whole
16 departments of metrics already in general pharmacology.
17 There is a much smaller group in the cutaneous field, and
18 in fact it will not be till the end of next year that you
19 will get to see from our lab group a book called Cutaneous
20 Biometrics.

21 When you look at cutaneous biometrics, if
22 you've looked at any of this literature, you know that
23 there is something highly peculiar. You notice that
24 remarkably placebos work extremely well, and then the

1 burden of the assay is how do you tell the active from the
2 placebo.

3 It is my intellectual bias that in fact we are
4 really resolving this problem, and I will give you examples
5 that when you really do the study properly, the placebo
6 effect disappears or is at least minimized. I therefore
7 call that the pseudoplacebo effect that is an artifact of
8 the lack of objectivity in our clinical trials.

9 Then the issue really is, how much of the
10 variance in these clinical trials that make them so
11 cumbersome is really a biologic variation in the patient
12 and how much is really simply due to the fact that we're
13 now only beginning to become serious about the science of
14 the metrics?

15 I do not want to give you a report card of my
16 poor observations over some years. So, instead I'm going
17 to give you a report card of somebody else. One of my
18 clever colleagues, H. Williams, and only indirectly related
19 to Roger Williams, had the temerity, which you could do in
20 the United Kingdom, to do such a study. He simply went
21 through the British Journal of Dermatology and took all of
22 the very best studies that we might use for generic
23 comparisons and asked the simple question, if I only take
24 the best studies and you pass the peer review process --

1 this is now forgetting those that never got published or
2 were never submitted -- how well are we trained to show
3 differences between two treatment groups?

4 If you just look at the upper right-hand
5 column, in 98 percent studies -- and you can see the 95
6 percent confidence limits if you want to become even more
7 disturbed -- the metrics were such and the statistics were
8 such that there was no hope of finding a 25 percent
9 difference, and in 70 percent of the studies there was no
10 hope in showing a 50 percent difference. Obviously, if you
11 believe this report card -- and I do believe Dr. Williams'
12 report card -- it means that there's room for improvement.

13 Now, I am going to show you one study, and I'm
14 going to tell you for those few people who are close enough
15 to the skin how I manipulated this to look interesting for
16 you intellectually.

17 This is a study of something that some of you
18 probably consider so mundane that you will not take it too
19 seriously. This is scaling of the scalp and the scaling of
20 the scalp here was using a standard zinc pyrithione shampoo
21 in one group and the placebo shampoo in another group.
22 This is a group of about 30 volunteers. On the horizontal
23 axis, you see the weeks of treatment. On the vertical
24 axis, you see the score.

1 What I would like you to see is that with the
2 vehicle there was no placebo effect. The computer best
3 fit, which is the line that you see, over time shows that
4 with one grader -- I was the grader, although I was backed
5 up by a professional grader. The professional grader and I
6 showed no placebo effect.

7 We then were able to take a look at the
8 treatment group. Again the little dots are the individual
9 values, but you see the computer fit. We showed on this
10 very enlarged scale a difference of 1 unit.

11 Now, for those of you who are more facile in
12 mathematics than I am, I think you can see that even in
13 this rather quality experiment, even if I did it, but I was
14 trained by professionals who know how to do it, that
15 telling the difference with some, say, 20 percent degree of
16 certainty between two formulations may be considerably more
17 difficult.

18 Now, on another imperfect experiment,
19 occasionally my industrial colleagues are kind enough to
20 let me help them plan clinical studies and then look at the
21 results. This study, chosen to be outrageous to you on
22 purpose, is a very simple study. This is a class 2 topical
23 corticosteroid, meaning almost the strongest that are
24 currently available, compared to its placebo. This is not

1 an attempt to tell the difference between two of the same
2 formulations.

3 We're measuring here something called
4 thickening, the thickness of the skin. This happened to be
5 psoriatic plaques, but the data in this experiment shows
6 exactly the same for all of the other parameters, including
7 itch.

8 What I would like you to see, there were two
9 visits. You can see the vertical line is the scale and
10 this is investigator 22. Investigator 22 happens to be one
11 of my personal friends, so I choose not to give you his
12 name because there's another investigator that I'm going to
13 show you in a minute.

14 Investigator 22 showed, A, no placebo effect --
15 that makes me feel very comfortable -- and B, a very large
16 difference. You don't need your personal statistician
17 sitting next to you. The active was very active.

18 But since these are almost always done in
19 multi-center studies, here is my friend, professor number
20 31 or investigator 31, and I would like you to see that for
21 thickening and all of the other parameters, this particular
22 investigator, because we don't have any internal controls
23 the way you do have for you colonic cells that you've been
24 talking about, couldn't tell the difference between a

1 highly potent corticosteroid and its vehicle.

2 Now, obviously if we're going to ask this
3 particular investigator to tell the difference between two
4 biopharmaceutical formulations, the innovator and the
5 generic, we're in bad trouble or the consumer is in bad
6 trouble.

7 Now when you take the four investigators
8 together, obviously you lose the discrimination of the
9 first professor because of the second professor.

10 These are issues that if we are going to be
11 forced to use clinical trials, that we're going to have to
12 deal with in the future.

13 Now, we're doing better in some areas. This is
14 a standard clinical photograph. All of you in the back
15 hopefully can see this is the acne vulgaris that you knew
16 as high school students. This was hopefully your friend's
17 and not you.

18 (Laughter.)

19 DR. MAIBACH: Due to the work of an engineer
20 actually at Procter, Mr. Cyrus Cook, he developed a very
21 simple system for photographing both sides of the face in a
22 very standard way. He was able with this system to solve a
23 dilemma that led to congressional hearings, namely should
24 dermatologists be using tetracycline or should

1 dermatologists not be able to use them, because in fact
2 before this method, half of the studies showed that
3 tetracycline in acne was a placebo and half showed some
4 efficacy. But once you got the proper metrics, then there
5 was no debate.

6 What you see in the last slide that I skipped
7 over very quickly is this is one particular slide from the
8 Procter group which in groups of only 25 subjects, they
9 were able to tell the difference between the placebo --
10 they still had some placebo effect -- the topical
11 tetracycline and the oral tetracycline. The teaching point
12 here is that once you get the metrics straight, you can do
13 a better job of discriminating.

14 But now the next part of it is, what diseases
15 are you going to tell your clinical investigators to us if
16 you want to tell the difference between one formulation and
17 another?

18 Well, I don't have a good example with a
19 generic versus an active, but this is an early study that I
20 was involved with many years ago where we were looking at
21 combination drugs. This is a quinolone plus a
22 hydrocortisone in a combination topically compared to the
23 quinolone alone, the vehicle alone, and the hydrocortisone
24 alone, the standard methodology for demonstrating efficacy

1 of combinations.

2 What I would like you to see here -- and you
3 don't need the fine details, and I can give you the
4 statistics and the publication -- is that if you take a
5 look in the far left panel, tinea pedis, the athlete's feet
6 between your toes, these formulations look identical. But
7 instead, if you go to the third panel, you take a more
8 monomorphous disease that we understand better, tinea
9 corporis, you can see clearly the combination is more
10 effective in the parameters that we measured than the
11 individual components.

12 So, not only do we have to learn how to measure
13 but we have to know the biology of the diseases that we
14 want to measure. All fungal diseases are not the same.
15 Namely, there are some clinical states like the ringworm of
16 the body that are far more homogenous and might give you a
17 much better chance of showing the difference between two
18 active formulations than those that are heterogenous like
19 tinea pedis, or athlete's feet.

20 Now, everybody in this room, not arguably but
21 certainly, knows more about statistics than I do, but all
22 of you shared with me that in high school or in college you
23 saw this slide. You saw the slide that, when we first
24 studied statistics, showed variation of the biological

1 event. Here we're talking about skin diseases. All of you
2 surely know that the differences that you see here can
3 occur by forces related to the heavens above, whatever
4 they're going to turn out to be, but there's big-time
5 variation when you try to measure clinical disease.

6 And all of you, when you took this same course,
7 looked at one of the hundred variations of this slide. In
8 fact, there are now whole textbooks that just tell you how
9 to determine power calculations.

10 But to give you some idea of the complexity of
11 power calculations, for any of you who read your
12 advertisements, our colleagues at SmithKline Beecham just
13 have put in the publications that it took them 3,000
14 clinical subjects to show the difference between a new
15 topical antiviral and its placebo. Obviously we want to
16 avoid doing clinical trials for bioequivalence that get us
17 into those numbers because I supposed you'd need 30,000
18 subjects if you wanted to do the same with two topical
19 formulations that are active that are not the big
20 difference between the active and the placebo. I won't
21 burden this point anymore.

22 Now, for the one or two dermatologists in the
23 audience here, I couldn't resist showing this smiling face.
24 This is arguably to me one of the cleverest skin-related

1 scientists that ever existed, the late Marion Sulzberger.
2 Marion Sulzberger gave us a hint of how we might improve
3 this when he volunteered for military service in World War
4 II. He gave up a very affluent life on Fifth Avenue and
5 New York University and joined the Navy.

6 In the Navy, he told us -- because he was
7 working with war gases, with nitrogen busted, where you
8 didn't want to study any more subjects than you had to
9 study, he suggested, and he was correct, that for some of
10 these things, you should decrease the variance between
11 parallel groups by using the same subject.

12 Now, he was certainly correct. We think the
13 reason for this is not only are you dealing with the same
14 subject but also the eye is much cleverer telling the
15 difference between the left and the right comparison than
16 different people.

17 Now, I don't know whether we could use paired
18 comparison studies. The agency's groups that have worked
19 with this for many years have not favored it for primary
20 drug approval. It's conceivable that it might be favored
21 and simplify the task, which must be shown of course, for
22 bioequivalence.

23 I will also say that at the opposite side we're
24 going to be publishing soon -- Ron Wester and others in our

1 laboratory -- that in fact the supposition that drugs do
2 transfer from one side of the body and get absorbed, which
3 has been assumed for years, is in fact correct. We now
4 have the kinetics to show that.

5 I'm going to end by saying clearly our
6 scorecard up today has been very poor. We're at most a C
7 minus. We're just getting by in comparing formulations to
8 each other that should be equivalent. Our power is
9 relatively weak because of the subjective way in which we
10 are forced to measure disease.

11 But there is a new field of dermatology
12 developing now. It's sophisticated enough to at least have
13 international meetings every few years, namely
14 bioengineering of the skin. Sometimes when you switch with
15 the subjective evaluation of parallel groups and you use
16 some of the mensuration techniques now readily available
17 through skin bioengineering, we may be able to sharpen up
18 the focus of how to do these clinical trials. But in the
19 meanwhile I am hoping that dermatopharmacokinetics advances
20 significantly so that we can be spared and our patients can
21 be spared this work.

22 Dr. Shah, I hope I've addressed the question.
23 Thank you.

24 DR. SHAH: I'd now request Professor Hans

1 Schaefer -- oh, I'm sorry. I'd now request Dr. Joe McGuire
2 to make a brief presentation on the dermatologic
3 considerations for the bioequivalency determination.

4 DR. ZIMMERMAN: I'll point out that our
5 committee has been joined by Dr. Kathleen Lamborn.

6 DR. McGUIRE: Good morning. It occurred to me,
7 as Dr. Maibach was speaking, that I probably should have
8 preceded him because some of the difficulties in metrics
9 are related to some of the considerations that I'm going to
10 illustrate.

11 It occurred to me in the first part of the
12 program that the gut is very different from the skin. Most
13 of you think that a way to get a drug to work is to get it
14 through the gut. That's true. If we apply something to
15 the skin and it immediately gets through the skin, it
16 really doesn't hit the target that we're aiming for.

17 The route of an agent applied to the skin
18 surface is varied. The stratum corneum is a very dense
19 membrane and is filled with inter-corneocyte lamellae,
20 which are structural lipids, which we'll say more about in
21 a minute.

22 But even in normal skin there are microfissures
23 in the stratum corneum, and these are especially amplified
24 in all diseases, especially dermatitic diseases and

1 psoriasis. There are special glands. There are special
2 organs in the skin, eccrine glands, pilosebaceous glands,
3 hair follicles, and all of these provide very rapid entry
4 for various types of molecules.

5 Lastly I should say that there are major
6 changes in the integrity of the epidermis by prior
7 treatment.

8 For those of you who don't know what skin looks
9 like, this is it. SC stands for stratum corneum, and you
10 see there are parallel lines there. Those represent
11 corneocytes separated by lipid lamellae. This is probably
12 the most impermeable part of the epidermis. VEP stands for
13 viable epidermis. These are the viable, growing, dividing
14 keratinocytes. And PD stands for papillary dermis, and the
15 squiggly things are blood vessels.

16 Well, once a molecule gets to this area and
17 hits the blood vessels, it's virtually out of there. It's
18 subject to hydroxylation, hydrolysis, sulfation, and
19 excretion either by the liver or kidney.

20 These two imaginary figures to the right are
21 concentration, and the major concentration of the molecule,
22 whatever is applied, is on the top of the skin, and then as
23 it moves through the viable epidermis and then it very
24 rapidly is excreted after it hits the papillary dermis.

1 The velocity of movement -- and I think Dr. Schaefer will
2 have some quantitative data on this -- is very slow and
3 then quite rapid as it moves into the papillary dermis.

4 Well, as I indicated initially, the aim of
5 treating skin disease is to treat some of the cells within
6 the skin. It's not simply to move through the skin and be
7 excreted. Here are examples of several different types of
8 treatments.

9 For stratum corneum, we use kerolytics such as
10 urea, salicylic acid, alpha hydroxy acids, lactic acid,
11 emollients, detergents, and I should have added sunscreens.

12 For the viable epidermis, we have a number of
13 compounds, the glucocorticosteroids, retinoic acid, and
14 calcipotriene.

15 For papillary dermis, similarly we use
16 glucocorticosteroids, retinoic acid, and calcipotriene.

17 The hallmark of the diseases in this category
18 are the major diseases of dermatitis, psoriasis, and acne.

19 If we look at the specific targets in stratum
20 corneum, we have the intracellular lamellae, which are lipid
21 structures, the corneocytes, which are basically dead basal
22 cells that consist primarily of keratin, and these
23 corneocytes show covalent bonding both to extracellular
24 lipids and to intracellular keratins. So, this is another

1 target for our therapeutic modalities.

2 In the viable epidermis, we have a number of
3 cells, suprabasal cells, granular cells, and the basal
4 cells, also melanocytes, a very special target, and if you
5 were treating with a depigmenting agent such as azelaic
6 acid, you're really interested in hitting the melanocyte
7 and missing these other cells. The Langerhans cell is an
8 antigen producing cell and a very important cell within the
9 epidermis. The viable epidermis also contains variable
10 numbers of lymphocytes.

11 The papillary dermis is quite rich. It
12 contains fibroblast, mast cells, endothelial cells,
13 lymphocytes, and each of these cells represents a specific
14 target in specific diseases.

15 Now, many people have attempted to identify and
16 develop in vitro measurements of various compounds on cell
17 types. For instance, in the corneocytes, function should
18 not -- that's a misprint there. In corneocytes cholesterol
19 synthesis and hydrolysis of cholesterol sulfates has been
20 measured. Fatty acid synthesis has been examined as well
21 as ceramid synthesis.

22 In keratinocytes there are a number of things
23 that can be measured ex vivo. Structural protein
24 synthesis. There are a variety of keratins that appear in

1 varying situations, and these are site-specific. Several
2 of the keratins are present in basal cells. A different
3 profile of keratin synthesis occurs in the suprabasalar
4 area.

5 The basal cells divide. They also produce
6 proteases as well as collagenases, and interestingly the
7 keratinocyte synthesizes collagens that are ultimately
8 found in the dermis. Integrins are synthesized by the
9 keratinocyte, and keratinocytes undergo an interesting
10 programmed cell death called apoptosis.

11 Fibroblasts also produce proteases, structural
12 proteins, and integrins.

13 Endothelial cells produce a variety of
14 integrins and also show a programmed cell death called
15 apoptosis.

16 Mononuclear cells are of several types and
17 they're found in the dermis and epidermis. Interesting
18 assays have been developed by a number of people showing
19 that glucocorticoids can inhibit the production of
20 cytokines by mononuclear cells. This has been a very, very
21 powerful way to predict efficacy of steroids. Mononuclear
22 cells also synthesize integrins and show apoptosis.

23 We'll have little to say today about
24 melanocytes, but this is a very specialized cell which is

1 involved in melanin synthesis, melanosome formation, and
2 melanosome transfer into adjacent keratinocyte.

3 The Langerhans cell is primarily involved in
4 antigen presentation. It plays an enormously important
5 role in many skin diseases.

6 Skin stripping has been raised as a possibility
7 of learning something about the kinetics of drugs in a very
8 regulated way. The question is, what can we learn through
9 skin stripping, through corneocyte harvesting? What
10 variables does the stripping itself introduce? And should
11 the same site or should a different site be stripped at
12 intervals following the application? And I'll show this in
13 my last slide.

14 If one is to consider tape stripping for
15 dermatopharmacokinetics, then the considerations would be
16 skin site application, the application of the drug. All of
17 these obviously would have to be highly standardized. The
18 site would have to be cleaned after application of the
19 drug, and then the corneocytes would need to be stripped in
20 a very reproducible way.

21 Now, the question is, if there are to be
22 successive strippings, should the same site or should
23 different sites be stripped? If you look at this cartoon,
24 this upper group would be stripping the same site, and look

1 at the bold as the material, and this is all fanciful. But
2 the material is moving down into the stratum corneum at the
3 same time as the stratum corneum is being stripped. Each
4 stripping changes the characteristic of the stratum
5 corneum.

6 On the other hand, if you strip different
7 sites, then this is site A, it's stripped, site B is
8 stripped as the material moves down further and further
9 into the stratum corneum. So, the wave of the drug would
10 be moving down toward the dermis.

11 In the last slide, I'd like to show you an
12 experiment that I did many years ago and did not publish.
13 I was looking for the hypercalcemic effect seen in squamous
14 carcinoma, and in order to produce this hypercalcemic
15 effect, which obviously was of some clinical relevance, we
16 needed to have an animal that could reproducibly develop
17 squamous carcinomas. The way we did that had been
18 established probably 20 years before, and DMBA was applied
19 in acetone, and after a certain number of weeks papillomas
20 appear and then carcinomas appear.

21 Well, the part of the experiment that we did
22 was to add the DMBA in DMSO, and at the end of about two
23 months, the technician told me that the mice looked really
24 pretty good, that not much was happening. I thought that

1 was peculiar, that maybe I should go back to the
2 instructions and do it the way that the book said to do it.
3 And so I did the DMBA in acetone and in four weeks there
4 were papillomas and in eight weeks there were cancers.

5 Well, at that time this was simply an
6 impediment to the experiment and I paid no attention to it,
7 but clearly I learned something very important about
8 permeation at that point, and that is that if you want to
9 do something to the epidermis or if you want to do
10 something to the skin, you have to deliver the agent to the
11 skin and not facilitate the penetration of the agent
12 through the skin. I'm sure, although we didn't measure it,
13 that the DMBA in this set of animals was in the urine in
14 hours. In this case it was in the skin for a long period
15 of time.

16 Well, these are some of the structural and
17 anatomical considerations for pharmacokinetics in the skin.
18 It evolved quite differently from gut. Please remember
19 that skin evolved in order to keep everything out that was
20 already on the outside and everything that's on the inside
21 the skin attempts to keep in. On the other hand, the gut
22 selectively absorbs what it wishes, and so we're dealing
23 with two entirely different physiological systems.

24 Thank you.

1 DR. SHAH: I'd now request Professor Hans
2 Schaefer to make a presentation on the
3 dermatopharmacokinetic principles as it applies to the
4 bioequivalency of topical drug products.

5 DR. SCHAEFER: First of all, I'd like to thank
6 you for the invitation. My affiliation is I'm Scientific
7 Director of L'Oreal. There is a dermatological company
8 affiliated to L'Oreal which is Galderma. I've no in-line
9 responsibility in respect to dermatological products.

10 Vinod, thank you very much for letting me come.
11 I'll try to be very short, very brief, and I'm very
12 grateful to Howard and to Joe for setting the stage so I
13 can rush on and go into the details.

14 As Dr. Maibach and Dr. McGuire pointed out,
15 there are different compartments in the skin. You see the
16 horny layer barrier in red in a very simplified draft. You
17 see the different targets which are horny layer, epidermis,
18 dermis, blood vessels, sebaceous gland. Please keep this
19 all the time in mind when we are talking about
20 dermatopharmacokinetics.

21 For the skin holds what holds for general
22 pharmacokinetics, that is the Bateman function, that is,
23 influx, elimination, and taken all together, this is the
24 concentration at the target site. As to timing, normally

1 in general, in normal skin the peak for any kind of
2 compound, with few exceptions, is at 6 hours, in diseased
3 skin at 1 hour. There's a distinct difference between
4 kinetics in normal and diseased skin.

5 This slide shows all the secrets of barrier
6 function. It is as simple as that. If you take subsequent
7 strippings, that is, in other words, you apply a
8 preparation on the skin, after a given time, remove the
9 surplus, and then take the horny layer layers away one by
10 one by applying tape strip and then analyzing what is in
11 this tape, then you find invariably this kind of kinetic,
12 that is, high concentrations at the upper side, low
13 concentrations at the lower side, and there is always a
14 gradient of 1 and a half to 2 orders of magnitude.

15 Every single layer protects the body by a
16 factor. Half, half, half, half, half, is let through in a
17 very low percentage. So, you have here in the upper parts
18 a reservoir, and the whole horny layer is the barrier, the
19 two corresponding parameters.

20 Now, in respect to stripping, we have done
21 numerous experiments with numerous compounds, and you see
22 here quite different compounds with different permeation
23 kinetics through the skin, likewise benzoic acid which has
24 the highest penetration rate in different concentrations,

1 and so on and so on. It's only to show you that we have
2 investigated quite a number of compounds, and we have found
3 in all these compounds that there's a straightforward
4 correlation between nanomoles of compound in the stratum
5 corneum in animals and what goes into and through the
6 animal in 4 days. This is permeation through the skin. A
7 strong correlation when you strip after 30 minutes.

8 Now, what is the target? As it has been said,
9 the target is not a systemic compartment. This target is
10 the skin. So, in the past we did the following. We
11 applied radiolabeled compound to volunteers, then took
12 biopsies, then sliced the biopsies subsequently, and
13 analyzed slice by slice the concentrations in respect to
14 different concentrations applied, in respect to different
15 vehicles, in respect to different timing.

16 Again, you always invariably end up with this
17 kinetic, that is, in the epidermis, high concentrations.
18 In the dermis, here is the vascular bed at this level,
19 lower concentrations and low concentrations in the low
20 dermis.

21 This is retinoic acid. Please keep this in
22 mind. We did at that time always the same kind of
23 experiments: first strip the horny layer away, then do a
24 biopsy, then measure the concentrations in the skin.

1 This is very bold, but you have to keep it in
2 mind. It's a fact.

3 The pivotal process is the distribution of a
4 compound from the surface into the horny layer. It's there
5 where it all happens because, as Howard said, as Joe said,
6 the subsequent process, the diffusion through the epidermis
7 is faster by orders of magnitude than the distribution in
8 the horny layer, and the diffusion from the epidermis into
9 the blood vessels is by orders of magnitude faster than the
10 entry into the epidermis. So, this is the time-limiting
11 process.

12 This is obvious to us. I hope this will become
13 obvious to you, that the kinetics depend on the liberation
14 from the vehicle. As I said, the vehicle does not
15 accompany a given drug through the horny layer. It
16 accompanies to the upper layers of the horny layer and then
17 is separation because imagine that you have an open 1
18 percent concentration of a corticosteroid in a vehicle,
19 paired to an accompanied effect, that is, the vehicle would
20 go together, then as much vehicle should enter as
21 corticosteroid. That would be a ratio of 1 to 1,000
22 because you have a 1,000-fold vehicle relative to the
23 corticosteroid, which is obviously not the fact.

24 This is obvious but it has to be said again and

1 again. It's at the target site and it's the time ratio
2 between presence and flux through the skin, which is
3 important for the therapeutic activity.

4 Now we come to the real thing. Imagine that
5 you apply hydrocortisone at different concentrations, a
6 logarithmic scale, to the horny layer and strip the horny
7 layer away. That's what you find.

8 Imagine a second set of experiments where you
9 strip the horny layer away first, then applied the drug,
10 the same drug, to the naked skin surface. That's what you
11 find, a difference of 100-fold which clearly demonstrates
12 the retarding effect, the barrier effect of the horny
13 layer, and which clearly demonstrates the dose-
14 pharmacokinetic relationship because they are practically
15 parallel, as you see, with minor differences.

16 However, there is not always a straightforward
17 concentration/pharmacokinetic relationship. This is again
18 hydrocortisone on a logarithmic scale, and you see that at
19 higher concentrations the curve is lowering. Here is in
20 comparison the curve relative to the denuded skin, that is,
21 without horny layer. You see again the scale. It's a 100-
22 fold difference.

23 Now, here we did vasoconstriction, and you see
24 that vasoconstriction up to here was predictive of the

1 concentrations in the skin. From up here at higher
2 concentration, it wasn't anymore. In other words, in this
3 case pharmacokinetics are more precise than
4 pharmacodynamics. Whether they are relevant or not for a
5 given case is another question. However, what you can say,
6 as long as you stay with this range, then yes, that's
7 perfect parallelism between the one and the other.

8 So, there is a clear-cut, though not always
9 linear correlation between the concentration of the
10 corticosteroid at the target site and vasoconstriction,
11 that is, between pharmacokinetic and pharmacodynamic
12 parameters.

13 Here is an example which has been done in
14 collaboration with Vinod Shah and with Lynn Pershing, who
15 is here. We investigated with different parameters two
16 different corticosteroids, and you see the
17 vasoconstriction.

18 The next slide shows the stripping, and going
19 back you see there is almost precise parallelism between
20 the two measurements, which is only to say there is a
21 straightforward correlation between the liberation and
22 distribution process of a given drug in the horny layer, as
23 measured by the stripping technique, and the diffusion into
24 the skin and into the body, as we have shown in the first

1 slides.

2 So, next to measuring the concentration profile
3 in different skin layers, and I have to emphasize the
4 slicing method cannot be a routine method because it needs
5 radiolabel, it needs volunteers, it needs biopsies, and you
6 need a number of biopsies. So, it's practically
7 unfeasible.

8 Next to this we can best follow the kinetics by
9 linking the stripping, that is, the concentrations in the
10 horny layer, by analyzing this distribution process
11 relative to the concentrations in the skin. So, one can
12 assume that when for a given drug and two similar
13 formulations the liberation/distribution process in the
14 horny layer is the same, the subsequent diffusion to the
15 target will be the same.

16 Now, the exceptions. The most important
17 question we always have to ask in respect to techniques
18 like this: What are the borderlines? What are the
19 exceptions? We're talking about the follicle. Is there a
20 possibility that drug enters into the follicle and escapes
21 the stripping technique because by the stripping technique
22 you take this part of the horny layer away, not this part.

23 Now, first we have to say there is down to
24 here, the skin is protected by a barrier too. There where

1 you see the red color, there is a barrier. I think I show
2 this in the next slide. This is the lower part below the
3 entrance of the sebaceous gland. That's the infra-
4 infundibulum. There is no normal horny layer. Whereas in
5 the acra-infundibulum, you see here the corneocytes
6 normally arranged. That is a barrier. So, it's only when
7 compound entered deep into the follicle, when they are
8 targeted, that yes, there is a problem.

9 So, can we assess this? Can we verify this?

10 Now, here is a typical case. That is,
11 testosterone, and you see here a peak close to where the
12 sebaceous gland is. Yes, testosterone is highly lipophilic
13 and obviously this is the slicing technique. We have
14 sliced it, and where we found an accumulation.

15 However, please look to the scale. It's a
16 logarithmic scale, so this accumulation, this slight
17 increase of the concentration, is relatively insignificant
18 to the concentrations here in the epidermis and in the
19 upper dermis up to here. It's only from up here, from 10
20 to the minus 6 molar, that yes, there is a difference.
21 Here up 10 to the minus 5 molar in the epidermis, no, it
22 doesn't play a role. So, in general you could say in this
23 case it doesn't really play a role.

24 Now here is a case where a compound has been

1 targeted to the follicle. It has been designed on purpose
2 to enter into the follicle. In fact, you see high
3 concentrations. This compound is fluorescent. It is a
4 synthetic retinoid. It is fluorescent and in fact it
5 enters into the follicle and the distribution is different.
6 Here is a case where I wouldn't dare to say the stripping
7 technique predicts this. Certainly not.

8 So, it's only when a drug is targeted to the
9 lower lumen of the follicle that one cannot expect the
10 liberation/distribution process of the skin surface to be
11 representative.

12 Let's go on. These cases we can again verify
13 them and by a relatively simple technique which is call the
14 follicular cast technique. In essence, what is it? It
15 means that you put magic glue on a glass slide. You press
16 it to the skin, leave it on the skin, and tear it off. The
17 upper part of the follicle comes with it. So, in fact what
18 we do in this case, we cut this part off and quantify what
19 is in this part relative to the normal stripping technique.
20 Then we can tell, yes, there is a follicular targeting or,
21 no, there is no follicular targeting.

22 But keep in mind this depends on the substance.
23 It depends not really on the compound. Once you are
24 dealing with a compound, a given compound, you know whether

1 it enters into the follicle or not. In most cases it
2 won't.

3 Now, since we have been talking about
4 corticosteroids and retinoids, I only wanted to show you an
5 example of an antifungal which is a cortisol, as far as I
6 recall. Again, you see here the stripping, that is, the
7 horny layer. These are the concentrations in the horny
8 layer. It's not the other way around, but you see clearly
9 here's the skin surface, the horny layer, the
10 concentrations, again this typical logarithmic gradient,
11 and here the subsequent distribution in the epidermis and
12 the dermis, kinetics which are absolutely normal and you
13 see the correlation between the two of them. They are
14 clearly linked by logarithmic functions.

15 Here is another extreme case which shows you
16 that, yes, you can distinguish. This is hydrocortisone
17 formulated in a liposome formulation. Here is the normal
18 formulation of hydrocortisone, the normal distribution,
19 high concentrations in the upper layers of the horny layer,
20 low concentrations in the lower layer, the typical
21 logarithmic distribution epidermis and dermis.

22 And here is the liposome formulation. Quite
23 obviously the liposomes have completely changed the
24 distribution kinetics in the horny layer. It's distinctly

1 different from this kinetic, and quite obviously this has
2 changed the distribution in the epidermis and the dermis,
3 that is, at the target site too.

4 So, in other words, this shows that, yes, in
5 certain cases you can tell the difference between two
6 different formulations, and it tells too that change in
7 characteristics in type of formulation, of course, does not
8 allow with this technique to prove bioequivalence. It
9 cannot be equivalent. Here we show that it is not.

10 So, to come to the conclusion in normal cases
11 of corticosteroids, retinoic acid, of undefinables, we have
12 shown that there is parallelism between the distribution
13 process, as measured by the stripping technique, and the
14 subsequent concentrations at the target site in the skin.

15 As soon as there is a change in phase, that is,
16 as soon as you're dealing with solid material, you cannot
17 compare the two anymore because solid material -- let's
18 say, part of hydrocortisone -- would be not dissolved, but
19 in crystalline form in the formulation, then you have to
20 deal with different dissolution kinetics, with
21 polymorphism, similar problems, and you cannot compare
22 them. New studies would be needed. So, we are only
23 dealing with dissolved compounds when we are talking about
24 the stripping technique.

1 The other exception is that whenever compounds
2 are specifically targeted -- but this is in most cases
3 solid material -- to the deep follicle, then of course one
4 should not compare them. But you can distinguish them by
5 the second technique, which I have shown, that is, the
6 follicular cast technique.

7 Coming from there, the obvious question: Is
8 there a distinct difference between hydrophilic and
9 lipophilic compounds? No, there isn't.

10 There is no class of compounds in which you can
11 use the technique relative to the other class where you
12 cannot use it. That's not the case.

13 It is the physical characteristics of the
14 formulation and it's the targeting which makes the
15 difference. It's not the form in itself; it's not the
16 compound in itself because once you have established the
17 kinetics for a given compound in a given formulation, under
18 the given condition in human volunteers, then yes, to my
19 experience you can compare them.

20 Thank you for your attention.

21 DR. SHAH: After hearing the different ways of
22 measuring the bioequivalency for a topical dosage form, I'd
23 like now slightly to consider how many bioequivalency
24 studies are needed if a firm is interested in manufacturing

1 more than one strength of the product, meaning two or three
2 lower strengths.

3 But before we go into that, as in the morning
4 we made some comparisons between the orally administered
5 drugs and the topicals, I'd like to bring to the attention
6 of the committee members that as far as the oral drugs are
7 concerned, oral immediate release drug products, the
8 bioequivalency studies are conducted at the highest
9 strength level, and all the lower strength products are
10 approved based on the composition similarities and the
11 dissolution profiles.

12 So, I'm trying to take a similar approach, even
13 though there are drastic differences between the topicals
14 and the dermatological drug products, that can we use the
15 same approach, like have the bioequivalence studies for the
16 highest strength and then approval of the lower strengths
17 made from the composition similarity and in vitro drug
18 release? That is the question that we have.

19 In order to do that, we have to make some
20 assumptions and certain requirements, the assumptions being
21 that the formulations, the two strengths, differ only in
22 the concentration of the active ingredient and there is no
23 difference in manufacturing process and type of equipment
24 used between the two strengths. As you recall, for the

1 topical drug products, the active ingredients, the amount
2 is somewhere between .05 percent or .001 percent, very,
3 very low concentrations.

4 So, here what we are indicating is only
5 differences in the small amount of the active ingredient
6 and no other difference, and the requirements being that
7 the reference listed drug, which is the innovator product,
8 is marketed at both the strengths, the higher strength as
9 well as the lower strength, and the generic product, the
10 test product, is determined to be bioequivalent to the
11 innovator product using the appropriate bioequivalency test
12 criteria.

13 It can be any method, either the
14 pharmacodynamic method, if the DPK method is acceptable, or
15 the clinical method, but it is found to be equivalent and
16 therefore the only difference would be like a small amount
17 of the drug.

18 Now, in order to apply the in vitro release
19 methodology, which is similar to the drug release
20 methodology, all the release rates should be measured under
21 the same test conditions, and the in vitro release rate
22 should be compared between the reference product at the
23 higher and the lower strengths and the test product at the
24 higher and the lower strengths.

1 Then you need to calculate the ratio, the
2 release rate of the higher strength over the lower strength
3 of the reference product, and the same thing for the lower
4 strengths. Based on this comparison, if this ratio is
5 similar to this ratio, then the proposal is, yes, they
6 could be given the biowaiver.

7 To show you some examples, like in this
8 particular case, it was concentrations of the two steroids,
9 the release rate of the higher strength was 45 units and
10 that of the lower strength in this particular manufacturer
11 was 16 right here. Whereas, in the case of a second
12 manufacturer, the two release rates were 21 and 7, but if
13 you compared the release rate ratios of higher strength
14 over the lower strength in both the cases, it turns out to
15 be nearly the same.

16 And that's what we are suggesting, that if the
17 release rates are nearly the same in both the cases, then
18 maybe we can give the waiver of the lower strength of the
19 test product, that is, this particular one.

20 To show you one more example, this is the
21 example of the hydrocortisone. The higher strength and the
22 lower strength here has the ratio of 1.63 from one
23 manufacturer. The second manufacturer, where they used
24 completely different formulations, which was manufactured

1 at the University of Michigan by Professor Flynn and others
2 -- even there also for the same strengths, the ratios of
3 the two strengths was about 1.63. So, what we are
4 suggesting again is that if this ratio is nearly the same
5 as this, if we consider this as a reference product, this
6 being the test product, then we can give the waiver for
7 this lower strength.

8 Now, some scientists say that, well, we cannot
9 just go by only two different strength measurements and say
10 that they're okay. We need to make sure that the release
11 rate between the two strengths is linear.

12 Well, we had done that. At least for one
13 particular drug, hydrocortisone, we manufactured several
14 different strengths and we found that both the strengths in
15 which we were interested, the one I showed you earlier,
16 they are all linear when we make an appropriate plot. So,
17 again, the suggestion is probably we can waive the lower
18 strength.

19 So, I come back to the two initial discussions
20 or the points that I would like to discuss now with the
21 committee and have their opinions as to whether the DPK
22 methodology can be used for the bioequivalency
23 determinations of all these different types of topical drug
24 products, and the second point being, can the in vitro

1 release test be used to grant the biowaivers?

2 Thank you.

3 DR. ZIMMERMAN: Thank you, Dr. Shah, and thanks
4 to all the presenters this morning.

5 We're actually running behind, but we need to
6 have the committee have the opportunity to discuss the
7 dermatological issues. So, we will shoot for a 17-minute
8 discussion period and try to adjourn by 12:15.

9 So, with that, I'm going to open the floor to
10 questions to our panel here. Dr. Brazeau?

11 DR. BRAZEAU: I guess I might need a little
12 education. I guess I'm bothered to some extent by the skin
13 stripping technique. When I think about assaying drugs,
14 the key assumption is that the sampling technique isn't
15 going to affect the values. In the material that you sent
16 us to read, you propose to do a skin stripping over a 3-
17 hour period, and I'm wondering about the impact of the
18 inflammatory process on this as you might be stimulating
19 cytokines over that period of time and is that going to
20 impact upon those values. I don't understand that the
21 sampling strategy is going to affect the values you get
22 because it seems to me it will.

23 DR. SHAH: I guess since that's an important
24 question, I'll give the opportunity for everybody to give a

1 response.

2 But let me just say initially I know it's scary
3 when everyone hears the skin stripping, but the skin
4 stripping is nothing but if you take scotch tape, you put
5 it on your arm and remove it. That's the skin stripping.
6 When you put it at the same spot and remove it about 10
7 times, 15 times, each time you remove the scotch tape, you
8 get a layer of the stratum corneum. Along with the stratum
9 corneum, you also get the drug which is embedded inside
10 that. So, all those samples are removed and then analyzed.
11 So, that particular scenario is not traumatic that one gets
12 worried when they actually see what's happening, but
13 without knowing that, it is really scary.

14 Hans?

15 DR. SCHAEFER: The stripping itself takes no
16 more than 10 to 15 minutes. It's after 3 hours or after 6
17 hours or after 24 hours, most normally after 30 minutes
18 that you strip the horny layer away. We take normally 10
19 strippings in order to quantify. We don't need more
20 stripping films in order to do a quantitative analysis. It
21 takes at least 50 strips to provoke an inflammatory
22 reaction. So, in this sense too, I would say it's a
23 noninvasive method. There wouldn't be any immediate
24 influence of an inflammatory process on the technique

1 itself.

2 DR. ZIMMERMAN: I have a question about
3 analytical methods. Presumably one is developing this
4 technique so that we don't have to use radiolabeled
5 compounds. But it seems to me that you're going to be
6 dealing with very low levels and low amounts, and trying to
7 quantitate these amounts in these skin strips might be
8 difficult.

9 Secondly, you have to have an extraction
10 procedure. I assume you dissolve the tape or whatever and
11 you need an appropriate extraction procedure.

12 So, are the analytical issues sort of rate
13 limiting?

14 DR. SHAH: To start with, yes. But right now
15 it is very simple. We have done at least about 10 to 12
16 different drugs, 6 different glucocorticoids, antivirals,
17 antifungals, and retinoids. You take about 10 strips. You
18 extract it in an organic solvent that extracts the drug and
19 maybe some of the junk also along with the glue and all.
20 But then you do the further extraction and you inject it
21 straight into the HPLC.

22 Yes, I would agree with your comment earlier
23 that, no, we don't want any radioactivity because what we
24 are comparing is the two formulations, the test

1 formulation, the reference formulation, and there is no
2 radioactivity or nothing. It's the direct comparison of
3 the two marketed or to-be-marketed dosage forms.

4 DR. ZIMMERMAN: Dr. Byrn?

5 DR. BYRN: Two questions. They're really a
6 little bit questions about your questions. Okay?

7 Number 2, can in vitro drug release be used for
8 granting a biowaiver for lower strength? What the issue
9 there is -- well, maybe you could say, but my understanding
10 of what the proposal is is that you would compare the rate
11 of release of two drug products that were the same, if I
12 could use one of Roger's words, except for concentration in
13 some in vitro test, and then if they both passed and were
14 correlated, then you would not need to do a BE study of the
15 lower dose product. Is that the proposal?

16 DR. SHAH: Right, exactly, because again some
17 of the requirements, as I identified, if there is
18 absolutely no difference between the two strengths except
19 the smaller amount, .1 percent or .05 percent of the active
20 ingredient. Otherwise there is no difference.

21 DR. BYRN: Now, would the active be in solution
22 in both of those or could it be partially in solution and
23 partially in solid? Is that an area of variability? Do
24 you see what I'm saying?

1 DR. SHAH: Yes, I do see that. It could be
2 either. It could be completely in solution or it could be
3 the other way around because again here what we are doing
4 is we are making a similar comparison between the reference
5 product. The reference product also has a similar ratio.
6 The R is the reference product. The T is the test product.
7 So, whatever was happening with the reference product which
8 went into the clinical studies and which is now approved,
9 now we have the anchor between the two higher strengths,
10 the reference higher strength and the test higher strength,
11 and we think that we do not need to be more concerned about
12 that.

13 DR. BYRN: Now, what I'm a little worried about
14 is solubility, let's say, of a corticosteroid in the
15 formulation. If you have a lower amount of corticosteroid
16 in the same amount of formulation and the proportion in
17 solution I think would be higher, right, in the low dose
18 formulation? That might be more bioavailable in that --
19 the amount in solution. So, there may be -- you see what
20 I'm saying? There may have to be a calculation done. I'm
21 not really that concerned with the idea, but you may have
22 to do some correcting.

23 DR. SHAH: The chemical calculations from the
24 equations and all have been done along with Professor

1 Flynn.

2 DR. BYRN: Okay. So, that's all corrected for.

3 DR. SHAH: Right.

4 DR. BYRN: Okay.

5 The second question is about number 1, and I'm
6 new to this so I'm very naive in this area. We know that
7 if the infection is in the follicle, that it may not --
8 let's say that if there is an infection in the follicle,
9 that the way the drug gets to that infection would be
10 different from the way it gets to an infection in other
11 parts of the skin. Is that a factor related to question
12 number 1? Do you see what I'm saying?

13 DR. SHAH: Yes, that's a factor and that's what
14 I would really like to discuss. Maybe I can request
15 Professor Schaefer to really give some more comments on
16 that. Hans?

17 DR. SCHAEFER: When there is an infection,
18 including an inflammation, then normally the follicle is
19 closed. The drug has to bypass the normal horny layer
20 sideways in order to enter into the infected area. The
21 likelihood that a drug then enters directly into the
22 follicle through the roof of a pimple is very low because
23 you have to deal with a lot of material in the infected
24 area, in the inflamed area relative to the non-inflamed

1 area.

2 When we are dealing with another scenario, that
3 is, I would say almost prevention of hyperkeratinization in
4 acne in order to prevent over a long period the process,
5 the pathological process, in acne, things are different.
6 Then we would have to look into it, but as I said, we can
7 look into this in specific cases.

8 However, up to now to my experience, the cases
9 where you see accumulation in the follicles in the lower
10 part are very rare. In fact, we have seen it once, and in
11 the other case it was aimed to reach the hair follicles.
12 So, it's not impossible. It's not excluded.

13 But still to my experience, the distribution
14 process in the horny layer takes place anyway and in my
15 book it's indicative for what happens in the follicle too
16 because there you have a release process in situ of a given
17 compound from the formulation to horny material anyway.
18 So, to my mind there shouldn't be much difference. That's
19 what can be said about this knowing that this has not been
20 investigated in that.

21 DR. BYRN: Just one last question, Chairman,
22 and I'll let other people.

23 One idea. First I thought maybe we should have
24 some kind of decision tree like is the follicle open or

1 closed -- you see what I'm saying -- and then make
2 decisions. But then I heard at the end I think you were
3 saying most of the time this isn't an issue anyway. So, I
4 don't know whether we need a decision tree.

5 But one approach to some of these questions
6 might be to try to have some kind of decision tree to rule
7 out certain cases and then apply it.

8 DR. SCHAEFER: May I add one aspect? If either
9 the innovator or the generic claims targeting to the
10 follicle and has shown it and specific activity that is a
11 split between inflammatory action on the epidermis and
12 activity in the follicle, which would be typical for
13 retinoids, then yes, you better ask the question of whether
14 this is suitable. But apart from that, for most
15 dermatological indications, no, I would say it makes no
16 difference.

17 DR. ZIMMERMAN: Dr. McGuire?

18 DR. MCGUIRE: I was thinking about some studies
19 that were done a few years ago showing retention of benzoyl
20 peroxide in the follicle and the benzoyl peroxide did not
21 arrive in the follicle through the stratum corneum. It
22 went directly in the follicle. What I'm saying is that we
23 have a lot of targets in the epidermis and some of those
24 targets are going to be reached through stratum corneum and

1 some are probably going to be reached directly through the
2 pilosebaceous apparatus.

3 DR. SCHAEFER: That's the typical case, Joe.
4 This is benzoyl peroxide in a non-dissolved form in a
5 suspension and as a wash which is applied short-term to the
6 skin, and then in fact you find, surprisingly enough,
7 entrance of particles deep into the follicle and
8 distribution from there. This is one of the exceptions,
9 yes, clearly.

10 So, that's why I said at the end of my
11 presentation whenever it comes up to solid material, half
12 dissolved or dissolved to a certain extent, then we have to
13 take care. There is no clear-cut proof that then this
14 method can be applied.

15 DR. ZIMMERMAN: Dr. Branch?

16 DR. BRANCH: One of the statements you were
17 making earlier on was the nature of the vehicle was not
18 really important. It was just the amount of drug that you
19 were comparing.

20 But the data you showed with the liposomal
21 preparation I thought was fascinating in that it looked as
22 though the kinetics, once you have got that initial
23 absorption, was different in the deep part. It implies
24 that the drug and the liposome actually travels right

1 through the skin. So, it sort of questions your primary
2 assumption that your vehicle is not an important component
3 in terms of looking at bioequivalence.

4 How confident are you that the vehicle and
5 whatever you're trying to dissolve it in -- it's a point
6 that was raised a little earlier -- the matrix that your
7 drug is presented could be a key factor in addition to the
8 concentration. That's one question.

9 The second --

10 DR. SCHAEFER: May I answer it immediately? I
11 obviously made myself misunderstood. The vehicle is of
12 utmost importance. There must have something gone wrong.
13 I didn't want to say that the vehicle is of no importance.
14 Quite the contrary. You have to stay in the same class and
15 same properties of the vehicle in order to be able to
16 compare bioequivalence.

17 Whenever you change the nature of the vehicle
18 -- I'll give you an example. You add salicylic acid -- you
19 increase the amount of propylene glycol by a factor of 2 or
20 similar changes. Not comparable, clearly not. So, the
21 vehicle is of utmost importance. You have to stay in the
22 same class in order to compare.

23 If ever you have an influence on the properties
24 of the horny layer itself, on its barrier and reservoir

1 function, it doesn't hold anymore. Let's be absolutely
2 clear about that.

3 DR. LAMBORN: You're saying that this
4 substitute assay would not pick up whether or not it's
5 bioequivalent if in fact the vehicles were different?

6 DR. SCHAEFER: Yes. I would say you would find
7 a difference anyway.

8 DR. LAMBORN: That's what I would think. What
9 you're talking about you would, in fact, be able to see by
10 that assay, but that would still make that assay valid
11 then.

12 DR. SHAH: Yes. With the difference in the
13 vehicles, you will find that there is a difference in the
14 DPK measurements, and that would be reflected upon and it
15 will make the product not bioequivalent.

16 DR. LAMBORN: Right. So, that's the whole
17 point I thought, that if there is a difference, such as
18 vehicle which impacts, then you would hope you would be
19 able to see that.

20 DR. SHAH: I think maybe the point Dr. Schaefer
21 was making at that time of the slide was the vehicle does
22 play a role as to how the drug is released and it comes to
23 the surface of the skin, but then the stratum corneum takes
24 over and that's why you do not measure the vehicle into the

1 stratum corneum but you measure actually only the drug,
2 otherwise there may be a thousand-fold difference in terms
3 of the different vehicles. I think that was the point Dr.
4 Schaefer was trying to get across.

5 DR. BRANCH: But the kinetics of the drug going
6 through the skin in the liposomal preparation, once you got
7 deeper to the horny layer, was very different. It was as
8 though the changes are not confined just to the outside,
9 but the changes are going right through.

10 DR. ZIMMERMAN: Dr. Mayersohn?

11 DR. MAYERSOHN: Vinod, how do you assess the
12 reliability of the methods currently used to measure
13 release rate from an ointment?

14 DR. SHAH: Right now only the clinical study
15 was done for the products. There are not many generic
16 products except for the glucocorticoids, and for
17 glucocorticoids we have the pharmacodynamic measurements.

18 DR. MAYERSOHN: The question was in vitro
19 release.

20 DR. SHAH: Oh.

21 DR. MAYERSOHN: You have an in vitro release
22 procedure. How do you assess its reliability or
23 predictability?

24 DR. SHAH: The in vitro procedure is not a

1 standard requirement. It has become a tool to assert the
2 sameness of the product between the pre-change and the
3 post-change product under the SUPAC-SS guidance. So, only
4 when the SUPAC-SS guidance got finalized in last May we
5 have now the in vitro release in place.

6 DR. MAYERSOHN: So, you wouldn't even look at a
7 comparison between formulations.

8 DR. SHAH: No. But I have some data. If
9 people have some time, either now or later, to show you how
10 the formulation factors would be affecting the in vitro
11 release rate.

12 DR. MAYERSOHN: So, you're not at a point where
13 you would even propose an in vitro release rate procedure
14 to help determine whether or not there was a potential
15 difference in formulations.

16 DR. ZIMMERMAN: They're proposing it for number
17 2, for lower strengths.

18 DR. SHAH: I'm proposing it only for comparison
19 of the lower strength for approval of the lower strength.

20 DR. MAYERSOHN: Within products.

21 DR. SHAH: Within the product.

22 DR. MAYERSOHN: No. I'm asking can it be
23 applied more globally. Can it reach the point where we're
24 trying to use dissolution data for all the products?

1 DR. SHAH: Yes. The answer is yes.

2 May I have permission to go on the floor, or
3 should I come back?

4 DR. ZIMMERMAN: You may have 30 seconds. The
5 committee is hungry.

6 DR. MAYERSOHN: Vinod, while you're searching,
7 I'll also make the same comment I made this morning about
8 animal models. This seems to be an ideal situation for
9 developing potentially useful animal models.

10 DR. SHAH: This slide shows the in vitro
11 release of about nine different manufacturers. As you can
12 see it -- and this is the compositions of all the nine
13 different manufacturers, what all the different ingredients
14 are. It is all taken out from either the labels or the
15 PDR, so I'm not disclosing any trade secrets.

16 But if we take a look at it, most of the
17 products fall into two categories, either this group or
18 this group, and that depends whether they have this
19 particular ingredient or these ingredients. You can see
20 that it can differentiate if there is a difference in the
21 formulation with the results in the release rate profiles.

22 DR. MAYERSOHN: Do you have any idea if this
23 correlates with in vivo dynamics?

24 DR. SHAH: We have some idea on at least two of

1 the drug products that we had studied. One was the
2 hydrocortisone, which Dr. Schaefer talked about it. He
3 showed the pharmacokinetic profile and the pharmacodynamic
4 profile. If we add the third leg of that, which is the in
5 vitro release or the liberation, they all are parallel with
6 one another. Faster release, higher concentration in the
7 stratum corneum, higher pharmacodynamic response. There is
8 a rank order relationship.

9 Similarly, we have done two other studies with
10 Dr. Stoughton and at Duke University where we had products
11 which differed significantly in their in vitro release
12 profile and they were different in terms of the
13 pharmacodynamic measurements of betamethasone valerate.

14 DR. MAYERSOHN: So, you're hopeful that you
15 could develop a reasonably rigorous in vitro procedure that
16 will correlate with in vivo data.

17 DR. SHAH: I would not go to that extent. It
18 will be the same way as you can say for the in vitro
19 dissolution aspects, and that's the reason I said that if
20 the in vitro is significantly different, then it's going to
21 give you a signal that there may be a difference in terms
22 of the bioavailability or the bioequivalency product. But
23 yes, given more time, more effort, we can develop the
24 method that would be in vitro/in vivo correlation.

1 DR. MAYERSOHN: I encourage you to do that.

2 DR. SHAH: Yes. Thank you.

3 DR. ZIMMERMAN: Dr. Williams has, I'm sure, a
4 short comment that he would like to make.

5 DR. WILLIAMS: Well, I'll be very brief. I
6 think Dr. Mayersohn is getting to a very critical point for
7 us, and it depends on how you look at the question. I
8 would say our view now of in vitro release is it's a signal
9 of inequivalence, but we feel uncomfortable using it as a
10 test of equivalence. Now, I think with some further
11 studies, some further research, we could move in the
12 direction you're talking about. Again, I like to think of
13 the test in vitro as sort of a canary in the mine so that
14 if you don't see any problem, you can be assured of
15 clinical comparability.

16 So again, I think, Mike, you're bringing to our
17 attention a good area of future research that we can talk
18 about.

19 DR. MAYERSOHN: Roger, I think with the
20 enormous amounts of money you're going to be saving the
21 United States citizenship with your procedures, some of
22 that money through the benevolence of Congress will find
23 its way back in your pockets to support some of this
24 research.

1 DR. WILLIAMS: That was not a setup comment.

2 (Laughter.)

3 DR. MAYERSOHN: Absolutely not.

4 DR. ZIMMERMAN: On that very optimistic note, I
5 think we will break.

6 In terms of consensus on this section, I think
7 we've talked a bit about Dr. Shah's number 1 question,
8 whether the DPK methods can be used for determination of
9 bioequivalence for all types of products. I think that we
10 agree that perhaps, if there's specific targeting to the
11 lower follicle, perhaps DPK may not be appropriate and we
12 may need to do more work in these areas.

13 I think there may be still a few questions
14 about the in vitro release being used for granting
15 biowaivers for lower strengths based on some of Dr. Byrn's
16 comments in the sense of if the compound of interest, if
17 the drug is not in solution in the higher doses, that in
18 fact you may have greater free drug, if you will, as a
19 percentage in the lower doses. That may be something that
20 needs to be looked at.

21 Are there other consensus? Dr. Lamborn?

22 DR. LAMBORN: I just want to clarify. So, what
23 you're saying is these are the things we have consensus on.
24 It does not imply consensus in the other direction. I'm

1 looking at number 1. Can we use these? And we're not
2 saying, yes, you can except for this.

3 DR. ZIMMERMAN: Right.

4 DR. LAMBORN: We're simply saying do not use
5 it.

6 DR. ZIMMERMAN: We're saying that there may be
7 a -- from what I'm hearing, there may be a question as to
8 whether that is appropriate for that --

9 DR. LAMBORN: But isn't there still also a
10 question with regard to the others? I didn't hear enough
11 discussion that we had all said we agreed that in all other
12 cases there was not a problem.

13 DR. ZIMMERMAN: That's what I'm asking. This
14 is the only one I've heard that there may be a problem
15 with.

16 DR. MAYERSOHN: Cheryl, what is handout from
17 Metzler, Sources of Variation? Did we talk about that?

18 DR. ZIMMERMAN: No, we did not. Oh, apparently
19 not yet. We may be talking about it later.

20 DR. MAYERSOHN: Okay.

21 DR. ZIMMERMAN: With that, we will stop for
22 lunch, and we will reconvene at 1:15. Thank you.

23 (Whereupon, at 12:25 p.m., the committee was
24 recessed, to reconvene at 1:15 p.m., this same day.)

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AFTERNOON SESSION

(1:31: p.m.)

DR. ZIMMERMAN: Ladies and gentlemen, I think we'll get started for the afternoon.

We will now begin an open hearing with speakers who have registered ahead of time. They will each be given 15 minutes to speak. Our first speaker is Dr. Carl Metzler with Nutwood Associates. Dr. Metzler?

DR. METZLER: As you try to help the agency answer the two questions that Dr. Shah addressed to you, sooner or later you're going to have to look at the variability in these metrics, and it may even be that by looking at variability in the metrics, it will help you to

1 answer the questions.

2 I want to talk this afternoon about the sources
3 of variation in the tape stripping assay only.

4 Now, it's my opinion -- and I recognize there
5 are some differences out there -- in the last 20 years
6 we've done very good, very well, done a good job, with oral
7 bioequivalence testing. I would be hopeful that as we move
8 into the bioequivalence of other dosage forms, such as
9 topical and inhalation, some of what we have learned in the
10 last 20 years can be carried forward to help us with that.
11 Dr. Shah sort of alluded to this this morning when he
12 talked about the lower strength problem.

13 The data I'm going to talk about was generated
14 in the Dermatopharmacology Laboratory at Little Rock, and
15 both they and I are paid by ALPHARMA. So, it lays out my
16 biases that you can evaluate accordingly.

17 I went to my database and drew out not at
18 random but haphazardly the data for two individuals, one of
19 which was the classic oral dosing form and one of which was
20 tape stripping. On this overhead, the blue is tape
21 stripping and topical. The red is oral where you have
22 samples of plasma. You have two scales of course because
23 in the classical oral we looked at concentrations in those
24 plasma samples, and in the tape stripping you look at the

1 amount of drug recovered.

2 I fudged the time scale to make it come out the
3 same. The tape stripping in this case was over 3 days, or
4 72 hours, and the oral was over 12 hours.

5 But you see you sort of suggest there that
6 those measures we looked at with the oral dosage forms,
7 area under the curve and Cmax, can also be useful metrics
8 with the tape stripping.

9 Now, this is one possible layout for a tape
10 stripping study. An individual has two arms, right and
11 left. On the arms you have the sides which I call the
12 thumb side and the little digit, but the professionals call
13 lateral and medial. Then on each side, you have assignment
14 of sites for stripping from the elbow down to the wrist,
15 and it's possible to get as many as 16 on one individual.
16 If you can get that many on that, it seems possible you
17 could divide it into two sets of 8 and put one formulation
18 on 8, another formulation on the other 8.

19 If you can do this, then of course, unlike the
20 oral dosing where the 1992 guidelines talk about using the
21 same individual on separate occasions, we use the same
22 individual on one occasion and therefore we avoid those
23 difficult issues of sequence effect and period effect,
24 those things that we don't quite know what to do with when

1 we do see them.

2 To build a statistical model of this, divide
3 the sources of variation into two classes, the fixed and
4 the random. An arm is fixed because we only have two arms,
5 right and left. We're not sampling from a big population
6 of arms. Likewise, side and site are fixed effects. The
7 random effects are subject and then certain interactions
8 with the subject, arm of subject, side of subject, and site
9 of subject.

10 Interpretation of this would be, subject arm,
11 for example, that in different subjects the difference
12 between arms will have some kind of random component in
13 addition to the right versus left. So, this is one way to
14 assign the sources of variability as fixed and random.

15 The two studies I'm going to talk about and
16 show the data from had this kind of layout. Each of them
17 had 6 subjects. We used both the right and left arms, of
18 course, both the lateral and medial sides. Four sites were
19 numbered from elbow to wrist. 22 tape strips were taken 4
20 hours after applying the drug, and only strips 17 to 22
21 were assayed. So, the first 16 were thrown away and 17 to
22 22 assayed.

23 Now, as you probably gathered from the
24 presentation this morning, there are a lot of issues in

1 this question about using the tape stripping assay to
2 measure drug and its disappearance and bioavailability and
3 bioequivalence. I'm not either qualified or have time to
4 talk about them. So, we're going to assume this is a
5 reasonable kind of experimental layout and look at the
6 data.

7 Taking that data, you get these estimates of
8 variance components from the two studies. Unfortunately
9 the major source of variation here is an error term, which
10 we cannot identify the sources of error. The next biggest
11 is subject. Subject and arm is considerable, and then
12 subject by site.

13 Now, rather than spending much time looking at
14 those numbers, if you look at the next slide, I have
15 graphed the sources of variability as a percent of the
16 total variability. So, you see error is the largest.
17 Between 40 and 50 percent of the variability in this tape
18 stripping study was an error term we couldn't identify
19 because of variability. More than 30 percent was due to
20 subjects. Now as I implied, if we measure two formulations
21 in the same subject, just as with the oral dosing
22 bioequivalence studies, we can remove that source of
23 variability so we get a more precise estimation.

24 The next largest is the subject by arm, and

1 these other two are minor. Subject by side, that is the
2 difference between the lateral and medial, from subject to
3 subject, is probably zero. There may be some site, but in
4 one study it was zero; in the other, small.

5 So, just in these studies, this graph shows the
6 relative size of the sources of variation.

7 Although the subject by site had a very small
8 variability, there was some evidence in both studies that
9 there was a trend. That is, if you look at the sites
10 numbered from the elbow to the wrist, there was trend
11 there.

12 This is the data from subject 1, and these
13 straight lines are drawn by the trend option in Excel, so
14 don't give them too much credibility. But what the
15 statistics showed, when done with the very reliable
16 statistical procedure, was there was a very small, perhaps
17 non-significant upward trend as you go down from the elbow
18 to the wrist.

19 So, what can we conclude just from these two
20 little studies in this one particular setup? Well,
21 subjects are a major source of variation and the design
22 should permit removing subject effects. One way to do that
23 would be to use them twice as we do in oral, but if you can
24 actually do 16 sites in a subject, you can probably remove

1 subject effect by studying both formulations in one
2 subject.

3 The subject by arm interaction is the second
4 major effect, although the arms aren't random.

5 Subject by site is the third largest effect,
6 but the sites may have a nonrandom effect.

7 So, what are the implications for this for
8 designing tape stripping studies which test bioequivalence?
9 Well, the first is the one I mentioned several times. You
10 want to test both formulations simultaneously in each
11 subject. Thus you remove that source of variation. You
12 also have no period effect, no sequence effect.

13 You probably ought to randomize formulations to
14 arms because that was a very large source.

15 And perhaps you should assign the sampling
16 times to sites in a nonrandom manner.

17 Contrary to the impression you may get from
18 many statisticians, randomization is not the Eleventh
19 Commandment. Randomization is very useful for removing
20 bias and other things, but there may be times when you
21 don't want to randomize. What I'm suggesting is what you
22 may lose by not randomizing down these sites you will gain
23 in a much decreased logistical problem. You may understand
24 that if you're going to apply drug to these 16 sites and

1 then do the stripping that you probably don't want to go
2 jumping around from site to site over time. It's just
3 asking for errors of mistesting.

4 That's all I had to say. Are there any
5 questions from the committee? I know I should use animals,
6 but what's your question, Michael?

7 (Laughter.)

8 DR. MAYERSOHN: Well, no. This gives a whole
9 new meaning to the arm of a study I think, Carl.

10 (Laughter.)

11 DR. MAYERSOHN: Carl, it seemed to me you were
12 nonrandomly assigning one formulation to one arm and then
13 to the other arm. Is that correct? Or did you divide each
14 arm in half?

15 DR. METZLER: You put one formulation only on
16 an arm.

17 DR. MAYERSOHN: Why not divide that? You have
18 two columns.

19 DR. METZLER: Well, you could. Just I think it
20 gives you a chance for making errors. You could do that.

21 DR. MAYERSOHN: But doesn't that get rid of the
22 arm effect, the arm form effect?

23 DR. METZLER: It could, right. I'd really
24 defer to someone who does this as to how logistically

1 difficult it is to do this and keep those sites absolutely
2 straight and separate and all that. But it's a
3 possibility, right. That would be another way to do it.

4 DR. ZIMMERMAN: Other questions from the
5 committee?

6 (No response.)

7 DR. ZIMMERMAN: Thank you.

8 DR. METZLER: Sure.

9 DR. ZIMMERMAN: Our next speaker will be
10 Christopher Rhodes, speaking on behalf of Barr
11 Laboratories, Incorporated.

12 DR. RHODES: Thank you very much, indeed. I
13 greatly appreciate the privilege of being able to speak to
14 you this afternoon. I am speaking to you on behalf of Barr
15 Labs.

16 The general topic that I want to talk about is
17 narrow therapeutic index drugs, and I am going to focus my
18 remarks specifically onto warfarin sodium because this is a
19 drug which has been the subject of much lively debate. A
20 great deal of heat has been generated on it. I'm not sure
21 if we've had much light.

22 But in your handout, I have given you the full
23 text of a paper on bioequivalency that I published earlier
24 this year. I hope it will be of some use, and I think that

1 in particular the references at the end of the paper you
2 may find to be of some help.

3 Now, the topic I want to address specifically
4 is, are the quality attributes of the generic product
5 presently approved such that we can reasonably say that the
6 FDA and the USP standards do give us a reliable assurance
7 of safety and efficacy? I want to very strongly endorse
8 the thesis that they are, indeed, quite satisfactory.

9 However, having said that, as you can see on my
10 next slide, I do realize that indeed, although the present
11 FDA standards have not only been remarkably successful in
12 this country, but have also proved to be a very useful
13 model in other jurisdictions, certainly we should not rule
14 out the possibility of refining these standards. We know
15 that the science is changing, and certainly we should be
16 prepared to consider all sorts of possibilities to how we
17 could refine these tests.

18 I'm going to suggest to you that any change in
19 the bioequivalency standard should only be made when there
20 is a proven scientific case for such a change. I think
21 that it would be very imprudent of us to be swayed by mere
22 fear tactics or unsubstantiated clinical anecdotes.
23 Certainly unless there are well-substantiated major
24 problems with generic products which are presently approved

1 for marketing, there should be no retrospective or
2 retroactive changes.

3 I do believe it is highly important that any
4 changes to bioequivalency standards should be made at the
5 national level by FDA, when appropriate, working in concert
6 with the United States Pharmacopeia on such matters of
7 potency and content uniformity.

8 I speak as an EU registered pharmacist, and I
9 find it very sad to see that while the EU is gradually
10 centralizing its drug approval process quite properly in
11 London --

12 (Laughter.)

13 DR. RHODES: -- while that is occurring, to see
14 some what I would almost call as pharmaceutical Johnny Rebs
15 trying to take the drug approval process away from the
16 national level.

17 Any decision about the change in bioequivalency
18 standards should be made on an individual drug basis. Each
19 drug stands or falls on the basis of its own
20 pharmacokinetic and pharmacodynamic properties. It is
21 inappropriate to think about moving a whole group of drugs
22 en masse into some new category.

23 Certainly if we are going to change
24 bioequivalency standards for a particular drug, we must be

1 assured that we have equal control over the innovator's
2 product as we do over the generic product. Therefore, such
3 factors as batch-to-batch variability, potency, stability,
4 and so on must be considered for both the generic and the
5 innovator's product.

6 Finally, I think that the physicochemical
7 classification system that we were talking about this
8 morning provides an excellent starting point for any
9 consideration as to what extent, if any, a bioequivalency
10 standard for any given drug should be tightened or
11 loosened.

12 Following from that, I would suggest to you
13 that the golden rule for bioequivalency standard changes
14 should be that if variation in the clinical response of
15 patients to different versions of the same drug product is
16 due to the inherent nature of the drug molecule per se,
17 rather than the drug product quality -- in other words,
18 rather than differences in formulation and processing
19 factors -- then it is counterproductive to reduce or
20 attempt to reduce intra or inter-subject variability by
21 tightening bioequivalency standards.

22 Turning specifically to warfarin sodium,
23 warfarin sodium has a high water solubility. It dissolves
24 very rapidly, and therefore dissolution is not a problem.

1 It has good membrane flux. Therefore,
2 absorption is not a problem.

3 It is basically a very stable molecule.
4 Stability is not a problem.

5 The way the tablets are made is by dry mixing
6 of ingredients, followed by simple, direct compression.
7 Ladies and gentlemen, this is a formulation exercise for
8 PHC-101. It is very simple, very basic. The formulation
9 and processing is robust and it yields products with
10 excellent quality attributes.

11 What about the clinical response to this
12 particular drug? Indeed, there is a lot of variability.

13 Now, I've chosen to take, as the standard
14 reference I used here among the number I looked at, the USP
15 DI, and the first thing we note is that the half-life of
16 warfarin is about 2 days. This means that if a patient is
17 receiving one dose a day and the dose is the same -- it's
18 not always the same, by the way, but if it is, then on
19 average, when a patient takes their daily dose in the
20 morning, they already have in their bloodstream about two
21 to two and a half doses.

22 Now, I want to tell you that when you look at
23 the content uniformity data for the Barr product, it is
24 excellent, but I also want to warn you that content

1 uniformity is not especially critical for this drug because
2 the fact that each dose only contributes about a third of
3 the total amount of drug in the body on any given day means
4 that content uniformity is going to be less critical than
5 for other drugs.

6 Now, warfarin, according to USP DI, quote, is
7 an indirect acting coagulant that prevents the formation of
8 active procoagulation factors. It's an indirect acting. I
9 have underlined that. It is not underlined in USP DI. But
10 there is a time lag, a significant time lag, from when we
11 get the drug to when we see the effect.

12 What is unusual about this drug, as I'm sure
13 most of you know, is that it is very, very susceptible --
14 or the effect of this drug, I should say, is very
15 susceptible to all sorts of changes. Changes in diet can
16 push the prothrombin times up or down. Therefore, it is
17 recommended that prothrombin times should be monitored on
18 1- to 4-week intervals for the duration of treatment.

19 But most important, ladies and gentlemen, is
20 this. When you look at data taken from anticoagulation
21 clinics where they are only using the DuPont-Merck product,
22 they find that many of the patients drift out of control.
23 Now, I'm in no way suggesting that the DuPont-Merck product
24 is not a good product. What I am saying is that it is an

1 inherent property of this drug molecule, its complicated
2 mode of action, the fact that it is so very dependent upon
3 diet and all sorts of other factors, that it is very
4 difficult to keep your patients in control.

5 Now, I'm not going to bore you with going
6 through lots and lots of graphs. I have in my time I think
7 seen over 600 biostudies, and after a while they all merge
8 into one gray mass. But when I looked at the Barr
9 biostudy, I was particularly impressed to see how very good
10 the comparison was between the test and the reference
11 product. There are other graphs. They've got more than
12 one strength. I just show this as an example to you.

13 In addition, I must tell you that recently I
14 had the privilege of discussing with Dr. Joe Latelle who
15 has recently completed a clinical study in which he
16 compared the Barr product with the DuPont-Merck product.
17 I've looked at the data. It is excellent. It's a very,
18 very well-designed study with very clear conclusions, and
19 indeed the Barr product is equally safe and effective. I
20 understand that that clinical study will be published in a
21 peer-reviewed journal early next year.

22 Thus, in conclusion, ladies and gentlemen, I
23 think it is very clear that for this drug, warfarin sodium,
24 the variation in clinical response is a function of the

1 inherent nature of the drug molecule and does not reflect
2 upon the product quality. The product quality, as is
3 determined by USP and FDA tests, shows that our present
4 standards are perfectly satisfactory.

5 Thank you, ladies and gentlemen.

6 DR. ZIMMERMAN: Thank you.

7 Are there questions from the committee? Dr.
8 Byrn?

9 DR. BYRN: I don't really have a question. I
10 just want to make a comment that I think in narrow
11 therapeutic index drugs we can do a lot of analytical
12 studies to verify that there is a minimal batch-to-batch
13 variability in these drugs with respect to all of the
14 attributes such as dissolution, potency, stability, content
15 uniformity, and so on. This might be a good place to start
16 for investigating some of these questions about sameness
17 because although I'm not an expert in bioequivalence, I'd
18 hate to see product variations hidden under inter-patient
19 variability in a bioequivalence study.

20 So, I think speaking as a person that's
21 interested in pharmaceutical processing, this is a good
22 area for us to work on to try to ensure excellent drug
23 quality.

24 And that's really all I had to say.

1 DR. RHODES: I agree very strongly indeed that
2 when you have a drug of this type, it is very important
3 that we do have extensive in vitro testing so, indeed, we
4 can find what the cause of the variability is, yes.

5 DR. ZIMMERMAN: Dr. Branch.

6 DR. BRANCH: I think in terms of determining
7 sameness of drugs, there's a fairly standard approach. The
8 issue you're raising is that of biological variation. It
9 would seem to me that if the major issue in hand is that
10 variation, then an adaptation of the design of your study
11 could show variance in the established product or variation
12 in response to the established product and to the generic
13 or the therapeutic alternative that's being introduced.

14 You didn't mention the design of the study of
15 the Barr product, but it would seem to me that it's not
16 beyond the realm of ingenuity to actually directly address
17 your hypothesis, to demonstrate the extent of variation,
18 maybe even the frequency of loss of control over time with
19 alternative products, and provide a hard data set which an
20 agency would be able to review on its own merits for that
21 particular entity.

22 DR. RHODES: Yes. Let me respond to that.
23 Firstly, the protocol used by Barr was that approved by FDA
24 and FDA gave approval when they saw the results of that

1 study.

2 One of the issues you raised is something that
3 I have addressed in one of the papers that I reference in
4 the handout, and that is this, that perhaps in the future
5 when we're looking at possible changes to bioequivalency
6 tests, we might want to consider including samples from two
7 different batches of both the innovator and the test
8 product. It's just another idea that we might want to
9 think about.

10 DR. ZIMMERMAN: Other questions?

11 (No response.)

12 DR. ZIMMERMAN: Thank you.

13 DR. RHODES: Thank you.

14 DR. ZIMMERMAN: We next have two speakers
15 speaking on behalf of the National Pharmaceutical Alliance,
16 Marvin Meyer and Lane Brunner. Even though we have two
17 speakers, they still only have 15 minutes.

18 DR. MEYER: Indeed, my sponsorship here is from
19 the National Pharmaceutical Alliance. It's also of
20 interest, however, and one of the reasons I'm interested in
21 this topic is because, as some of you know, there has been
22 a lot of initiatives at a variety of states. I come from a
23 state that I'm told in January of this year there will be
24 legislation introduced that is centered in part around the

1 NTI list. So, if I could have the first transparency.

2 I think many of you know, but perhaps not all
3 of you know, what the origin of this NTI list is. Back in
4 the mid-1980's, there was a generic scandal, which I think
5 most of you are aware of, and the FDA compiled a list of
6 drugs and drug products that they wanted to be certain were
7 examined in terms of their reliability from generic
8 companies. So, I believe it was from the Commissioner's
9 office there was this mandate to develop this list of,
10 quote, important drugs that shouldn't be overlooked.

11 Subsequently in the SUPAC-IR Guidance, Appendix
12 A, this list has been appended as drug products that should
13 be looked at carefully before or even if bioequivalence
14 studies should be waived in response to substantial changes
15 in formulation.

16 The bottom line to that is this list was never
17 intended as a negative formulary to be used by states to
18 preclude generic substitution.

19 If you haven't seen the list -- in fact, it's
20 in the handout that the committee has been provided with --
21 there are 24 drugs on it. What I'd like to do is talk
22 about six of those drugs that are on the narrow therapeutic
23 list that we've actually been involved with testing and/or
24 reviewing of data. I'll go alphabetically except I now

1 shifted -- any slide will do. That's fine.

2 (Laughter.)

3 DR. MEYER: The first one I want to talk about
4 is carbamazepine. That's one that's up there high.
5 Everyone talks about it's a critical drug. With
6 sponsorship by the Food and Drug Administration, we did a
7 study on carbamazepine, 24 subjects, looked at the
8 innovator product and importantly three generics that are
9 available in the American marketplace.

10 You can see from the data that the Cmax values
11 were very close. All the generics were virtually on top of
12 each other, slightly higher than the innovator product.
13 The Tmax's. The innovator was slower than the generics.
14 They were all very close and somewhat more rapid. And in
15 terms of AUC, all of the values were virtually on top of
16 each other again.

17 Using the 90 percent confidence limits, they
18 all ranged between 80 and 125 except for one Cmax
19 comparison. That was 126. Indeed, that would have failed
20 the upper limit of 125, but if you consider multiple dose
21 use of this drug, a Cmax value that's a little bit high
22 isn't going to have any effect on the therapy of this drug.

23 This is kind of an old drug but it is on the
24 narrow therapeutic list. We did this study a number of

1 years ago, looked at three products. These three had no
2 guaifenesin in them. We did three others. The even
3 numbered products with guaifenesin. You can see the Cmax
4 across the marketed products of this narrow therapeutic
5 index drug, 5 percent difference; AUC, 2 percent
6 difference. So, again, there didn't appear to be any real
7 problem associated with these marketed products.

8 This is not a generic versus brand comparison
9 because there is no generic version of dilantin, but it's
10 an interesting exercise to see just how variable phenytoin
11 is in a panel of volunteers. The interesting part about
12 this study is product 1 and 4 that are listed there are the
13 same lot of dilantin, and 2 and 3 are also different lots.
14 So, we have three lots with one replicate administration.

15 It looks to us as though this drug product is
16 pretty reproducible. Phenytoin itself apparently is pretty
17 reproducible. All of the Cmax values range from 1.71 to
18 1.79, AUC's from 53 to 54, very, very tight data. I would
19 submit that if a firm comes up with a bioequivalent version
20 of the innovator phenytoin, that it passes the FDA, there
21 shouldn't be a problem with this narrow therapeutic index
22 drug.

23 Primidone is another narrow therapeutic index
24 drug we looked at. We looked at three lots of the

1 innovator, two old formulations, one new formulation, and a
2 generic version that's in the marketplace. All of the
3 confidence limits for Cmax and AUC, making all comparisons,
4 were within 80 to 125, and I think graphically you can see
5 these products are all superimposable.

6 Theophylline, another product that was on the
7 NTI list. We did this study a number of years ago of three
8 marketed products, marketed dosage forms. A 4 percent
9 difference in Cmax, a 4 percent difference in AUC, 0 to
10 infinity. Again, I don't really see a reason for this
11 product being on the NTI list, in terms of bioavailability
12 anyway.

13 Then Dr. Rhodes showed you one slide. I have
14 some supplementary data for the four strengths of the Barr
15 warfarin product. I think Dr. Rhodes made a good point in
16 terms of the physicochemical characteristics of warfarin.

17 Look at how tight the data actually are. What
18 I've plotted here or given in the table, test over
19 reference ratio as a percent, along with the confidence
20 limits, Cmax for the 2 milligrams strength, 98 percent;
21 2.5, 103 percent; 5 milligrams, 103; 10 milligrams, 102.
22 The AUC's range from 98 to 102 for the Barr over the
23 innovator firm. Confidence limits, worst case there was an
24 89 and a 110. So, the limits are very tight. This is a

1 very, very tightly controlled study, a well-designed study,
2 and clearly in my mind suggests that warfarin sodium
3 tablets of this particular generic brand should be
4 interchangeable with the innovator company.

5 Finally, some conclusions. I think that we
6 need to communicate and it's unfortunate that people of
7 Roger's status have to go around the country correcting
8 state boards of pharmacy and state associations and
9 legislative bodies, but unfortunately he has been forced to
10 do that. People don't understand that when FDA published
11 this NTI list, it was not a negative formulary. It was to
12 trigger particular forms of information that would be
13 required perhaps post-approval not preclude approving
14 products at the state level once they've been approved by
15 FDA.

16 There are numerous reasons to monitor patients
17 and titrate the dosage regimen that might trigger an NTI
18 classification. Included are changes in patient response,
19 drug-drug interactions, changes in clearance, patient
20 compliance, and bioinequivalent products. I think there
21 are lots of examples in the literature of A through D. To
22 my knowledge, there are no examples of E, bioinequivalent
23 products that should be titrated because of
24 bioinequivalence. In my judgment there are no well-

1 documented examples of an inequivalent product that caused
2 the difficulty for an FDA rated AA or AB product that was
3 manufactured in accordance with good manufacturing
4 practices.

5 Finally, I believe that the available data does
6 not support a need for FDA to modify the present standards
7 for approval of drug products on the basis of
8 bioequivalence studies whether or not they are NTI drugs.

9 Thank you.

10 DR. ZIMMERMAN: Are there questions for Dr.
11 Meyer?

12 (No response.)

13 DR. ZIMMERMAN: I guess not.

14 DR. MEYER: I used an animal model.

15 (Laughter.)

16 DR. ZIMMERMAN: Thank you.

17 Dr. Brunner?

18 DR. BRUNNER: Dr. Zimmerman, members of the
19 committee, thank you for the opportunity to come and speak
20 before you.

21 My name is Lane Brunner. I'm an assistant
22 professor of pharmaceuticals at the University of Texas at
23 Austin. My responsibilities include teaching
24 biopharmaceuticals and pharmacokinetics to graduate and

1 undergraduate students, as well as being a clinical
2 pharmacology consultant to physicians and pharmacists.

3 I'm here on behalf of the National
4 Pharmaceutical Alliance, and I've been asked to speak about
5 my experiences on the national campaign against the
6 substitution of generically equivalent NTI drugs. And I
7 will be brief.

8 I became involved in the NTI issue last
9 February when rulings were before the Texas Medical Board
10 of Examiners to restrict the substitution of NTI drugs.
11 That action was defeated, but that was only the beginning.

12 Since that initial involvement, I've traveled
13 to various states to speak with state legislators and
14 boards of pharmacy about issues of bioequivalence and
15 substitutability of NTI drugs. So far I've been active in
16 Texas, Colorado, California, Wisconsin, and North Carolina.
17 Before you is an overhead of 22 of the states that have
18 either pending legislation, pending talks, or legislation
19 has been passed.

20 I've also been involved at three of the
21 regional meetings of the American Association of Colleges
22 of Pharmacy, as well as the National Association of Boards
23 of Pharmacy.

24 At each hearing or meeting, the issue is the

1 same: What is the science behind the substitutability of
2 NTI drugs?

3 To many of us the science is simple,
4 straightforward, and nearly intuitive. However, this might
5 not be the case to those who do not have a scientific
6 background. Unfortunately, these are the individuals who
7 are often responsible for creating our state laws.

8 Despite the apparent simplicity behind FDA's
9 guidelines for bioequivalence studies, sometimes politics
10 clouds the issue.

11 Not surprisingly, attempts to make the issue of
12 NTI drug substitution controversial have been made by brand
13 companies with a vested interest in preventing NTI drug
14 substitution. Most notably, this has been perpetuated by
15 DuPont-Merck, whether representing themselves or as their
16 front organization, the Health Alliance for NTI Patient
17 Safety.

18 DuPont-Merck originally began their attack on
19 NTI drug substitution by petitioning the FDA to stop the
20 approval of a generically equivalent product to their
21 warfarin sodium product, Coumadin. The FDA reviewed the
22 petition and flatly denied DuPont-Merck. The FDA's
23 decision was based on the lack of scientific evidence of a
24 potential national health risk.

1 After this denial, DuPont-Merck began a
2 nationwide state-by-state campaign to prevent NTI generic
3 substitution. Since there was no clinical scientific basis
4 for their claims, they decided to take the issue before a
5 non-scientific organization or body, that is, the state
6 legislators. This is where scare tactics and fear might
7 gain support. Currently the issue has been brought before
8 you to those 22 different states. This week alone the
9 issue is being discussed in New Jersey, Washington, and
10 Virginia.

11 I'm not sure if any of you have ever tried to
12 explain pharmacokinetic principles or statistical methods
13 to a senator, but at times it can be a bit of a challenge.
14 So often, arguments turn political rather than remaining
15 scientific.

16 DuPont-Merck has been lobbying the state
17 legislators, physicians, pharmacists, and boards of
18 pharmacy to severely limit or prevent the substitution of
19 generically equivalent NTI drugs, specifically the warfarin
20 sodium product. They continue to do this even though the
21 FDA has approved an AB rated, therapeutically equivalent
22 warfarin sodium product.

23 DuPont-Merck, in their lobbying effort, has
24 mounted an advertising campaign which also calls into

1 question the FDA's ability to approve generically
2 equivalent NTI drugs. When the issue of NTI drug
3 substitution is brought before the state legislative
4 bodies, the lawmakers are told by DuPont-Merck and the NTI
5 Alliance that there is a national crisis in drug therapy.
6 However, no scientific or clinical evidence is ever
7 presented. What is presented are anecdotal stories.

8 Fortunately, DuPont-Merck has only had limited
9 success and has been largely rejected based on their lack
10 of scientific or clinical evidence of a problem, but they
11 have been successful at eroding the public's confidence in
12 the generic approval process by the FDA and have achieved
13 special restrictions in certain states.

14 The opponents of NTI drug substitution appear
15 to have a lack of understanding regarding the methods used
16 by the FDA for approval of generic drugs. What is not
17 understood is that the FDA guidelines evaluates the rate
18 and extent of absorption. It is also not understood that
19 the range of 80 to 125 percent represents the range for
20 which the mean and the 90 percent confidence interval must
21 fall. What is often quoted to lawmakers is that the two
22 generic NTI drugs can vary in blood concentrations by up to
23 45 percent, in addition that the amount of drug in a
24 generic can range from between 80 to 125 percent that of

1 the brand. Obviously, these are simply not true.

2 Unfortunately, DuPont-Merck, the NTI Alliance,
3 and the respective experts continue to confuse and startle
4 state legislators. At present there is no scientific or
5 clinical evidence for changing the current FDA guidelines
6 for the approval of generic versions of NTI drugs. Instead
7 what would be prudent is to increase the education and
8 understanding of those clinicians, scientists, and even
9 lawmakers who may not be aware of the current FDA
10 guidelines.

11 As a scientist and a pharmacist, I find the
12 tactics used by DuPont-Merck and the NTI Alliance
13 reprehensible. I strongly encourage the committee to
14 reaffirm the FDA's approval process and to condemn efforts
15 to oppose the substitutability of therapeutically
16 equivalent NTI generic products. We need to stop the
17 erosion of confidence in the FDA that is being perpetuated
18 now at the state level.

19 Thank you for your time.

20 DR. ZIMMERMAN: Thank you, Dr. Brunner.

21 Are there questions, comments from the
22 committee? Dr. Branch?

23 DR. BRANCH: Could you provide some sort of
24 sense or perspective of the power of the local state

1 legislature to actually be in competition with the FDA?

2 DR. BRUNNER: Well, to give you a little bit of
3 background, what was initially brought about -- I'll use
4 Texas as an example, since that's my home state -- is when
5 the FDA rejected DuPont-Merck's petition and when DuPont-
6 Merck started going state to state, they went to the State
7 of Texas with the attempt to establish a mini-state FDA to
8 oversee the bioequivalence or bioavailability of this small
9 group of drugs. Of course, that was immediately rejected
10 because Texas doesn't need any more legislation in that
11 sense.

12 But what happened is they convinced one of the
13 state legislators that in order to increase or be aware of
14 patient safety, they needed to treat this group of NTI
15 drugs very specially. So, what happened is, because of the
16 lobbying effort, it got passed through one of the
17 committees and was postponed but at the last minute was put
18 onto a different bill and it was passed in Texas.

19 Now, what's currently happening is it is before
20 the Board of Pharmacy, as well as the Texas Medical
21 Examiners Board, to create a list that the law should
22 pertain to. So, I believe in January they'll be meeting to
23 determine which of the NTI drugs of those 24 will be part
24 of the new laws that are restricting the substitution of

1 their products.

2 DR. ZIMMERMAN: Other questions?

3 (No response.)

4 DR. ZIMMERMAN: If not, thank you.

5 DR. BRUNNER: Thank you.

6 DR. ZIMMERMAN: Now we have an opportunity to
7 hear some comments from the general audience. DuPont-Merck
8 would like to clarify its position on Coumadin and generic
9 warfarin in response to statements that have been made just
10 now. Dr. Richard Levy, the Vice President of Regulatory
11 Affairs, has asked to speak, and we will give him two
12 minutes to comment.

13 DR. LEVY: Yes, thank you very much.

14 Our position is not that generic products
15 should not be approved. We asked and submitted a citizens
16 petition prior to the approval of the Barr product that
17 individual bioequivalence be used because we think it's a
18 better approach. We've accepted the product has been
19 approved and that other products may be approved based on
20 average bioequivalence.

21 What we've done at the state level is to simply
22 say that things are not quite certain on an individual
23 patient basis, despite average bioequivalence or
24 potentially even based on individual bioequivalence, and

1 because there's a simple blood test that can be done, which
2 is a prothrombin time, to determine whether the patient's
3 therapeutic response to a substituted formulation is the
4 same as their response to the innovator formulation, that
5 physician should be aware at the time of switch. We have
6 not specifically ever asked that a product not be approved,
7 only that physician notification should be required.

8 We have not been making much of anecdotal
9 reports. We are collecting information. There are some
10 patients in whom the only identifiable change has been a
11 change in formulation. There is one patient who was on
12 Coumadin, then to the Barr product and back to Coumadin,
13 back to Barr, and back to Coumadin. Each time the Barr
14 product was the one that was associated with a higher INR
15 level which is the measure of the therapeutic effect of
16 warfarin, and in each case on Coumadin it was lower. There
17 are several other cases where patients were not tried twice
18 on Barr but only once and we saw the same thing.

19 So, we're not saying that there is a known
20 danger, that there is scientific evidence to prove that the
21 products are not interchangeable. All we're saying is that
22 given the limitations of our ability to predict on an
23 individual patient basis and the simplicity of allowing
24 physicians to know and check the prothrombin time, that

1 physician should be made aware.

2 Thank you.

3 DR. ZIMMERMAN: Are there questions for Dr.
4 Levy from the committee?

5 (No response.)

6 DR. ZIMMERMAN: Thank you.

7 Are there any other comments from the general
8 audience that you'd like to make to the committee? If so,
9 please come to the mike, identify yourself and your
10 affiliation, and you'll have two minutes. Dr. Yacobi?

11 DR. YACOBI: I'm Avi Yacobi from Taro. I have
12 two comments.

13 First of all, about warfarin, I believe I
14 simply would like to reiterate what Dr. Meyer said and also
15 what Dr. Chris Rhodes said about warfarin. I know this
16 product very well, and I think the pharmacokinetic data is
17 so robust that individual bioequivalence wouldn't make any
18 difference in the final conclusion.

19 The other comment that I have is about
20 dermatopharmacokinetics. I think I'm aware of this
21 methodology. I'm familiar with it and I've seen a lot in
22 the literature. The methodology is sensitive, is
23 validatable, is specific, and I believe it's time to use it
24 for bioequivalence evaluation.

1 Thank you.

2 DR. ZIMMERMAN: Any comments?

3 DR. MAYERSOHN: Avi, in your last comment, you
4 were speaking specifically about the stripping method?

5 DR. YACOBI: Correct.

6 DR. ZIMMERMAN: Are there other comments that
7 you would like to make to the committee? Anybody?

8 (No response.)

9 DR. ZIMMERMAN: Okay. If not, then we will be
10 closing the open public hearing and moving on to our next
11 topic.

12 For the remainder of the afternoon, we will be
13 hearing about narrow therapeutic index drugs, and the
14 moderator for this session will be Roger Williams and he
15 will at first give us an overview of the issue. Dr.
16 Williams.

17 DR. WILLIAMS: Well, thank you, Dr. Zimmerman.
18 I would say we are moving on to another topic, but I would
19 also say that the prior presentations in the open public
20 hearing were directly related to what I'll be talking about
21 and what we will be talking about before the committee in
22 the next several hours. I hope the committee will indulge
23 me because I'm going to be touching on a number of topics
24 that perhaps at first might seem not entirely connected,

1 but I do think there's a deep connection to them.

2 I might say to the committee that I think in
3 some ways this committee is at a central focal point for
4 some of the topics that I'll be touching on, and I think
5 it's a very exciting set of topics.

6 I think if I started out by saying I were going
7 to adjust the efficacy standard in the United States, that
8 would cause a vigorous debate, and actually it has caused a
9 vigorous debate if you look at congressional legislation
10 over the last few months.

11 I think today we have talked about changing our
12 equivalence standards, first this morning for drugs that
13 are highly soluble/highly permeable. Now we're also
14 talking about them in the context of population and
15 individual bioequivalence.

16 I might also start out my remarks by pointing
17 out to you that the draft guidance I think is in your
18 information package. I might say to the audience it's also
19 on the Internet now, so if you don't have a copy, please
20 look on the CDER web page and you will see a draft,
21 tentative, preliminary guidance that focuses on the topic
22 that we have discussed before this committee on many
23 occasions.

24 I emphasize that the document is draft, and the

1 agency is encouraging explicitly firms that they not apply
2 the guidance now. It's explicitly stated in the preamble,
3 and I'll try to explain why that's the case.

4 Nonetheless, I am delighted that the guidance
5 is available and I think it reflects some very deep,
6 powerful science thought about issues and bioavailability
7 and bioequivalence. Of course, you know I would always
8 congratulate the working group for their efforts in getting
9 the guidance as far as it has.

10 Now, I will move through some of my overheads
11 quickly, but I will use slides that I have shown the
12 committee on several occasions perhaps.

13 I think the United States overall has a
14 wonderful process for assuring product quality, and many
15 things work to make that happen. Pioneer manufacturers,
16 generic manufacturers, and the agency itself have worked
17 together to create products in the marketplace that have I
18 think an extraordinary high standard of quality.

19 It all begins in the IND phase for the pioneer
20 product. There are changes post-approval for the pioneer
21 after manufacture that we pay attention to. There's the
22 period of multi-source manufacturers, and of course we pay
23 close attention to that. And then for both pioneer and
24 generic manufacturers, there is the post-approval change

1 that we watch over very carefully collectively to make sure
2 that all these products still stay the same in some way
3 relative to the clinical trial material on which safety and
4 efficacy data were based. That brings the sameness issue
5 that we talk about that the agency and the industry have
6 sort of a communal commitment to assuring sameness barring
7 intentional change.

8 I do say the time here is a long time, 75 or
9 more years, and it also extends over the shelf-life of the
10 product. And I always say it's a daunting science and
11 technical challenge that I would say has been a principal
12 topic for this committee on several occasions.

13 Now, I'm going to talk about the change
14 concept, and I would hope that always the committee would
15 understand me when I say that change affects both pioneers
16 and generics. The whole concept behind SUPAC was to
17 develop a consistent set of recommendations that would
18 apply both to pioneers and generics.

19 It's certainly true that switching occurs here
20 for the pioneer product even when multi-source products are
21 not available. You will see in the SUPAC that at times
22 SUPAC recommends a bioequivalence study in a post-approval
23 change setting.

24 But I would like to focus some of my next few

1 comments on the issue of generic substitution.

2 As you know, the agency has worked very hard
3 with this committee and many other people to assure the
4 quality of multi-source products, and on this particular
5 overhead, you'll see what I would call the basic tenets,
6 the conceptual principles, of Hatch-Waxman which is that a
7 generic should generally follow the same quality controls
8 as the pioneer product with the exception that
9 bioequivalence studies, which we talk about frequently
10 before this committee, are substituted for the very
11 expensive preclinical and clinical safety and efficacy
12 studies of the pioneer product.

13 Now, there have been at times over the last
14 several years where I would say that the agency has had to
15 confront the possibility of a two-tiered quality system for
16 generics versus pioneer. I might say that I personally
17 have always tried to resist that. I do not want to have a
18 different set of quality approaches between pioneer and
19 generic products.

20 I would also say that this committee at various
21 times has struggled with the issue of both pharmaceutical
22 and bioequivalence and we've talked about these on many
23 occasions. These are the two hurdles that must be gotten
24 over to achieve therapeutic equivalence.

1 I might argue that the science and technical
2 issues with regard to the documentation of pharmaceutical
3 equivalence are exciting, are challenging, and I'm
4 delighted to see that we have very sophisticated chemists
5 on the committee who can help us with some of these
6 deliberations in the coming months and years.

7 Of course, we also focus on bioequivalence, and
8 you've heard in vitro studies, pharmacodynamic studies.
9 Dermatopharmacokinetics now is a new approach which was
10 discussed earlier today. And it's all very exciting. I
11 might argue that the science of comparability is certainly
12 not dull for those people who think it might be.

13 Now, as you also know, the United States has
14 determined as a society that we will publish the approved
15 products in the Orange Book. I think this is a very
16 remarkable document. I keep encouraging people to read it,
17 and they say, Roger, are you crazy? It's so boring. But
18 actually to me it's exciting because it reflects a lot of
19 science thought and certainly a lot of hard work on the
20 part of both innovators and generics.

21 These are the criteria that you see expressed
22 in the first four bullets in terms of pharmaceutical
23 equivalence and bioequivalence, but we also must remember,
24 as one of the earlier speakers emphasized, that we insist

1 on manufacturing according to good manufacturing practices
2 and we insist on comparable labeling. If all those
3 criteria are met, then an oral solid dosage form in the
4 United States can be given an AB rating and substituted in
5 all 50 states according to the agency for all aspects of
6 safety and efficacy.

7 Now, with that little brief introduction, I
8 would now like to turn a little bit to the issue of narrow
9 therapeutic index drugs because in some ways life is
10 getting complicated, and as many of my staff remind me, I'm
11 the one who has been complicating it.

12 (Laughter.)

13 DR. WILLIAMS: First of all, I would like to
14 say to the committee that -- and it gets back to something
15 that I said this morning, that there are safety and
16 efficacy considerations as well as product quality
17 considerations.

18 For the most part, I would say this discussion
19 focuses on product quality, and it is also certainly true
20 that the agency speaks to the health care community and the
21 patient in labeling to speak to drugs that are defined as
22 narrow therapeutic index drugs.

23 Now, I support this. I think it's entirely
24 appropriate. There are drugs for which the practitioner

1 needs to take a special care in terms of dosing and
2 monitoring. I think we would all agree that warfarin is
3 one of those drugs. Notice I said drugs now and not drug
4 product. I think I'm talking about the active moiety that
5 creates the clinical safety and efficacy.

6 We actually have a CFR definition of what a
7 narrow therapeutic range or index drug is, and you will see
8 occasionally in product labeling that a drug is defined as
9 a narrow therapeutic index drug.

10 I might say that definition and the criteria
11 for those definitions are not the business of OPS. You'll
12 recall this morning that I said the new drug review process
13 is conducted out of the Office of Review Management, and
14 those judgments about the active moiety and its safety and
15 efficacy, in terms of being narrow therapeutic index, would
16 be the responsibility of the Office of Review Management
17 under the direction of Dr. Lumpkin.

18 However, turning now to OPS and its
19 responsibilities, OPS does and has concluded that under
20 certain circumstances narrow therapeutic index drugs
21 require increased product quality, recommendations, or
22 requirements.

23 Now, I might argue that that's a good question
24 for the committee. Is this appropriate? Do we want to

1 single out a category of drugs for which we would like to
2 say additional product quality tests are required? I don't
3 know if the committee wants to discuss it today, but I
4 certainly think it's an excellent topic for the committee
5 to discuss sometime and I would certainly facilitate that
6 discussion in any way possible.

7 But for whatever reason, the agency has already
8 taken that decision and you will hear discussion about that
9 decision in the context of our SUPAC approach from Mr.
10 Sporn, who's head of the Office of Generic Drugs. We did
11 single out drugs to be defined as narrow therapeutic index
12 drugs for which we wished additional quality controls.

13 There is also a compliance policy guide that
14 you see on here with that strange set of numbers where that
15 is also the case.

16 Now, I might also mention that in the
17 individual bioequivalence document, you will see that it's
18 an intent of the agency also to request that narrow
19 therapeutic index drugs be singled out for an additional
20 level of quality control that I will try to explain in just
21 a few minutes in the context of individual bioequivalence.
22 I would refer the committee to page 15 of the document
23 where there's a very brief statement that we will always
24 scale, if we adopt individual bioequivalence, for narrow

1 therapeutic index drugs.

2 So, I hope it's very clear that in our product
3 quality approaches we are not speaking to the health care
4 community or to the patient. We are speaking to the
5 pharmaceutical manufacturer and asking them under certain
6 circumstances to exert additional tests to assure product
7 quality for this category of drugs. I think that's a very
8 important distinction, and if anything, I would say we are
9 doing this so that we can assure the health care community
10 and the patient that when substitution occurs, no
11 additional precautions are necessary.

12 Now, I would emphasize that the agency does not
13 agree with the statement of a prior speaker that you need
14 to test the prothrombin time again when you switch from one
15 formulation of warfarin to another. We would not recommend
16 that either for the pioneer or the generic. So, if
17 somebody is started on the generic product and switches to
18 the pioneer, we do not recommend that they get an
19 additional prothrombin test.

20 We feel, as some of the prior speakers said,
21 that the natural variability in the way the patients take
22 this drug, as well as its pharmacodynamics and the effect
23 of diet and many other factors, far outweigh in terms of
24 variability any of the variability you might see that

1 arises from switching from one formulation to another.

2 This is also a general position of the agency,
3 that we do not recommend additional tests when any generic
4 or any formulation is switched from one manufacturer to
5 another or during the period of exclusivity or patent
6 protection for a pioneer when switching occurs there. It's
7 a very broad principle that I think the agency stands
8 behind solidly and for good reason: based on our
9 experience and based on the level of testing that we
10 require.

11 Now, I will point out that in the labeling of
12 warfarin -- and this is the labeling for the pioneer
13 product Coumadin -- it does refer to the fact that it is a
14 narrow therapeutic index drug. I'm delighted that the
15 labeling emphasizes that it's the drug that's narrow
16 therapeutic index and not the drug product.

17 I will point out now -- and you'll hear more
18 about this from Mr. Sporn -- that we do have these PAC's
19 that are being developed, the post-approval change
20 documents. Those are defined to control the quality of
21 products in the marketplace in the presence of post-
22 approval change. Switching occurs there for all products,
23 both pioneer and generic.

24 Now, I'd like to turn now to the fact that we

1 are in the process of discussing a possible change in the
2 way we look at bioequivalence both from a metric and
3 statistical standpoint. I won't belabor this because I'm
4 sure the committee understands this quite well. This is
5 our current approach where we have the goal posts of .8 to
6 1.25. We log-transform the data, and I might remind this
7 committee that they made that recommendation to us, that
8 log transformation occur. That decision was based on the
9 fact that we were primarily interested in the ratio of the
10 comparison as opposed to the difference.

11 There's a slight levity here. You remember I
12 said barring intentional change. Well, intentional change
13 in my mind is the world of new drugs, the 505(b) world. We
14 live sometimes in the world of 505(j) when we talk about
15 sameness. I always encourage people who say that they've
16 got a better generic product to not talk to me, to take
17 their product to the world of the 505(b) and have it
18 approved as a pioneer new drug.

19 Now, as the committee well knows, we are
20 engaged in a discussion about moving to a different
21 approach, and the different approach is exemplified in this
22 side of the equation which is a new criterion that is based
23 on a series of articles and conceptual understandings that
24 appeared over the last several years and that have been

1 quite exciting to us inside the agency, and I think also
2 quite exciting outside the agency, in terms of possibly
3 changing the way we do business.

4 The entire approach is based on the concept of
5 prescribability and switchability, and I use this
6 particular overhead to exemplify that. When a patient
7 first visits the doctor, there may be a period of
8 prescribability where the dose is adjusted and titrated to
9 an optimal dose, and then at steady state, there is a
10 persistent fluctuation which should be maintained in the
11 presence of change relative to different drug products.

12 I think you can see down here there is the
13 concept now in the current U.S. marketplace of perhaps
14 starting on the pioneer product, moving to one generic,
15 moving to another generic, and even moving back to the
16 pioneer product.

17 There is also the concept of change in the
18 presence of post-approval change for both the pioneer
19 product and either of the generics.

20 So, you can see that I think as a society and
21 in terms of the science and technical challenges, we have a
22 lot of work to do to assure the patient and the health care
23 community that all of these formulations can provide the
24 same therapeutic benefit one to another compared.

1 And you'll see that I do not single this out
2 particularly as a generic problem but also a problem both
3 for the pioneer product and the generic product.

4 Now, you will see -- and I will not belabor
5 this in terms of my presentation now -- that we have
6 concepts of individual and population bioequivalence. I
7 certainly know that the committee will read this guidance
8 very carefully. I hope they will resonate to many elements
9 of it because those elements have been discussed before the
10 committee on several occasions.

11 What we are talking about in considering going
12 to this new criterion is the concept of perhaps looking
13 more closely at variance than we have in the past. You'll
14 see over there on the right that if I just look at this
15 part of the equation, it looks very similar to what we do
16 now.

17 But individual bioequivalence also includes a
18 subject-by-formulation interaction variance term, which is
19 σ_D , and also a comparison of the within-individual
20 variances of the test and reference product. On top of it
21 all, it relates those variances and mean difference to the
22 within-subject variance of the pioneer product.

23 Now, again, I won't go into all of this, but I
24 think the science of this approach is quite compelling.

1 What I think needs to bear further discussion is the public
2 health justification for the need for this equation. I
3 don't need to perhaps remind the committee, but that was
4 one of their main discussion points when it came up before.
5 What is our justification for moving to this new approach
6 which is more burdensome from the standpoint of requiring
7 replicate study designs? You cannot get this equational
8 information without doing replicate study designs for the
9 test and reference product.

10 I think the burden of the justification does
11 fall on the agency, and we certainly willingly take up that
12 burden and hope to continue to make the argument and the
13 justification publicly, as well as before this committee,
14 at the appropriate times.

15 Now, I will say -- and perhaps I'm speaking now
16 more to the audience -- that there was a meeting in Boston
17 in November. All I can say is I must have developed a very
18 thick skin after being in Washington over seven years
19 because it was a vigorous debate, and I wouldn't say that I
20 came out of it in a strong position. Some people have
21 described the meeting as a train wreck, and I suppose
22 that's a pretty accurate description.

23 But I will say this. I think it was a good
24 meeting and I think it clarified for me something that was

1 quite important which is you can have a very abstract
2 scientific discussion, but it's also an important part of
3 the public process in the United States to gain the
4 understanding and concurrence of all the stakeholders. I
5 came away from that meeting feeling that many of the
6 comments directed at me and at the agency were right on and
7 that we did need to build a better public process for the
8 debate about moving to this new approach.

9 Towards that end, I think the agency has agreed
10 to do several things.

11 First of all, as we usually do, we would like
12 to form an expert committee. The formation of that
13 committee is occurring right now to help us with some of
14 the deliberations.

15 We are going to have a public workshop in March
16 of 1998 where we discuss it publicly, and there will be a
17 consensus report out of that workshop.

18 We would like to share as much of our data as
19 possible that forms the basis for the justification for
20 this new approach. I would argue that we would like to
21 have a very good, high quality public discussion now about
22 the science and justification for moving towards individual
23 bioequivalence, working with all constituencies as best we
24 can.

1 Then at the end of that process, I would like
2 to repropose the guidance as a level 1 guidance again for
3 public comment.

4 So, I think you can see that the agency wants
5 to take a very deliberative approach to this. We recognize
6 the challenge of it. At the same time I think we're very
7 convinced that it has a compelling scientific
8 justification. We want to do the right thing and move
9 forward in a good way. I might argue to the committee that
10 at the appropriate time I will certainly bring it back
11 before the committee for their consideration and discussion
12 as they wish.

13 Now, I might also say, before I turn to the
14 issue of narrow therapeutic index drugs, that coupled with
15 the guidance you'll see also population equivalence
16 approaches. Those particular approaches are directed
17 specifically to the pioneer manufacturer during the IND
18 phase of drug development. Population equivalence
19 approaches do not require replicate study designs, and in
20 that sense we do not feel that the population approach
21 advocated in the guidance adds in any way particularly to
22 the burden of pioneer manufacturers as they develop new
23 drugs.

24 The primary reason for recommending population

1 approaches during the pre-approval period for an NDA is
2 because it doesn't involve switching, and if there's no
3 switching involved, there's no particular need for
4 individual bioequivalence. I want to emphasize that, and I
5 don't see that position changing on the part of the agency.
6 It's not subject to a scientific debate. It's more a
7 conceptual understanding that I think we agree on now, and
8 I can't imagine further discussing changing agreement,
9 although I would welcome that discussion if it's
10 appropriate.

11 But individual bioequivalence does apply to
12 both the generic and pioneer product in the presence of
13 post-approval change requiring an in vivo study. That's
14 also very clearly delineated in the guidance document and
15 it certainly applies to the generic manufacturer at the
16 time of approval to gain market access.

17 Now, I'd like to turn a little bit and perhaps
18 close with the issue of narrow therapeutic index drugs current
19 approaches and what it all means for narrow therapeutic
20 index drugs. For those on the committee who've looked on
21 page 15, you will note that it says we do not have criteria
22 now for narrow therapeutic index drugs, and that's
23 absolutely true. For that reason, the agency doesn't feel
24 that it can comment on which drugs to apply constant

1 scaling to or not. You'll hear more about our attempts to
2 develop criteria from Dr. Balian when he speaks later on in
3 the course of this particular part of the session.

4 I want to say a little bit about our goal posts
5 and perhaps why we are considering scaling for certain
6 narrow therapeutic index drugs. I apologize to the
7 committee for going over this and I always wonder, when I
8 say this, if I'm going to say the right words, not being a
9 statistician.

10 But essentially what we do now in terms of
11 declaring bioequivalence is to ask that the ratio of the
12 means for our bioequivalence metrics, Cmax and AUC, be
13 within a confidence interval where the goal posts are minus
14 20 percent of the reference listed drug metric or plus 25
15 percent of the reference listed drug metric. That's a
16 symmetrical confidence interval on the log scale, of
17 course, as the committee knows. We ask that the confidence
18 interval of the observed ratio of the means be within those
19 boundary points.

20 Now, let me just run the committee through
21 something that I'm sure they know quite well. This is an
22 example of a product that meets the point estimate but
23 fails the confidence interval, and you can see it does so
24 because the mean is getting close to .8. And the

1 confidence interval of the observation falls outside the
2 lower goal post.

3 This is the converse example where it fails on
4 the upper side.

5 Here's an example of two generic products.
6 This particular representation alludes to the commonplace
7 statement in the marketplace that two generics can differ
8 by 40 percent. If one is 20 percent below and one is 20
9 percent high on the log scale, you can imagine two generics
10 could be in the marketplace differing by as much as 40
11 percent in either AUC or Cmax.

12 The agency would not agree that that's a
13 reasonable possibility because the reality is as you start
14 to move closer in your point estimate to either boundaries,
15 the number of subjects required in a study to show
16 bioequivalence increases. So, you could imagine that a
17 product could be 19 percent lower but to show equivalence,
18 if that were truly the situation, it would probably take
19 hundreds of subjects in that bioequivalence study.

20 Because most bioequivalence studies have, say,
21 30 to 40 people in them, we actually start to see people
22 fail the confidence intervals when they differ about 5
23 percent or 10 percent. Historically the agency, when it
24 looks at means, usually sees differences of less than 5

1 percent. So, the agency would not agree that it's possible
2 to see generics in the marketplace differing by as much as
3 40 percent in their performance metrics, and in fact we
4 have no instances of that being the case.

5 This, to conclude this part of the
6 presentation, is an example of a study which in fact shows
7 bioinequivalence. A lot of times we deal with situations
8 where the point estimate may be very close to 1, but just
9 because of variability and numbers of subjects in the
10 study, they haven't been able to show bioequivalence
11 according to the goal posts and the confidence interval.

12 Now, that leads me to the issue of narrow
13 therapeutic index drugs and why the agency would be
14 interested in narrowing the goal posts for narrow
15 therapeutic index drugs. Let me see if I can speak to that
16 very briefly.

17 Right now -- and I might use warfarin or
18 phenytoin as an example -- for the products we let into the
19 marketplace, as you heard from an earlier speaker, the
20 point estimate is very close to 1 for the generic relative
21 to the pioneer product. Of course, we're delighted with
22 that. It means that the generic is a fine formulation and
23 it's mimicking the performance of the pioneer in a good
24 way.

1 However, our current goal posts would allow a
2 product in the marketplace to differ by, say, 10 percent or
3 more, and for that reason the question arises for these
4 narrow therapeutic index drugs, should we change our goal
5 post approach such that that would not occur?

6 Now, the way we would do this, according to the
7 principles of individual bioequivalence is to let the
8 variability of the reference product control the goal
9 posts. You heard an allusion to that somewhat indirectly
10 earlier today when somebody alluded to phenytoin.

11 Now, let me say, for example, that I think the
12 pioneer product of phenytoin is a well-manufactured
13 product. It does show low intra-subject variability for
14 both the drug substance and the drug product, and our
15 expectation is that that low variability, if individual
16 bioequivalence were applied, would drive the goal posts
17 down to, say, 90 to 111 as opposed to 80 to 125. You can
18 see I'm using the symmetric approach on the log scale.

19 Now, why would that be a public health
20 advantage? I think it would be a public health advantage
21 from the standpoint that we would not allow products in the
22 marketplace, say, for warfarin to differ in their means by
23 12 percent. I think if you know the nonlinear kinetics of
24 warfarin, you can see there's a justification for that. I

1 don't think we would want a warfarin product where the mean
2 difference truly was 12 percent difference. Because of the
3 nonlinear kinetics, we could imagine that if it were 12
4 percent higher, some patients would get in trouble.

5 So, the motivating concept behind always
6 scaling for a narrow therapeutic index drug, according to
7 the principles of individual bioequivalence, is to assure
8 that such products don't get into the marketplace.

9 Now, of course, there is a burden associated
10 with this because if the true mean difference is within,
11 say, 90 to 111, more subjects would be needed to pass the
12 confidence interval boundaries.

13 I look forward to this discussion before the
14 committee at the appropriate time. If it occurs today,
15 that's fine, but that's the motivating factor or approach
16 or concept by saying always scale for a narrow therapeutic
17 index drug.

18 Now, I might remind the committee that always
19 scale for narrow therapeutic index drugs means that if you
20 had a highly variable narrow therapeutic index drug, you
21 may actually widen the confidence intervals. Again, I
22 think there's a public health argument for it and a
23 fairness argument that if the innovator, the pioneer
24 product, even if it's a narrow therapeutic index drug,

1 shows a high degree of variability, that the generics
2 shouldn't themselves have to pass a narrower boundary than
3 the innovator itself would have to pass.

4 Fortunately, we think there are very few
5 instances of a highly variable narrow therapeutic index
6 drug because I think you can imagine the therapeutic
7 challenge of dosing such a drug would be considerable.

8 Now, I want to close, and I apologize to the
9 Chair for going on perhaps longer than I should have, but I
10 do think some of these points are so important.

11 There's one last thing I would like to say and
12 that's this. It's critical for the agency, working with
13 this committee or other stakeholders as appropriate, to be
14 able to move to better science. I would be very disturbed
15 if our discussions, as we move to better science, as we
16 consider moving to better science, would somehow be used to
17 attack products that are currently in the marketplace. I
18 would not want individual bioequivalence concepts that we
19 are talking about now in a very preliminary way to be used
20 to suggest that any product in the marketplace, either
21 pioneer or generic, is somehow not a good product. This is
22 a very important point for the agency, and as a matter of
23 fact, it has been discussed in the courts and the courts
24 certainly endorse that.

1 I might also argue that all products -- you
2 know, it's true of an agency and an industry that over time
3 products become outdated in the way they're manufactured,
4 and the products that were approved 25 or 50 years ago in
5 this country would not perhaps be manufactured and
6 controlled in the same way as they would be if they were
7 approved today.

8 I might draw the committee's attention to the
9 fact that for both the ICH stability document and the ICH
10 impurity document, Q1A and Q3A, it has been a particular
11 challenge for the agency, working with industry, to not
12 make those guidances apply retroactively. It's very
13 burdensome and the justification for it is difficult.

14 So, as I say, we always want to do better, but
15 it does not imply that currently available products in any
16 way have problems associated with them. I think it's
17 important for the agency to endorse this not only for
18 generics but also for pioneer manufacturers.

19 Now, having said all that, I will turn it back
20 to the committee. I guess, Dr. Zimmerman, thank you very
21 much. I do apologize for going over, but I think you can
22 see there were some very important things I had to get on
23 the table.

24 DR. MAYERSOHN: Cheryl?

1 DR. ZIMMERMAN: Dr. Mayersohn has a question
2 for you, Dr. Williams.

3 DR. MAYERSOHN: Roger, this isn't so much a
4 question as a comment. I think you know early on I was
5 fairly skeptical about the concerns leading to the issue of
6 individual bioequivalence, and I look forward to seeing the
7 documentation of the problem. However, I must say that
8 from my understanding of what you just said, you are taking
9 a very healthy view of the problem and the approach to its
10 solution. So, maybe being beaten up once in a while isn't
11 so bad.

12 (Laughter.)

13 DR. WILLIAMS: Thank you.

14 DR. ZIMMERMAN: Yes, Dr. Goldberg.

15 DR. GOLDBERG: Roger, after the discussion we
16 had this morning on the BCS, I was wondering whether that
17 could be tied in with this rather than therapeutic range.
18 I think that if a drug is problematical in absorption, then
19 I think the need for something like individual
20 bioequivalence is much greater than if there's no question
21 or problem with absorption of the drug. So, I think a tie-
22 in between the BCS and this would be a good approach rather
23 than narrow therapeutic window. For example, warfarin
24 doesn't seem to have any problem with absorption, but I'm

1 sure some of the drugs on the NTI, as well as other drugs,
2 may have.

3 DR. WILLIAMS: I think it's an excellent point,
4 Dr. Goldberg. I might say that I think the committee
5 probably has noticed that as we work to kind of move away
6 from what I call the one-size-fits-all -- you know, life is
7 easier when everything is the same, and we're going to get
8 caught up in challenges that we need to work together on
9 hopefully in a productive and positive way. I would say a
10 specific challenge is what you alluded to.

11 Now, you saw from Dr. Hussain's presentation
12 this morning that we are going to say that the
13 biopharmaceutic classification would not apply to a narrow
14 therapeutic index drug. Yet, at the same time you heard
15 Dr. Rhodes point out that warfarin is a highly soluble,
16 highly permeable drug and perhaps could be approved on the
17 basis of dissolution only. Now, this is what makes life
18 interesting in Washington, and it's why I get a high
19 salary.

20 (Laughter.)

21 DR. WILLIAMS: So, it's a hard challenge and we
22 have to work together on it. I don't have an answer to it
23 right now, but I thank you for pointing it out.

24 DR. ZIMMERMAN: Well, I think we'll move on to

1 our next speaker who is Douglas Sporn who is going to talk
2 to us about the SUPAC approach and issues involved there.

3 MR. SPORN: Fortunately, because of what the
4 previous speakers have covered, my job is going to be
5 relatively easy. I'm mostly going to fill in a few blank
6 spots and underline some of the things that were said
7 earlier. I want to talk about what is the list, just to
8 make sure everybody has seen it and knows what we're
9 talking about. Marv Meyer already talked about the generic
10 drug scandal. I want to discuss that a little more. I'll
11 show you the regulatory definition and actually talk about
12 how --

13 DR. ZIMMERMAN: Mr. Sporn, would you move your
14 slide up?

15 MR. SPORN: Then actually talk about the
16 application in the SUPAC.

17 I haven't been here for the entire meeting
18 today, but I've heard a number of people mention SUPAC and
19 I'm not sure everyone knows what that stands for: scale-up
20 and post-approval changes. It's a concept that Roger
21 coined and it basically is a series of guidances the Center
22 is putting out for the pharmaceutical industry and for our
23 reviewers that gives our best opinion of what tests and
24 filing requirements would be for various changes depending

1 on the dosage form. As Roger mentioned, we have three that
2 are out now: one for immediate release, one for semi-
3 solids, and one for modified release. And we have two or
4 three more that are in the wings being developed.

5 Just real quickly, this is the list. You may
6 not be able to read it in back. I think it is in your
7 handouts. This is probably the list that Marv was looking
8 for. I stole it at lunch.

9 (Laughter.)

10 MR. SPORN: Let me give you a little more
11 background about how this came about during the scandal
12 because everything Marv said is correct. You have to kind
13 of put yourself back at the time of the scandal when there
14 was really a national scare about what was going on because
15 the investigations were just getting started and people
16 really didn't know the extent of the problem in the generic
17 industry.

18 Partly to get a quick snapshot of what was
19 going on, it was decided that FDA headquarters and the
20 field would do a survey of products and test them against
21 USP and other standards, compendial and application
22 standards, to see if they were in compliance or not. It
23 was decided this had to be done very, very fast.

24 There is a regulatory definition of narrow

1 therapeutic index drugs. I'll show it to you in a minute.
2 I can tell you it is not the definition that was applied.
3 There wasn't time to be that thoughtful.

4 What happened, Dr. Bruce Burlington, who was
5 head of the Office of Generic Drugs at that time, basically
6 went to all the new drug clinical division directors and
7 said, give me a list of drugs that you'd be concerned about
8 if there was a problem somewhere out there. This was done
9 like on the back of an envelope overnight. That's the
10 list. That is how it was put together.

11 It's just unfortunate that it has sort of taken
12 a life of its own on now, and we have people coming into my
13 office volunteering to be declared narrow therapeutic
14 because they think it will in some ways help in the world
15 of competition.

16 This is the regulatory definition. It somehow
17 got in the CFR. You're going to hear more about what is
18 going on to really define what the criteria should be. I
19 will say this definition and the issues associated with the
20 terminology, and what it implies has been discussed with
21 the Medical Policy Coordinating Committee which Roger and
22 Bob Temple head, and you'll be hearing more about that.

23 Now, I just wanted to wrap up by giving you a
24 couple of examples. You've heard what Roger said about

1 there are places in the SUPAC where we have said, okay, if
2 you have a narrow therapeutic index drug, you do something
3 different. In both IR and MR, that mostly takes into
4 account a change in components or composition, things that
5 you would allow to be changed and then testing using
6 dissolution wouldn't be allowed if it was a narrow
7 therapeutic index drug, whatever that means.

8 For example, here we have under level 2 and
9 level 3, which is a certain amount of change in the
10 excipients of an immediate release product. For an IR
11 product, we're saying if there's a change in grade or if
12 there's any qualitative or quantitative change in the
13 excipients, we're recommending that an in vivo
14 bioequivalence study be done. That's the type of
15 additional safeguards we're putting in on these SUPAC
16 documents.

17 Probably we would continue to apply this once
18 we identify what is a true narrow therapeutic index drug,
19 but all that is open to reconsideration as well. I think
20 this is going to be a long, interesting process to really
21 determine what is the criteria, what are the products that
22 meet the criteria, and then decide with your help what sort
23 of restrictions should we put in the post-approval world to
24 make sure these products perform as they're supposed to.

1 Thank you.

2 DR. ZIMMERMAN: Are there questions from the
3 committee? Dr. Byrn?

4 DR. BYRN: I had a question about the generic
5 drug problems of 1989 to 1994. Two kind of summary
6 questions. Did all of those problems involve drugs that
7 were on the list? Essentially all?

8 MR. SPORN: No. In fact, a survey was done of
9 many drugs, including almost all the ones that were on the
10 list, and no problem was found.

11 DR. BYRN: Okay. So, what were the main drugs
12 that were involved in those problems?

13 MR. SPORN: It would be a long list. Don Hare
14 is probably out here who could answer --

15 DR. BYRN: Because I had heard, for example,
16 carbamazepine was one of them.

17 MR. SPORN: I don't know if carbamazepine was
18 caught up. There was a problem at one time. I don't know
19 if it was associated with the scandal or not.

20 DR. BYRN: What I'm really curious about is,
21 was manufacturing inequivalence the cause of the generic
22 drug problems from 1989 to 1994?

23 MR. SPORN: There were a number of things that
24 happened, but the bottom line was there was essentially

1 fraud committed. There was selective reporting,
2 nonreporting.

3 DR. BYRN: And were those on lots that weren't
4 passing that were inequivalent? That was my understanding
5 but --

6 MR. SPORN: These products were approved based
7 on the assumption that the data submitted to the agency was
8 truthful, and in many cases it was ont truthful.

9 DR. BYRN: So, it really involved the
10 submissions, not passing lots --

11 MR. SPORN: Right.

12 DR. BYRN: -- not submitting correct data. I
13 guess another way, not submitting correct data that it's
14 bioequivalent and then later passing lots that were not
15 equivalent.

16 MR. SPORN: Right.

17 DR. BYRN: It was actually having inequivalent
18 lots to start with.

19 MR. SPORN: In one very notable case, the
20 innovator was compared against the innovator, but it was
21 disguised as being the generic firm's application.

22 DR. BYRN: I guess I'm trying to understand
23 more of the background. We don't know I guess the
24 motivation, but in your opinion was that done because the

1 particular lots that the generic company made would not
2 pass?

3 MR. SPORN: The motivation was money.

4 (Laughter.)

5 MR. SPORN: Anytime a blockbuster drug is
6 coming off patent, generally I think the feeling is that
7 the first person to get an approval is going to capture the
8 biggest share of the market. So, it is believed a number
9 of firms, in order to get there first, said this is the
10 quickest route to get FDA's approval and really worry about
11 how to manufacture it later. So, in some cases two sets of
12 books were kept.

13 Was there another question?

14 DR. BYRN: No, those were the two questions.

15 DR. ZIMMERMAN: Other comments, questions?

16 (No response.)

17 DR. ZIMMERMAN: Thank you.

18 I think we're going to take our afternoon
19 break. We will reconvene in 20 minutes.

20 MR. SPORN: Can I say one other thing since one
21 of the speakers alluded to the Medwatch reports that had
22 been submitted to the agency about warfarin? That is true.
23 DuPont-Merck provided 26 such reports. We looked at all
24 reports like that. We take them very seriously. There is

1 a group inside CDER that is convened just to look at
2 alleged therapeutic inequivalence cases, to analyze them,
3 and find out what is behind them, if we can.

4 We have not finished looking at those 26, but I
5 can tell you preliminarily, based on the data we provided,
6 we're not able to conclude because the patient was switched
7 to a generic that that was the source of the problem. Now,
8 maybe when we dig deeper, it will come out differently, but
9 that's the early indication that I have.

10 DR. ZIMMERMAN: Thank you.

11 (Recess.)

12 DR. ZIMMERMAN: Ladies and gentlemen, we'd like
13 to get started. Our first speaker for the afternoon will
14 be Dr. Rabi Patnaik, and he will be speaking about
15 individual bioequivalence.

16 DR. PATNAIK: Thank you, Dr. Zimmerman.

17 Dr. Williams has already set, so to speak, the
18 table for me, so I will probably skip a few of the slides
19 which I have given to the committee.

20 The objective of my presentation is not to
21 focus on the methodology of individual bioequivalence or
22 the concept and to discuss that, but the discussion will be
23 as it pertains to drugs in general and specifically to so-
24 called, quote/unquote, narrow therapeutic index drugs.

1 What I plan to do is to introduce a little bit
2 of the concept and the criteria which Dr. Williams already
3 sort of briefly presented to the committee, and then I will
4 show you some examples of what I'm talking about. Then
5 afterwards, I will discuss what are the next steps to the
6 whole issue of individual bioequivalence as it pertains to
7 drugs in general as well as to, quote/unquote, narrow
8 therapeutic index drugs.

9 Now, for consideration for assessment of
10 bioequivalence of drug products, what one should consider
11 maybe -- Dr. Williams has already alluded to these two
12 concepts of prescribability and switchability. Individual
13 bioequivalence is more concerned with the switchability end
14 so that we can assure, when the drug products are switched
15 within one patient, safety and efficacy are assured.

16 The other factor that needs to be considered
17 maybe and important is reference variability which is very
18 important when switching should occur.

19 And thirdly, to some extent, therapeutic index
20 of the drug should also be considered.

21 These are the three salient factors one should
22 consider.

23 Now, currently we are having average
24 bioequivalence concept. You might have heard about it, and

1 probably you have heard -- several times these committee
2 must have gone through this subject. It focuses on the
3 population averages of the test and reference, but it
4 doesn't say anything about distribution of the metric
5 between the test and reference. In other words, we don't
6 know anything about the statistical parameters. It also
7 ignores the subject-by-formulation interaction.

8 The second factor is the issue of switchability
9 is not addressed in average bioequivalence.

10 As we heard from Dr. Williams, one size fits
11 all. We have the same standard for highly variable drugs,
12 for narrow therapeutic index drugs, quote/unquote, and also
13 for other drugs.

14 The concept which I will be just presenting as
15 an example to just explain to you the concept, it will have
16 more incentive for the generic or any drug manufacturer to
17 manufacture less variable formulations.

18 What essentially the concept is, it has got
19 three components. One is the difference in the averages of
20 the two products, test and reference. This is the variable
21 and variance component. These two components add together,
22 we say that they should be less than some bioequivalence
23 limit.

24 Now, what are those parameters? This is the

1 test and reference mean. This is the difference in the
2 within-subject variability of the test and reference
3 product, and this is the subject-by-formulation
4 interaction. This is the upper bioequivalence limit which
5 is similar to the average bioequivalence limit which we
6 have currently with respect to the mean differences.

7 Now, when we add some variance terms to this
8 concept, we have a variance allowance given in the
9 bioequivalence and it is scaled to the within-subject
10 reference variability.

11 So, essentially we are not diverting that much
12 in this concept from the average bioequivalence concept
13 except that we assume that the test variance of the within-
14 subject of test and reference are similar, so it cancels
15 out. And there is no subject-by-formulation interaction.
16 So, this is also nonexistent. So, ultimately we come
17 across with an expression where we only consider the mean
18 differences.

19 Now, in this concept, this equation, when you
20 plot it, the upper limit of the bioequivalence criterion
21 versus the within-subject standard deviation of the
22 reference product on a log scale, it becomes the CV. You
23 get a relationship like that, that more is the variability,
24 higher will be the upper limit. So, what happens, if the

1 variability is high, one can get the bioequivalence limit
2 raised.

3 So, this concept was worked on by the working
4 group of the individual bioequivalence project. We first
5 thought over that products which have a difficult product
6 or problematic product but shows lower bioequivalence --
7 lower within-subject variance will have to have stricter
8 goal posts. So, what the working group developed is that
9 will have a reference scaling of all the products whose
10 variability is more than a certain specified number, and
11 below that the goal post will not be reduced. It will
12 remain constant. So, some of the drug products which show
13 less than -- in this case it's .2 -- will remain as the
14 .125, and those which have got more than .2 will be scaled
15 to the reference listed drug variance.

16 So, we have two scales but conceptually one can
17 think, as Dr. Williams suggested, that for certain products
18 which have got so-called narrow therapeutic index drugs,
19 one can make it much stricter for bioequivalence
20 assessment. So, we are pretty sure that it will not pose
21 any safety risks.

22 But depending upon what are the drugs, one has
23 to look at what variability it is. If a drug which has got
24 high variability, intra-subject variability, but it is

1 narrow therapeutic, if we govern our policy with respect to
2 the intra-subject variability of the reference product,
3 then it has to be scaled and it might be widened.

4 So, we are in a very preliminary stage and we
5 have to look at various drug products. We have a very
6 limited data set to look at. So, what we did -- some of
7 you might have also seen this data set, but I just wanted
8 for the benefit of this committee that we have very limited
9 12 studies which are having 34 data sets which have been
10 analyzed using this criteria. What I will do is to show
11 you what kind of values we got and how it really comes out
12 to be interesting enough.

13 They're all replicate design studies and most
14 of them are healthy subject and some of them have got
15 target populations. They represent different dosage forms.

16 Just for the interest of time, I will just look
17 at the Cmax. We have analyzed both AUC and Cmax, but I
18 will just show some selected data analyzed on Cmax.

19 Now, what this is is this is the plot in order
20 of the lowest value. Over here is the test/reference ratio
21 on a log scale for the Cmax. The test is much lower. The
22 test value is much lower than the reference which is 13-14
23 percent. On the right-hand side, it goes as high as 15
24 percent higher than the reference.

1 So, we can see in 34 data sets there's a whole
2 gamut of values one gets in terms of the mean values and
3 the averages -- differences. So, a lot of Cmax value, you
4 can see that the ratios are very close to 1. Some of them
5 are, the test is higher than reference, and here the test
6 is lower than reference.

7 In average bioequivalence, this is what we see,
8 but when you add the variance terms, the point I'm making
9 here is that you always assume the test variability and
10 reference variability, within-subject variability are
11 almost similar. So, we shouldn't even consider it because
12 the subject is its own control, and also there should not
13 be any variability between the two formulations.

14 But as you can see here, here is about 50
15 percent lower test variability, 50 percent lower than the
16 reference, as high as about 70 percent higher than the
17 reference. A whole gamut of variability differences we
18 have seen. This is the same thing, test/reference ratio of
19 the within-subject variability for Cmax.

20 Now, this is another term. The term sigmaD is
21 the subject-by-formulation interactions. This is again
22 rank order from the lowest value to the highest value. The
23 statistical experts in our working group suggested that any
24 value less than .15 probably is not that important from

1 this interaction behavior, the subject-by-formulation
2 interaction behavior. Anything above .15 is quite
3 important.

4 So, you can see out of about 9 data sets out of
5 34, we saw subject-by-formulation interaction more than
6 .15. But this is just the observations.

7 Finally, which is very interesting here, it is
8 the within-subject variability of the reference product.
9 Now, it starts from about 10 percent all the way to 50
10 percent within-subject variability of the reference
11 product.

12 So, just looking at this data, if we say from
13 20 percent is our regulatory cutoff point from which we'll
14 start scaling with respect to the reference listed product,
15 you can see there are a lot of data sets in which we scale
16 it to the reference listed drug, within-subject
17 variability, and below .2, irrespective of whether it is
18 low or high, we'll keep it as constant .2.

19 So, the observations that we have seen that in
20 data sets, which is very limited, we have this variability
21 differences in test and reference. We have to some extent
22 observed some subject-by-formulation interactions, and we
23 see that the reference variability actually ranges from 10
24 percent to 50 percent depending upon the type of drug.

1 Some of the assumptions which we make for
2 average bioequivalence may not be true, and here we see
3 about 8 out of 34 data sets within-subject variability,
4 reference more than 20 percent, and the within-subject
5 variability ratio test/reference, you can see 50 percent
6 lower than the reference to 200 percent higher than the
7 reference. And in 8 of 34 subject-by-formulation
8 interaction, we see for AUC, and 10 out of 34 we see for
9 Cmax.

10 So, this is very limited. I'm just showing
11 this just that the committee will appreciate that with this
12 very limited data set, we have observed this, which is that
13 for narrow therapeutic index drugs we can reference scale
14 it to make it tighter so that if there is a concern about
15 safety and efficacy by using this concept.

16 Now, what we are saying essentially -- and Dr.
17 Williams has already alluded to this fact -- is that it
18 addresses the correct question, this concept, which is the
19 switchability, and it considers the subject-by-formulation
20 interactions, which is important because I have some
21 interaction with the two different formulations that's not
22 very ideal for that subject or that patient.

23 Now, there will be an incentive for less
24 variable drug product because the question is such that

1 this test variability is lower than the reference
2 variability. That is much easier for the criteria to pass
3 the bioequivalence testing.

4 The scaling method which we discussed with
5 respect to the reference product, it will be for both
6 highly variable drugs, as well as for certain agency-
7 specified or defined narrow therapeutic index drugs. So,
8 it has got the benefit of a whole diverse classes of drug,
9 drugs in general, but we can pay specific attention to
10 special classes of drug.

11 Here also, because we are looking at all kinds
12 of intrinsic factors in the formulation drug substance, as
13 well as the type of product, the way we are assessing
14 bioequivalence we can use more common general population
15 rather than a very fixed, healthy general population. So,
16 it will be easier for people to do this study.

17 Now here, as all of you know, yesterday it went
18 on the Internet and today the guidance, preliminary rough
19 draft guidance, has been published, and there will be a
20 Federal Register notice about the availability of this
21 guidance. It is available for public comment. So, we are
22 planning to get and we are hoping that we will get a lot of
23 comments about this and then act on it and consider it and
24 review it. Then the working group will go through it very

1 carefully, and then we'll do whatever we can do to get it
2 into a modified version.

3 What are the next steps in this whole
4 development of individual bioequivalence? We have
5 published it, so number 1 is already done.

6 The agency has broadly shared the data
7 publicly, whatever data the agency has in house, how to
8 share the data so that people can have an appreciation who
9 wants to look at the data.

10 Then as Dr. Williams alluded to the fact that
11 expert committee is forming to look into all sorts of --
12 the implication of the individual bioequivalence concept
13 and how it should be applied. We'll get a whole gamut of
14 advice from this expert committee.

15 On March 16th to 18th, a joint FDA/AAPS
16 workshop has been scheduled to discuss about narrow
17 therapeutic index drugs and individual bioequivalence and
18 that will help us to develop public consensus.

19 Then afterwards, after the meeting, then the
20 expert committee will probably reconvene and offer their
21 recommendation.

22 Then the agency may repropose the guidance
23 based on the whole gamut of activities and then have it
24 again for public comments.

1 Just to see the last one, this is the working
2 group of individual bioequivalence. All of the working
3 group has worked very hard from 1992 onwards and especially
4 more emphatically for 1994 down to come up with the
5 guidance as well as all the analysis and developing the
6 concept and deciding on this scaling system. We're looking
7 forward to getting the comments from everybody.

8 Thank you very much.

9 DR. ZIMMERMAN: Thank you.

10 Are there questions from the committee? Dr.
11 Mayersohn first.

12 DR. MAYERSOHN: Rabi, you said there were 12
13 studies in the files. This represents one of them? What
14 you just presented represents one of those studies?

15 DR. PATNAIK: These are all 34 data sets of 12
16 studies. Some of them have got more than one analysis.

17 DR. MAYERSOHN: I see. Is there any way to
18 characterize them in terms of the classification system we
19 talked about today?

20 DR. PATNAIK: Not all of them we can do it.
21 For some of them we can do.

22 DR. MAYERSOHN: Is there at least a rank order
23 correlation between those that are most troublesome and
24 classification 4 or 3 or 2? Do you understand my question?

1 DR. PATNAIK: Yes, I understand about the BCS
2 classification 1, 2, 3, 4.

3 DR. MAYERSOHN: Yes.

4 DR. PATNAIK: We are planning to do that and
5 look at if there is an absorption problem. For some of the
6 data, we haven't looked at it, but I'm sure that the
7 working group is going to look at, from a BCS standpoint,
8 what kind of drugs and how they relate.

9 DR. MAYERSOHN: I would hope there would be
10 some common characteristics shared by those that are most
11 troublesome that have the greatest variability, and I
12 encourage you to look at them.

13 DR. PATNAIK: Yes, but I can tell you that just
14 looking at the data sets -- because we have worked on these
15 data sets so much, I can say that some of the data there,
16 they pass average bioequivalence, they pass individual
17 bioequivalence, and they're highly permeable/soluble drugs.

18 DR. MAYERSOHN: All of these compounds?

19 DR. PATNAIK: No. I can tell you a few of them
20 which I can recall.

21 DR. MAYERSOHN: That are troublesome?

22 DR. PATNAIK: That are easy. They're non-
23 troublesome. They can easily pass both.

24 DR. MAYERSOHN: And that's what you would have

1 expected.

2 DR. PATNAIK: Yes.

3 DR. MAYERSOHN: Okay.

4 DR. ZIMMERMAN: Dr. Goldberg?

5 DR. GOLDBERG: Dr. Patnaik, you talk about the
6 agency defining NTI drugs.

7 DR. PATNAIK: Yes.

8 DR. GOLDBERG: Will that be based upon the CFR
9 classification or on Dr. Burlington's list? How is the
10 classification going to be done?

11 DR. PATNAIK: Dr. Goldberg, I cannot say
12 because it's all up in the air what will be the criteria,
13 how it will be developed, and the process to be followed,
14 what will be the criteria. I think really John Balian is
15 going to talk about it. I do not know how the whole list
16 will be developed, by what definitions or what criteria to
17 be used at this time at least.

18 DR. GOLDBERG: Assuming that the agency does
19 classify some drugs as NTI, will they require retrospective
20 studies?

21 DR. PATNAIK: I guess not, but I'm not really
22 in a position to tell you which are already on the market
23 -- that's what you mean. Those that are already on the
24 market, whether to do another study, even the new criteria

1 on this individual bioequivalence, whatever form it takes,
2 to show that they are still bioequivalent by the new
3 methodology. Is that your question?

4 DR. GOLDBERG: Yes.

5 DR. PATNAIK: I do not know. I don't think so,
6 but again I'm not the person to make that decision.

7 DR. GOLDBERG: Okay. Thank you.

8 DR. ZIMMERMAN: Dr. Branch?

9 DR. BRANCH: I got very confused as to the
10 mathematical analysis and the linkage to NTI. Essentially
11 as I heard Roger talking about it earlier, there was an
12 idea that with the narrow therapeutic index drugs, you
13 would allow the pioneer drug to set the variance, and if it
14 was tight, then the competitor would have to be equally
15 tight.

16 But what you presented was actually a variance
17 to upper limit relationship in which you said if it was
18 below 20 percent variance, then it would become fixed. It
19 seems to me that what you've actually proposed is exactly
20 the opposite of what you stated. What you have proposed is
21 easing the criteria on any drug where the pioneer/reference
22 has a bigger variance than 20 percent. If it's tighter
23 than 20 percent, you're just keeping the status quo as it
24 is right now. So, it seems to me that the linkage between

1 this analysis and NTI is arbitrary and nothing to do with
2 that.

3 Can you help clarify?

4 DR. PATNAIK: Yes. Probably you misunderstood
5 what I said. Currently for all drugs if we apply the
6 individual bioequivalence criteria, irrespective of
7 whatever classification you have got, then what we'll have
8 that the working group has come up with the concept of
9 constant scaling and reference scaling.

10 By that, what I mean is for all drug products
11 as a conceptual basis, that when within-subject variability
12 is of the reference listed drug, pioneer drug, innovator
13 drug, is .2 or less than .2, if one uses this criteria and
14 the upper limit is controlled by the magnitude of the
15 within-subject variability of the reference product, then
16 if it is less than .2, then it will be narrowed if it is
17 less than 1.25.

18 So, to avoid that, the drugs which have no
19 problem but they have intrinsically lower within-subject
20 variability, there is no reason for the narrowing the upper
21 limit.

22 DR. BRANCH: Your point is taken. Warfarin is
23 a good example.

24 But my point is that essentially the narrow

1 therapeutic index drugs -- we've just heard today the vast
2 majority of them are right down in that box which is going
3 to stay exactly the same as it is now. The implications of
4 what you're proposing has nothing to do with what's going
5 be down in the bottom left-hand corner. It has everything
6 to do with what's going to be in that graph that goes up on
7 the opposite extension. According to what you're saying,
8 any drug that has a large variance in the pioneer drug, you
9 will be able to have wider goal posts.

10 DR. PATNAIK: Yes.

11 DR. BRANCH: So, the focus of this initiative
12 has nothing to do with narrow therapeutic index drugs. It
13 has to do with changing the goal posts for drugs that have
14 inherent variability.

15 DR. PATNAIK: You will make it much more
16 tighter for accepting -- for determining bioequivalence
17 because now instead of the higher limit to be 1.25, you are
18 going to make it less.

19 DR. BRANCH: But you said that that's going to
20 be fixed. You're not going to change --

21 DR. PATNAIK: No, no. I mean currently for the
22 majority of drugs that's what I'm saying, for special,
23 whatever the agency comes up with, a list of drugs or how
24 to identify certain drugs. Whether they will call it a

1 narrow therapeutic index drug or a special class of drugs I
2 do not know, but for special drugs which needs to pay
3 careful attention, they may be assessed to a lower
4 bioequivalence standard --

5 DR. BRANCH: But if you apply the data that we
6 saw for warfarin earlier today to that graph, can you
7 interpret what change, if any, this new analysis would
8 provide for that specific instance, given that the variance
9 that we saw was in the region of between 5 and 10 percent
10 in those studies?

11 DR. PATNAIK: If you see that -- now, if it is
12 less than 20 percent, which is over here --

13 DR. BRANCH: I think the data we saw earlier
14 today was around about 10 percent. So, it's the extreme
15 left-hand bar that would be represented by warfarin in that
16 if it was in that data set.

17 DR. PATNAIK: So, what will happen is that it
18 will probably come towards the lower than .2. What we are
19 saying here, irrespective of whatever it is, below .2 will
20 keep it as constant but it's not going to --

21 DR. BRANCH: So, it will make no difference to
22 the narrow therapeutic index drugs, which is what I was
23 saying.

24 DR. PATNAIK: It makes a difference because it

1 will be lower. The bioequivalence limit will be lower
2 because we'll not constant scale it. We'll scale it to
3 whatever reference variability shows.

4 DR. LAMBORN: Could I ask perhaps the same
5 question in a different way? If I understand it, you're
6 saying that for the non-narrow therapeutic index you would
7 use this lower bound, but for the narrow therapeutic index
8 you would not have a lower bound, but would allow them to
9 go further down the line?

10 DR. PATNAIK: Yes.

11 DR. LAMBORN: So, the solid line that you're
12 proposing there would not be employed for the narrow
13 therapeutic index at the lower end. You would continue
14 down that line below.

15 DR. PATNAIK: Yes, that is the point. The
16 point is now for all drugs -- what is the thinking is that
17 for all drugs we'll have the concept to a constant scaling
18 as well as the reference scaling. But for certain drugs
19 which have been identified, instead of going to this level,
20 it will be dictated by whatever within-subject variability
21 dictates.

22 DR. ZIMMERMAN: Dr. Byrn.

23 DR. BYRN: I just wanted to go on. I was
24 talking earlier about not -- I think one of the goals of

1 manufacturing should be to minimize the variation in
2 pharmaceutical manufacturing. In other words, the
3 manufacturing people don't want to add to the already
4 existing clinical variation any more variation. So, I'm
5 not sure that we shouldn't have the dotted line for all
6 drugs.

7 One of the problems you may get into from going
8 across with some, say, non-narrow therapeutic index drug is
9 that it would reduce the incentive to control manufacturing
10 of the reference drug product. I think it might ultimately
11 benefit the public health to put as many incentives as we
12 could on innovators as they're developing the drug and
13 marketing it during the period that's on their patent to
14 tighten up their manufacturing as much as possible.

15 Now, maybe there's a decision, well, it's going
16 to cost more and this improved cost isn't gaining anything
17 in the public health. But to me it seems like we want to
18 use the dotted line for all drugs. It would be an
19 incentive then to do the very best job we can in the
20 manufacturing end and that way any variation that you're
21 seeing is just due to patient variation.

22 DR. PATNAIK: Yes, but here there are two
23 things. One issue is that by following the reference
24 listed drug variability, we become too restrictive for

1 every drug which should not be that restrictive because now
2 we are having 1.25 which is like an average bioequivalence
3 criteria.

4 DR. BYRN: Right.

5 DR. PATNAIK: So, most of the drugs have no
6 problem. Some of the drugs are highly variable drugs which
7 where you see that one can maybe safely widen the goal
8 posts, the bioequivalence limit. For certain drugs also on
9 the same token a difficult drug or some drugs which need to
10 be restricted, we can reduce it.

11 DR. BYRN: I think you're arguing in effect
12 what I said, that going along the line at 1.25 for a non-
13 narrow therapeutic index drug is the most cost effective
14 drug product and you're not gaining anything by staying on
15 the dotted line.

16 But myself -- and I don't know how much we're
17 talking about in cost and maybe that's a way to determine
18 it. It seems like in the perfect world, if we could build
19 in an incentive to manufacture the drug exactly the same
20 every time, even a non-narrow therapeutic index, that would
21 be in the best interest of public health.

22 DR. PATNAIK: Yes. That is we're saying of the
23 reference listed drug having the less variability.

24 DR. BYRN: Right. I'm just trying to argue for

1 moving the concept of less variability from narrow
2 therapeutic index drugs, which I very much favor, to all
3 drugs.

4 DR. PATNAIK: But what is happening right now,
5 if a product has got high variability in the reference
6 listed drug or the innovator drug has got high variability,
7 the generic or another multi-source product should have
8 either that variability or should match that variability --

9 DR. BYRN: Right.

10 DR. PATNAIK: -- so that they can show
11 bioequivalence.

12 But with this new concept, you can see that if
13 your variability of the test is lower than the reference,
14 so this becomes a negative value, then this is a higher
15 value than if it is lower than the test. So, the whole
16 thing, keeping the rest of the thing constant, might have a
17 lower value. It is easier for the firm which is conducting
18 this test to pass the bioequivalence limit.

19 So, here is a big incentive for the
20 manufacturer of a multi-source product or if they're trying
21 to change the formulation to have as good a formulation as
22 they can manufacture.

23 DR. BYRN: Now, one other question. Is this
24 concept in the draft guidance?

1 DR. PATNAIK: Yes.

2 DR. BYRN: This concept of going across?

3 DR. PATNAIK: Constantly.

4 DR. BYRN: Okay.

5 DR. ZIMMERMAN: Dr. Brazeau?

6 DR. BRAZEAU: I'm wondering if you would be
7 better off, because I think we got confused in your
8 nomenclature, if you would subdivide drugs like they did
9 with the biochemical classification system to maybe having
10 different classes of drugs with narrow therapeutic windows,
11 a high variability, low variability, narrow. Because what
12 we were doing was getting confused in the different
13 nomenclature. So, I think if you differentiate.

14 Now, in the study data that you showed us, I
15 think it would also help if you showed us which of those
16 drugs, or maybe just by colors of those graphs, of those
17 bars that you showed us, correspond to different types of
18 drugs, like you were talking narrow therapeutic window or
19 highly variable. Because it's hard to follow that and the
20 data is from multiple studies. You said there were some
21 controls. There were some normals and there were some test
22 subjects. I have a hard time to interpret all that.

23 DR. PATNAIK: The objective was not to really
24 focus on the application of the data with respect to the

1 narrow therapeutic index drugs. The reason was that we
2 have not yet defined what should be criteria for
3 identifying or saying narrow therapeutic index drugs. All
4 I wanted to show is that this concept of reference scaling
5 using this criteria could be applied if the agency chooses
6 to make a little bit more stricter criteria for certain
7 drug products such as narrow therapeutic index drugs.

8 DR. BRAZEAU: Well, what we had was a
9 discussion on what we were trying to talk to. What do you
10 mean? When is it a highly variable drug?

11 DR. PATNAIK: A highly variable drug is what we
12 have said, generally identified as those drugs that show 30
13 percent or higher intra-subject variability. Several
14 meetings, several consensus reports have showed that if
15 those intra-subject variability or within-subject
16 variability is more than 30 percent, it is supposed to be a
17 highly variable drug.

18 Some of the drugs which have got high first
19 pass usually are very variable. So, 30-40 percent within-
20 subject variability is not very fair for those type of drug
21 products.

22 DR. ZIMMERMAN: Dr. Byrn?

23 DR. BYRN: I had another question on the
24 meaning of the subject-by-formulation, the sigmaD squared,

1 term.

2 DR. PATNAIK: Okay. Do you want me to explain
3 to you what it is?

4 DR. BYRN: Yes, would you explain? Let me try
5 to explain it and you could tell me whether you agree with
6 it.

7 Does that mean that the given patient is -- the
8 formulation that they're given affects the blood level
9 significantly? In other words, if it's above .15, does
10 that mean that those drugs that have a σ^2 above
11 .15, the formulation affects the blood level significantly
12 patient by patient?

13 DR. PATNAIK: It is so that it is the
14 manifestation -- that high value is the manifestation of
15 the lack of congruence of the means between test and
16 reference for various subjects. For example, just given a
17 perfect example like this, this is a reference and this is
18 test values for different individuals.

19 DR. BYRN: This is a great slide.

20 DR. PATNAIK: This is perfect bioequivalence.
21 Whatever you get for the reference, you get for the test.

22 Now, increased bioavailability of the test so
23 that the reference has got low bioavailability, then test
24 will not be average bioequivalence because the test shows

1 higher response because all of them are increasing. All of
2 them are staying in the same parallel way.

3 Now, increased bioavailability in a subset of
4 subjects, which is the lower value here, some of these
5 subjects in which -- they remain constant here for other
6 subjects, but here it goes the test response is higher than
7 the reference for these subjects. This is probably a
8 subset of population.

9 Now, subject-by-formulation interaction is
10 increased between-subject variability. That's what we are
11 saying, that here for the reference you have got a lower
12 variability, for the test you have got higher variability.
13 More lack of congruence of means, which has been shown
14 there. There are some subjects is going -- stay parallel.
15 Some subjects are going down, their response, and some
16 subjects going up.

17 In fact, for some of the data sets -- I will
18 just show one or two -- you see a lot of incongruence of
19 the responses. Some of them might be --

20 DR. BYRN: Now, if I was a manufacturer, if I
21 looked at this data, wouldn't I say, okay, in these
22 particular products I better reverse engineer the innovator
23 product and make exactly the same product if I was a
24 generic manufacturer? Do you see what I'm saying?

1 DR. PATNAIK: Yes.

2 DR. BYRN: Exactly the same formulation,
3 exactly the same components, et cetera as close as I could.

4 DR. PATNAIK: Yes, you can do that, but the
5 whole thing -- some of them are random occurrences, some of
6 them may not be genuine.

7 DR. BYRN: It could be the case -- say, this
8 lower one -- that this patient, if they take ibuprofen from
9 one company -- and it might be the innovator -- it takes
10 their headache away. If they take it from another company,
11 it doesn't take their headache away. Is that a proper
12 interpretation?

13 DR. PATNAIK: Well, yes, it depends on which
14 one you're comparing to which one. The point is that some
15 of them are random. Some of them are not that random,
16 maybe representing something in the formulation or the
17 subject.

18 DR. BYRN: Do we have any idea what's causing
19 this?

20 DR. PATNAIK: There are several theories that
21 have been put forward.

22 DR. ZIMMERMAN: I'm wondering if we can't move
23 on to our final speaker because then we'll have an hour
24 to --

1 DR. BYRN: Okay, we can discuss this.

2 DR. ZIMMERMAN: -- work Dr. Patnaik over the
3 coals. We'll get you back, Dr. Patnaik.

4 DR. PATNAIK: Okay.

5 DR. ZIMMERMAN: Our next speaker is Dr. John
6 Balian who will talk about criteria.

7 DR. BALIAN: Thank you, Dr. Zimmerman.

8 My apologies to the audience for my back, but
9 considering that I'm not much taller than the podium,
10 probably I'll not block your view.

11 (Laughter.)

12 DR. BALIAN: The title of my presentation is
13 Narrow Therapeutic Drugs: Definition. When preparing
14 these overheads, I seriously considered replacing the word
15 "definition" with a question mark because there are
16 scientists and individuals out there who say, what narrow
17 therapeutic drugs? They do not exist. Still others say,
18 you know one when you see one. Also, others say that it's
19 an old issue or rather an issue that deals or affects all
20 drugs only. After all, when was the last drug considered
21 to be a narrow therapeutic drug that was approved and
22 marketed?

23 In any case, no matter what approach we use,
24 the bottom line is that it's an issue that, as we see from

1 the earlier presentations, is not going to go away very
2 easily. Instead of avoiding it, our bosses, Dr. Williams
3 and Dr. Lesko, decided to take the challenge to resolve the
4 issue. So, they asked me to form a working group and they
5 charged the working group to craft a clinically relevant
6 and scientifically defensible definition of narrow
7 therapeutic drugs and also outline criteria and
8 characteristics for assessing these products.

9 Now, from all you heard earlier, you might be
10 expecting that this is actually what I'm going to do today.
11 My apologies because the real motive of my consideration of
12 putting a question mark there was actually a direct
13 question to the advisory committee and the audience is, how
14 do you define narrow therapeutic drugs? What criteria and
15 characteristics do you use, and how can you give us
16 direction? I guess after that, I can maybe stop my
17 presentation.

18 So, why are we bothering with this issue?
19 After all, it's very difficult and very challenging.
20 Besides the fact that currently it's one of the hottest
21 topics under discussion, I have listed some of the issues.
22 These are only some of them.

23 It is very useful both for the drug development
24 review and prescribing process to have scientifically

1 defined criteria which are missing currently.

2 Narrow therapeutic drugs are frequently
3 mentioned in most of our guidances that are out there in
4 the public already, and those under consideration now and
5 even the one that was released today, the individual
6 bioequivalence, they refer to it and actually now they are
7 simply saying that there will be a working group that will
8 come up with this definition. So, the pressure is on us.

9 Also as far as our office, the Office of
10 Clinical Pharmacology and Biopharmaceutics, we consider
11 this a true clinical pharmacology issue of concentration
12 versus effect and give the challenge to the pharmaceutical
13 industry to conduct proper pharmacokinetic and
14 pharmacodynamic studies in identification of these drugs.

15 I will skip the next three bullets because they
16 were touched upon extensively by earlier speakers.

17 The drug interaction and the special population
18 issue is listed here because these are circumstances where
19 there is potential of drugs that are otherwise of wide
20 therapeutic range could shift the dose-response curve to
21 such a degree where after the interaction or in these
22 special populations they can become narrow therapeutic
23 drugs.

24 Lastly, the over-the-counter issue. During

1 consideration of a product for over-the-counter, obviously
2 narrow therapeutic drugs are exclusion criteria.

3 So, what is a narrow therapeutic drug? It's a
4 drug that commonly exhibits adverse effects which limit its
5 therapeutic use in doses close to or overlap those needed
6 for therapeutic effect. Now, this is a very basic
7 definition that I think we all can agree upon except that
8 it does not assist in scientific measurements or in
9 identifying drugs except for post facto.

10 Also, during the discussion here, we heard many
11 terms and nomenclature for this, whether it's range or
12 window or index or ratio. Now, purists like Dr. Tom Tozer
13 inform me that indices and ratios are high or low, while
14 windows and ranges are narrow or wide. So, my hope is
15 maybe we can come up with a terminology today that can
16 eventually be universally acceptable.

17 You saw this slide earlier. Mr. Sporn showed
18 it. These are the current regulatory definitions of narrow
19 therapeutic drugs. It relies upon these three basic
20 parameters.

21 A less than two-fold difference in the median
22 lethal dose, or the LD50, and the median effective dose,
23 ED50, values.

24 The second one is less than a two-fold

1 difference in the minimum toxic concentration and the
2 minimum effective concentration in the blood.

3 And finally, these drugs for their safe and
4 effective use, dosage titration, and therapeutic monitoring
5 is necessary.

6 Now, these definitions are actually used by
7 many other regulatory agencies as well, either very similar
8 or with some variation.

9 Now, there's a problem with these criteria and
10 definitions. The first two are obtained from animal data,
11 and we're not sure how clinically relevant they are. Also,
12 these are currently very rarely available. We do not
13 require LD50's anymore.

14 And the third one, for therapeutic monitoring,
15 this is a concept once a drug is identified as a narrow
16 therapeutic drug, but not a criteria or a definition per
17 se. And also, it's very widespread. It's used for many
18 drugs.

19 Now, narrow therapeutic drugs are widely
20 discussed but unfortunately very rarely written about.
21 Three different members of our working group conducted
22 extensive literature search and review and very little was
23 found. So, that's another reason why I would like to rely
24 upon the advisory committee and members of the audience

1 very heavily today.

2 What we're going to propose today is a very
3 innocuous definition, the simplest approach we could take,
4 and that is the definition for a narrow therapeutic drug is
5 the degree of the overlap between effective doses or
6 concentrations and doses or concentrations which cause
7 unacceptable toxicity define a narrow therapeutic drug.

8 Now, our hope is that following today's
9 discussion we can maybe come up with a workable definition.

10 I will not bore you with a discussion of
11 concentration versus effect and dose-response curves, but I
12 would like to make a couple of points as to the reason why
13 we chose this specific language, in particular the part
14 where it says degree of the overlap.

15 We chose this wording. We had two things in
16 mind. One was the current definitions, the part where it
17 said less than a two-fold difference in the minimum toxic
18 concentration and the minimum effective concentration. We
19 considered that that's workable, of course, if the source
20 is from human data, from human PK/PD studies.

21 The second reason is that there's a school of
22 thought out there that it doesn't really matter how wide
23 the window, so-called therapeutic window is. What actually
24 matters, what's critical is the overlap or the closeness of

1 the efficacy and toxicity at the higher end of dosing only.
2 A drug can be given from 10 milligrams to 1,000 milligrams.
3 It still can be considered a narrow therapeutic drug if the
4 recommended dose of 1,000 is very close to serious
5 toxicity.

6 Since a definition is not likely to be
7 definitive, a series of criteria or characteristics need to
8 be outlined for proper classification of these drugs.
9 Probably at the end these criteria will have to be weighted
10 as well.

11 Some considerations for this process are listed
12 here and some of these can be considered as eventual
13 characteristics while others simply complicating factors or
14 issues for consideration when the drug is a narrow
15 therapeutic index drug.

16 The first one is what's again in the current
17 definition of the CFR, and that's a less than two-fold
18 difference in the minimum toxic concentration and the
19 minimum effective concentration in the blood. Few of the
20 drugs that were listed earlier in the SUPAC guidance can
21 meet this definition, but most that we consider or think of
22 narrow therapeutic index actually fall out of this range.

23 The second one, non-linear kinetics over the
24 therapeutic range, is certainly a criteria. Now, I don't

1 mean to say all drugs that fall in this are narrow
2 therapeutic drugs.

3 The third one, the case of high inter- and
4 intra-subject variability. Probably in this day and age in
5 the current drug development environment, any drug that has
6 high variability and is potentially narrow therapeutic
7 index probably will not make it to the finish line, but for
8 most of the other drugs, this is an issue.

9 Therapeutic drug monitoring is a consequence,
10 as I mentioned earlier.

11 Saturable protein binding, accumulation and
12 cumulative toxicity. Those are issues that may complicate
13 a narrow therapeutic drug.

14 Special populations and drug interactions, as I
15 mentioned earlier, they may shift the curve for an
16 otherwise wide therapeutic drug.

17 Therapeutic category. I have that there
18 because of our experience with oncology. Most cancer
19 drugs, probably all cancer drugs, are narrow therapeutic
20 drugs, very highly toxic and yet we use them because of the
21 risk/benefit issue.

22 And therapeutic indication. Aspirin when used
23 for iron type pyrexia or used for headache, at the dosage
24 used, it's not a narrow therapeutic drug, but when used for

1 antirheumatic purposes, certainly the doses used there
2 overlap the toxicity curve.

3 So, the objectives of my presentation and the
4 working group objectives are basically to get your input,
5 solicit your input -- and members' of the audience -- to
6 help us devise a clinically relevant and scientifically
7 defensible definition of narrow therapeutic drugs and also
8 to outline criteria and characteristics for assessing these
9 products.

10 Also, we would appreciate some clear direction
11 for us as to where to head with this once we have a final
12 product. Do you think it should be a guidance, a position
13 paper, a review article?

14 And also should we revisit the Code of Federal
15 Regulations? Should we rewrite the definitions that are
16 there right now?

17 Finally, I would like to thank the working
18 group members. Dr. Al-Habet, who's assisting me right now.
19 Dr. Dennis Bashaw is in the audience. Mahmood, and also we
20 appreciate all the help and direction we received from Dr.
21 Williams, Lesko, Dale Conner, his participation, and Mark
22 Vogel.

23 Thank you.

24 DR. ZIMMERMAN: Thank you.

1 We'll be open for a committee discussion now,
2 and so any of the speakers who have spoken this afternoon
3 are fair game, shall we say.

4 Before we start I think that the questions that
5 I've formulated during this afternoon discussion, of
6 course, revolve around the narrow therapeutic drug
7 classification. So, I think the questions that I think we
8 need to talk about is whether there's really a need for the
9 agency to single out a certain group of drugs as a class to
10 have a higher level product quality management, and could
11 this be done on a case-by-case basis is one of the things
12 that I've been hearing.

13 Secondly, if we decide that, that that's
14 appropriate, then how should the narrow therapeutic drug
15 classification be defined both in terms of what drugs are
16 there and what terminology we're going to be using?

17 With that, I'll open the discussion. Dr.
18 Brazeau had her hand up.

19 DR. BRAZEAU: I had some other considerations
20 for Dr. Balian. A couple of questions that I didn't see in
21 the considerations that I think are important. What are
22 you going to do about drugs that have active metabolites?
23 Because particularly those active metabolites might
24 contribute to the toxicity.

1 The second area would be what about tissue
2 binding. You've mentioned protein binding, but what about
3 tissue binding? These are all areas that I think need to
4 also be in your consideration. If you are going to talk
5 about a narrow therapeutic window drug, you deal with drugs
6 that don't have active metabolites, or how do you deal with
7 that?

8 DR. BALIAN: As far as the active metabolites,
9 when I say drug, actually I mean any active moiety, any
10 active species of the drug. So, an active metabolite -- if
11 it meets the criteria, yes, it is a narrow therapeutic
12 drug, then the parent can be considered as a narrow
13 therapeutic drug.

14 For the second one, we appreciate the input.
15 Tissue binding should be a consideration.

16 DR. BRANCH: I'd like to make a comment and a
17 suggestion. The comment is that I think this is a very
18 important conceptual approach and I think it's important
19 from the perspective of the trend for drug development
20 review to ask the question, should drug therapy be
21 individualized to patients, particularly drug dosage. I
22 think what you're doing is actually helping identify those
23 drugs where it's particularly relevant and important. So,
24 I think the focus in my view is within the area of

1 individualization.

2 I think that the issues go way beyond
3 therapeutic exchange and generic substitution and actually
4 much more relevant to an initial part of an NDA process of
5 how best to use the drug. The key contribution of this
6 area is actually going to be in drug labeling or advice to
7 physicians on how best to use drugs.

8 If that is an underlying premise, what is the
9 definition? I think that the starting point that you
10 raised -- I think I would add a couple of qualifying
11 clauses. I think in terms of efficacy, I would say
12 clinically relevant efficacy. I think in terms of
13 toxicity, keep to the one that you've said, which is
14 unacceptable toxicity. These are definitions that are
15 outside individual drugs that are generic and they relate
16 to quality of life.

17 I think there is one problem I have with the
18 schema that you have which may be theoretically correct if
19 you go to huge increases in dose. But the real problem
20 that you face is that the adverse reaction frequency is
21 very low and your efficacy you're hoping to get
22 universally. So, you've got differently constructed
23 frequency distribution curves that you're talking. I think
24 that maybe some of the discussion should focus around those

1 issues.

2 Getting into tissue concentration, dose-
3 dependent kinetics, those sort of things are getting into
4 levels of detail which are probably inappropriate at this
5 stage. I think you should keep this as a very general
6 topic and I think it has much broader implications than you
7 sort of implied in the initial workup for it.

8 DR. ZIMMERMAN: Dr. Williams?

9 DR. WILLIAMS: Dr. Zimmerman, I'd just like to
10 endorse what Dr. Branch said because as we leave the realm
11 of product quality and move into the realm of safety and
12 efficacy and clinical pharmacology, I'm always impressed
13 about how much information we might really need to address
14 some of the questions that we're discussing now.

15 I would come back to that particular overhead
16 that John showed, the dose-response curve for both efficacy
17 and toxicity. Now, I would argue that that is an
18 individual dose-response curve and not a population dose-
19 response curve. We rarely, I think perhaps if ever, see
20 those kinds of dose-response curves in a new drug
21 application.

22 I would also argue that we rarely see dose-
23 response curves for an adverse event at all.

24 So, it's interesting a lot of the information

1 we might need to make a judgment of a narrow therapeutic
2 range drug in the clinic probably aren't available from the
3 new drug development process.

4 DR. ZIMMERMAN: I have a question. If we're
5 talking about not the new drug applications, but the
6 ANDA's, it seems to me there's a lot of information in the
7 literature, population, pharmacokinetics, strategies such
8 as meta-analysis, and all these kinds of things. Can't we
9 get information from the literature and from things that
10 have already been published or submitted that would allow
11 us to ease the burden on individual generic firms?

12 What I'm thinking about is some of the within-
13 subject variability. Some of this stuff is published. We
14 should be able to get some information from things that are
15 already in the literature. Is it just not accessible? I
16 don't really understand. For a drug that has been on the
17 market for a long, long time, it seems to me we'd have a
18 lot of data from the innovator product on inter-subject
19 variability.

20 DR. BALIAN: We do have that data on the drugs,
21 for example, on theophylline and warfarin, phenytoin, and
22 we looked at them. However, it's not assisting us in
23 coming up with a definition. We do have all the different
24 dose-response curves for these drugs, but as Dr. Williams

1 said, for the new drugs, the new molecular entities, we
2 hardly have the data to make such an analysis.

3 DR. ZIMMERMAN: Aren't we talking about
4 bioequivalence here? I thought that it was framed this
5 morning we're not talking about bioavailability. We're
6 talking about bioequivalence. So, for bioequivalence,
7 you're talking about you had an innovator product that's
8 being used in the population for a long time. That data
9 should be available somewhere I would think.

10 DR. LAMBORN: But can't you also have
11 bioequivalence moving from the agent used in the clinical
12 trial to the agent actually being scaled up for marketing
13 or early post-marketing changes? I agree there's another
14 end, but I think we do have to address the ones that are
15 happening before you have that long history.

16 DR. BRANCH: In terms of what Roger said, he
17 said you don't get the adverse drug reaction data, I would
18 hazard a guess that something like 40 percent of drugs are
19 introduced to the market at doses that are subsequently
20 reduced. They're reduced because they're found to have an
21 effect that wasn't actually wanted. So, I think probably
22 the data is available.

23 Going back to the issue of should this be
24 couched in terms of bioequivalence, I think that the

1 bioequivalence aspect is probably the most easily regulated
2 and tightly controlled, but the real issue here is the
3 biological difference on how best to use a drug and I still
4 think this issue of narrow therapeutic window drugs has
5 greater potential impact for public care when focused on
6 new drug development. I would really like to see this
7 document that you're preparing at this stage be done with a
8 view to having an impact both in drug development as well
9 as generic substitutions.

10 DR. ZIMMERMAN: Dr. Byrn?

11 DR. BYRN: I wanted to go back to the other
12 question. Maybe let me make one comment.

13 I agree, though, with the slide that if drugs
14 showed a lot of inter-patient variability, a lot of them
15 would not make it to the marketplace today because I think
16 most companies have a number of products that they're
17 looking at, and unless this is a phenomena that's
18 widespread among all the candidates, it's most likely that
19 they would drop that primary candidate and go to a
20 secondary candidate. Unless it's something related to the
21 actual action of the material, they would do everything
22 possible to find a drug that didn't show all this inter-
23 subject variability.

24 DR. ZIMMERMAN: Dr. Williams?

1 DR. WILLIAMS: I'm going to take the liberty on
2 writing on one of my overheads, and I apologize if it's
3 hard to see. But again, one of the reasons I enjoy the
4 discussion of this so much is because it makes explicit
5 many of the things that we take on assumption or haven't
6 adequately addressed in the past.

7 I think it gets to the issue of this
8 therapeutic window that we talk about. I might again
9 emphasize the distinction between what I see as the
10 population therapeutic window versus the individual
11 therapeutic window.

12 Now, I'll use phenytoin as an example. In a
13 drug level laboratory, phenytoin says you should range
14 between 10 and 20 milligrams per liter, and that that's
15 population range. But I might argue that after a patient
16 is titrated to, say, 15 milligrams per liter, by working
17 with the physician during the prescribability phase, that
18 you might want that individual to, say, range plus or minus
19 20 percent around that average. Now, that's a very
20 different range, say, 12 to 18, than the population range,
21 and I think it's that individual patient range that we miss
22 so often.

23 I would also argue that I think in the course
24 of the discussions tomorrow when we move to the realm of

1 clinical pharmacology, you will see that there are a lot of
2 equivalence questions there as well. A drug-drug
3 interaction question is an equivalence question. A food-
4 drug interaction is an equivalence question. When you put
5 somebody on dialysis and then you change their levels, that
6 becomes an equivalence question. I think again it's an
7 individual dose-response relationship.

8 Now, I want to come back to what Dr. Zimmerman
9 said. I think you're probably right, that if you really
10 looked at the available data, you might be able to tease
11 out some of this information. As you know, the agency does
12 a meta-analysis of the safety data as part of the
13 assessment of a new drug application. In that meta-
14 analysis, individual patients may have different doses and
15 show different degrees of toxicity depending on the dose
16 level.

17 But I would argue, in my mind at least, there's
18 a motivation, perhaps going back to what Dr. Branch said,
19 to perhaps change the way we do drug development to perhaps
20 tease out some of this information in a better way. I
21 think it could also be done perhaps in an even more
22 efficient way than we do now. So, I don't think it
23 necessarily has to invoke increased regulatory burden.

24 DR. BYRN: What happened over here, Roger?

1 That's a better manufactured drug over on the right.

2 DR. WILLIAMS: It's interesting. You can get
3 involved in interesting questions, and I would also point
4 out the fact that we have experts in the audience who can
5 talk about this better than I can. Specifically Dr. Hauck
6 and Dr. Anderson are with us today, and I would encourage
7 the Chair to turn to them and see if they have any
8 comments.

9 But there is this mean variance tradeoff that
10 we talk about. Let's say this is a reference product. I
11 won't say whether it's generic or innovator. Then you get
12 to the question, what if you had a better absorbed and less
13 variable product? Is that equivalent or is it better?
14 Does it belong in the world of 505(b) or can it stay in the
15 world of 505(j)? I think that's what individual
16 bioequivalence poses to us, whereas before we perhaps
17 didn't deal with the question in such an explicit way.

18 DR. BYRN: Also, I think we would probably want
19 to try to build in incentives to go to the right-hand side
20 there so that we can get better products.

21 DR. WILLIAMS: Well, if I could add. We do
22 have incentives now, you know, the three years of
23 exclusivity with AB.

24 DR. BYRN: That would be good, yes.

1 DR. WILLIAMS: I think what we're trying to
2 imagine in the world of (j), you could be a little bit
3 better.

4 DR. BRAZEAU: But, Roger, in your scenario of
5 going from 10 to 20 versus 12 to 18, I'm not sure in every
6 drug you're going to see a difference in the endpoint of
7 the patient. Those are blood levels. You might not see a
8 difference in a patient between a blood level of 12 and 18
9 as long as their seizures are controlled.

10 DR. WILLIAMS: Well, it's certainly an
11 excellent observation, but I guess I would say that if you
12 had a patient on phenytoin titrated to 18 and then you
13 dropped them on down to, say, 10 or 12, they might be
14 within the population range. The blood level laboratory
15 would come back and say you're perfectly fine, don't worry.
16 But you might find that that particular patient loses
17 control with that change in the level.

18 DR. BYRN: If you could go up closer to 18,
19 then you'd have fewer breakthroughs.

20 DR. WILLIAMS: And particularly with the
21 nonlinear kinetics of phenytoin. Well, that's expressed in
22 the blood level.

23 DR. BRAZEAU: But I will say that I think you
24 always have to look at the therapeutic endpoints. While

1 blood levels certainly are useful indices, are you
2 achieving the goal that you want in that patient, the
3 reduction in blood pressure that you want to see?

4 DR. ZIMMERMAN: Dr. Mayersohn.

5 DR. MAYERSOHN: John, there are a couple of
6 issues with regard to the figure on page 3. I always
7 learned that the measure of potency is along the x axis,
8 the EC50, ED50, ET50, and yet you're suggesting the issue
9 be resolved along the y axis, as I understood it. Is that
10 right?

11 DR. BALIAN: You mean the concentration versus
12 the response?

13 DR. MAYERSOHN: Yes.

14 DR. BALIAN: Well, I'm not looking at
15 concentration per se. The clinicians would maybe say dose,
16 but one of them, dose or concentration.

17 DR. MAYERSOHN: But that wasn't my point. I'll
18 get back to that in a second.

19 I heard you -- I may have misunderstood --
20 saying the relationship along the y axis response to
21 toxicity where the curves flatten out is what defines the
22 index. Is that correct?

23 DR. BALIAN: Yes. The overlap of the curve
24 there, yes.

1 DR. MAYERSOHN: So, you would take your top
2 curve and look at the curve just below it where they
3 flatten out, and that would be your definition of --

4 DR. BALIAN: Well, we have to take into
5 consideration -- you probably have to draw distributions
6 underneath those curves.

7 DR. MAYERSOHN: Yes. I realize this is a
8 hypothetical.

9 DR. BALIAN: When you have those distributions,
10 the bell-shaped curves under those curves, you will run
11 into the overlap.

12 DR. MAYERSOHN: That's a unique perspective.
13 I've never heard that proposed before. I could be wrong.

14 DR. WILLIAMS: Dr. Zimmerman, I would agree
15 with Mike. I think you would drop that down to your x axis
16 which is your dose or concentration and express your ED50
17 in terms of dose. But then I think in the individual
18 population there would be a range around that metric, and I
19 think what John is talking about, overlap in the range
20 between the efficacious dose and the toxic dose.

21 DR. MAYERSOHN: Oh, okay. Still overlap is
22 relative to the x axis.

23 DR. BALIAN: Right.

24 DR. MAYERSOHN: Oh, I'm sorry. I

1 misunderstood.

2 The other issue, and it's one you have to be
3 careful of -- for example, Gayle mentioned one example of
4 it -- is whether you use dose or concentration on the x
5 axis. Just as an example, if you use dose and the drug has
6 a maximum solubility, which is fairly low, you may never
7 see toxicity. On the other hand, if you establish a
8 concentration in the blood from IV dosing, for example,
9 there would be a clear concentration-toxicity relationship.
10 Right?

11 DR. BALIAN: Sure.

12 DR. MAYERSOHN: On the other hand, if you have
13 an active metabolite, as Gayle was proposing, you would see
14 that with dose and you wouldn't see it with apparent
15 concentration. So, this is clearly a potentially confusing
16 issue.

17 Finally, it's even more confused by should you
18 use unbound plasma concentration, which you probably
19 should, as opposed to total concentration. Phenytoin is a
20 good example.

21 Just comments --

22 DR. BALIAN: Right.

23 DR. MAYERSOHN: -- to drive you more crazy than
24 you already are.

1 DR. BYRN: I've got questions for Rabi.

2 DR. ZIMMERMAN: Well, go ahead.

3 DR. BYRN: I want to go back to our curve that
4 we had that went down and then comes across at 1.25.

5 DR. PATNAIK: Yes.

6 DR. BYRN: As I was discussing, if we just went
7 ahead and made the dotted line the solid line -- and I'm
8 just exploring this out loud now -- in the realm of
9 bioequivalence, we wouldn't need to define, would we,
10 narrow therapeutic index drugs because everything would be
11 forced to fall on this line. So, I'm sure we need to
12 define those, but with respect to bioequivalence, if we
13 just took the line straight on down, we wouldn't need that
14 definition, would we or would we? Maybe we could put the
15 line back up.

16 DR. ZIMMERMAN: Please come to the overhead.

17 Are we confusing narrow therapeutic index drugs
18 with highly variable drugs?

19 DR. BYRN: Well, yes. I think what was being
20 said is that we go across the solid line for everything but
21 narrow therapeutic index/highly variable drugs. Those
22 drugs we come on the dotted line. Then I was saying, well,
23 if we say on the dotted line for everything, we have an
24 incentive to the manufacturers to make less variable

1 products as minimal as they can, and Rabi was saying, well,
2 yes, but it may not be necessary.

3 But now I'm wondering the consequence of going
4 on the solid line -- I mean, the dotted line all the way
5 down would mean that we wouldn't have to define narrow
6 therapeutic index drugs for bioequivalence. We'd just use
7 this line, and that would be our definition of approval of
8 an ANDA. We'd just draw the line. If it fell on it, fine;
9 if it didn't, more work would have to be done.

10 The advantage of this, Roger, would be this
11 would give the innovators an incentive to make a less
12 variable product. We have to debate whether the costs of
13 that are worth the public health, you know, any gain in
14 public health or not.

15 DR. BRAZEAU: I think that's a very good point.
16 One of the questions that Roger asked us about was the
17 public health justification of doing that. I think what
18 Steve has proposed is a very valid question. Certainly
19 it's like apple pie and motherhood. We'd like the therapy
20 to be best for patient, individualized, but there is a
21 cost-benefit ratio.

22 I think where we're getting confused, what's
23 made this afternoon extremely confusing to me is that we're
24 mixing highly variable drugs with narrow therapeutic index

1 windows, and that's what's making the whole thing
2 confusing. I think what Steve has proposed is a way to
3 help us sort through those.

4 DR. PATNAIK: I will just make a couple of
5 comments.

6 When you follow the reference variability,
7 within-subject variability, and the implied upper
8 bioequivalent limit, it gives you some sort of a little bit
9 of curvilinear function. Now, if you go all the way to 0
10 -- that means if you have got 10 percent -- it will be
11 somewhere between 1.1. Whereas, for some nonproblematic
12 drugs, you might need 100 subjects to pass that. So, we
13 have to think about the power of the study to pass such a
14 strict bioequivalence criteria.

15 If it is necessary or not -- unnecessarily
16 widening your form just because the variability is low, is
17 it necessary? But now we are doing it. The proposal is
18 now currently we have got the average bioequivalence
19 criteria which for most of the drugs this is working, and
20 for highly variable drugs, whereas to pass the current
21 bioequivalence criteria, you need a lot more subjects to
22 raise the power. So, it's much more burdensome to the
23 sponsors of the study to take more number of subjects to
24 show bioequivalence, although the intrinsic variability is

1 due to the drug substance or maybe because of the first
2 pass effect, the biological effect.

3 So, what we are saying, that when you have got
4 a highly variable drug, from a safety and efficacy
5 standpoint it's not having much more risk to widening it
6 because the reference variability is quite high. But for
7 most of the drugs -- I will say about 80 percent of the
8 drugs -- which are approved -- I'm talking about multi-
9 source drug products -- there is no problem at all if the
10 variability is 20 percent or less to keep it at this level.
11 If you want to reduce it to make it much stricter, you
12 might want to have more number of subjects to raise the
13 power.

14 For certain drug products, like Dr. Williams
15 suggested, it will be reference scaled because of the
16 concern for particular, specific drugs. So, everything is
17 a reference scaling complete up to 0, and if you have to
18 reference scale everything, even if one has got 5 percent
19 within-subject variability, it will be like 98 to 102. You
20 cannot be more than 1.02 percent. But is that necessary if
21 you're totally governed by the -- or controlled by the
22 reference listed drug within-subject variability?

23 DR. BYRN: But if we did go along that line, we
24 wouldn't need to define highly variable or narrow

1 therapeutic index drugs. Everything would just be on the
2 line. It would be a moot point.

3 DR. PATNAIK: That's true, if you have only one
4 thing. That's why we are saying that the working group
5 suggested that if you completely reference controlled by
6 the reference variability -- if it is reference scaled, you
7 can go as high and you can go as low as the variability
8 dictates. But here we are saying that most of the drug has
9 got no problem. 1.25 is all right because it is
10 bioequivalent. So, it's nonproblematic drugs with which we
11 are pretty confident about safety and efficacy. Then
12 there's no reason why we cannot do it.

13 DR. ZIMMERMAN: Dr. Williams?

14 DR. WILLIAMS: Just to emphasize a little bit,
15 Steve. If you always scale, it becomes a terrific resource
16 burden for standard drugs. So, really what I would like to
17 imagine is that our list of narrow therapeutic drugs, if we
18 ever get to that point in life, would be a very small list.
19 It may be only 5 or 10 drugs in the marketplace that we
20 would want to always scale.

21 The other issue that you brought up, Steve,
22 which is a very important one, is an incentive for better
23 products. I think this equation does that. I might argue
24 that it does it via these terms in the numerator.

1 Remember, I think a small numerator is good. Right, Rabi?
2 So, if you reduce the value of this entire term, it helps
3 you pass the goal post. If you make a less variable test
4 product, it will help you pass the goal post.

5 So, I actually see this equation kind of
6 chugging away in a nice public health way from the start of
7 drug development because the reality is it's not this being
8 the generic and this being the pioneer. This is actually
9 the first iteration of the reference product. The next
10 time the pioneer has to do a bioequivalence study, this
11 becomes the test. So, you will always be encouraging over
12 a period of hundreds of years maybe less variable products.
13 So, we've got to take a long view here.

14 But I would argue that this is a very powerful
15 part of this equation because right now we sort of have an
16 incentive to have highly variable pioneer products because
17 it makes it harder for the generic to pass the goal post.
18 Now, I would argue that's kind of a bad public health
19 equation to create that situation, and we all know there
20 have been examples of highly variable reference drugs to
21 which generic substitution becomes very difficult.

22 DR. ZIMMERMAN: Did you have a comment?

23 DR. LAMBORN: I think when I was looking at the
24 line along there, we were talking about moving it down in

1 that lower range. I can envision two public health
2 tradeoffs and one actually being the case where someone
3 would manufacture something to a very tight standard far
4 beyond what is needed for the actual therapeutic benefit
5 and in that way preclude generics which we would say
6 sometimes are beneficial from a public health standpoint in
7 terms of making the agent more accessible. So, it's a very
8 complex thing.

9 I think one of the things that I felt this
10 afternoon has been that we keep shifting between the
11 concept of individual bioequivalence, the concept of what
12 do we do with highly variable drugs, and somehow we've
13 plugged those two right in the middle of a discussion of
14 narrow therapeutic index. Maybe we need as a group to say,
15 all right, right now let's talk just about the issue of
16 what else can we give you in terms of advice on how to
17 define this group. Then we know that individual
18 bioequivalence may be a tool which we may later want to
19 apply. But it's sort of like we're having trouble focusing
20 is my sense.

21 DR. WILLIAMS: Dr. Zimmerman?

22 DR. ZIMMERMAN: Yes.

23 DR. WILLIAMS: Can I just endorse what Kathleen
24 said because in some ways I think this equation -- I feel

1 like I'm selling a Hoover vacuum cleaner sometimes when I
2 talk about it because it really does solve multiple
3 problems. It solves the issue of highly variable drugs.
4 It solves the issue of not neglecting subject-by-
5 formulation interaction. It solves the issue of always
6 encouraging better formulations. And if we decide as a
7 society to look at narrow therapeutic index drugs, it also
8 creates a mechanism to change the goal posts for those.
9 So, it's a very rich equation. I think you will see
10 tomorrow that it has applications beyond just
11 biopharmaceutics questions.

12 But I would agree with Kathleen that maybe the
13 focus of this is the criteria for a narrow therapeutic
14 index drug. I think that's what you were saying.

15 DR. ZIMMERMAN: Well, along those lines, I was
16 looking through the handout from Dr. Balian on regulatory
17 definitions currently of narrow therapeutic drugs, to
18 quote, "For safe and effective use dosage titration and
19 therapeutic monitoring necessary." You pointed out that
20 the criticism of this would be that dosage titration and
21 monitoring is very widespread.

22 That may be but it's only routine for certain
23 drugs, drugs that need to have things like -- well, for
24 example, gentamicin, things that need to be monitored

1 clinically all the time. Phenytoin is another one.
2 Theophylline is another one. So, there are really just a
3 handful of compounds that actually are clinically monitored
4 to stay within a range. It seems to me that clinical
5 practice is what will be defining narrow therapeutic range
6 drugs in the sense of what is actually monitored.

7 DR. BALIAN: Well, I guess that can be divided
8 into several sections. One is dose adjustment and
9 titration without looking at concentration. Most drugs now
10 approved probably will fall under that category. Most of
11 the drugs are titrated and there is dose adjustment. Now,
12 the issue of gentamicin and theophylline and phenytoin,
13 there is dosage adjustment based on the therapeutic drug
14 monitoring in the sense that there are concentration levels
15 and then based on there is -- and yes, there is a handful
16 of those that fall under that category, yes.

17 But again, that's not a criteria or a
18 definition of a narrow therapeutic index drug. It's simply
19 a concept and something that we have identified as such,
20 and hence we want to monitor them. In the definitions
21 right now, it indicates that that's a definition of it.

22 DR. BRAZEAU: But wouldn't you want to devise a
23 definition that will be able to incorporate some of the
24 things that Dr. Zimmerman has talked about as far as being

1 able to monitor. As we get more sensitive monitoring
2 techniques like glycodialysis, we may be able to get a
3 better grip on what's going to be the therapeutic window
4 and different things. So, whatever definition you have
5 certainly has to include aspects of that.

6 DR. BALIAN: Sure.

7 DR. WILLIAMS: Might I say I like your
8 definition because I think it has a simplicity. If it's
9 measured in a drug level laboratory, it becomes a narrow
10 therapeutic index drug. I don't know how many are
11 measured, but isn't it just a small 10 to 20 maybe?

12 DR. ZIMMERMAN: Yes. There's not a lot.

13 DR. WILLIAMS: Five to 10?

14 DR. BRAZEAU: But is that going to change as we
15 get more sensitive analytical techniques?

16 DR. WILLIAMS: Well, but I think if the new
17 drug development process says at the end of that process
18 that you should monitor patients by a drug level
19 laboratory, that's fine. We'll add them to the list when
20 it comes time for generic substitution.

21 DR. MAYERSOHN: Roger, I thought this was the
22 decade of kinetics-dynamics. I thought many of your NDA's
23 are going to have inherently these kinetic-dynamic
24 relationships. You can run almost everything you want from

1 that.

2 DR. WILLIAMS: Well, certainly it's true there
3 are far more studies now, and Larry might want to speak to
4 that. But again, I emphasize that I think what we need to
5 look at is more individual dose-response relationships, and
6 I think we almost never see those.

7 DR. ZIMMERMAN: If you're trying to define
8 narrow therapeutic drugs, you look at the clinical
9 practice, you figure out which ones have to be monitored,
10 doesn't that give you an idea of what are -- where you have
11 to monitor it, doesn't that give you an idea that those
12 compounds are narrow therapeutic drugs?

13 DR. MAYERSOHN: I think historically that has
14 been the case, but people are rethinking this whole issue
15 on a practical level as to what we consider to be narrow
16 therapeutic may not be any longer.

17 DR. ZIMMERMAN: In terms of practice, you're
18 only going -- well, I come from Minnesota, which is the
19 managed care capital of the United States.

20 DR. MAYERSOHN: No. That's Arizona.

21 DR. ZIMMERMAN: No, no, no. I don't think so.

22 DR. MAYERSOHN: I beg to differ.

23 (Laughter.)

24 DR. ZIMMERMAN: And the health care systems are

1 not going to allow you to monitor things you don't have to.
2 I'll let the clinician speak to this.

3 DR. BRANCH: It goes back to, I think, which is
4 the cart and which is the horse. The issue is as the drug
5 is being developed, if you need to individualize dose in a
6 patient, if a dose ranging strategy is the safest, most
7 effective way of giving that therapy, that is what a
8 clinician calls a narrow therapeutic window drug. If you
9 can just give a straight dose and not worry about it, then
10 it isn't. At the simplest level, that's what drives it and
11 it's only the minority way you've got nice, easy,
12 convenient blood levels that you can refine that process,
13 but that's a consequence of the drug fitting into that set
14 of criteria.

15 So, if you want to create a criteria for a drug
16 that's being developed and the process that's being
17 developed as you're trying to define what is the dose and
18 what is the shape of the dose-response curve, which is
19 really the function of the NDA, that's the time you come up
20 with the identification of whether it's a narrow
21 therapeutic window drug.

22 DR. WILLIAMS: Maybe the committee solved
23 John's problem and the working group can stop.

24 (Laughter.)

1 DR. BALIAN: There is different variations of
2 monitoring -- you have to consider that -- the PK or the PD
3 monitoring and also monitoring other than for dose
4 adjustment and titration purposes. For example, we monitor
5 clozapine by monitoring blood counts. We don't consider
6 that a narrow therapeutic drug because the toxicity is
7 idiosyncratic and not dose-related.

8 DR. ZIMMERMAN: Other comments?

9 DR. MAYERSOHN: Cheryl, I'll just make one more
10 in the form of a question I think. My impression is that
11 the industry, both proprietary and generic, does a pretty
12 good job in formulating the solid drug products. If that's
13 true, assuming it would take a huge amount of extra energy
14 to have a small increment in performance -- if that's true
15 -- then what we're bouncing up against are the intrinsic
16 variables we can't control, and that is the characteristic
17 of the molecule per se and the biological system. That's
18 the impression I have. Roger, I don't know if you have
19 formed that opinion or not.

20 DR. WILLIAMS: Well, I take it as a good point,
21 and I would refer back to what Dr. Rhodes said to us. The
22 reality of warfarin, for example, is it's a facile drug.
23 It's readily manufactured and readily made.

24 But I would still argue that there's a public

1 health issue here connected with the goal posts which would
2 say to a warfarin manufacturer that we are not going to let
3 you into the marketplace if you get outside, say, a narrow
4 boundary.

5 Now, I think the reality is if you have a good
6 product where the mean is close to 1, the ratio of the
7 means, you are still going to have to do many people in
8 your bioequivalence study to get past a narrower set of
9 goal posts.

10 But I would still argue that irrespective of
11 the basic observation that you can make these products
12 readily and that they're robust products, it still in my
13 mind doesn't excuse the need to perhaps narrow the goal
14 posts for those products. It just means that we as a
15 society would not let things in that deviate, say, by 12
16 percent or 15 percent.

17 DR. ZIMMERMAN: Steve?

18 DR. BYRN: Also, just to go on with what I was
19 saying earlier today, that if you have a highly variable
20 drug, it's possible that you don't have your manufacturing
21 process under control because it's hidden behind the
22 variability -- you see what I'm saying -- in the intrinsic
23 variability. If you have this goal post narrowing concept,
24 then this would put an incentive that you normally wouldn't

1 have. You just say, oh, it's widely variable. Well, maybe
2 there are certain things you can do or maybe there is just
3 the right way to formulate it. If you could have this goal
4 post narrowing incentive, it could drive it to at least the
5 least variable we can get.

6 DR. BRAZEAU: It's almost like you're almost
7 trying to feather out the different variables.

8 DR. BYRN: Right, and when you have a highly
9 clinically variable drug, it could conceal a manufacturing
10 variation that if you could figure out it was there, you
11 could get out of the system.

12 DR. GOLDBERG: If you tease out the
13 manufacturing and the variability of manufacturing is
14 reduced to 0 and you have a certain variability due to the
15 drug, you've not done anything to improve drug therapy. If
16 the manufacturing variability adds to that -- it has been
17 added to function -- then I would agree with you.

18 DR. BYRN: I'm not a clinician but I like
19 Roger's diagram where he had a wide variation and then it
20 went to a narrower, higher variation. What I'm worried
21 about is in a given patient -- on the broad scale -- and
22 I'm not a statistician. But on the broad scale you have a
23 lot of variability due to the drug molecule and then you
24 have manufacturing variability. So, you have a lot of

1 variation. But with a given individual, you may only see
2 the manufacturing variation, and that gives you a lot of
3 peaks and valleys. If you could narrow that manufacturing
4 variation, then that particular individual can have better
5 therapy even though on the whole -- you see what I'm
6 arguing?

7 DR. GOLDBERG: Yes, but it has been my
8 experience and it has been years in the industry that when
9 you have manufacturing variability like that, that comes
10 out of QC evaluation. You see the differences.

11 DR. BYRN: Yes, and I agree. We have a number
12 of other tests to test manufacturing variability, and we
13 want to use all of those in spades on any narrow
14 therapeutic or widely variable drug. We really want to use
15 those extensively.

16 DR. ZIMMERMAN: Dr. Williams?

17 DR. WILLIAMS: I think we're touching on
18 something that's quite important, and if the committee
19 looks on page 5 and looks at the equation for population
20 equivalence approaches in the guidance, the draft,
21 preliminary guidance, Steve, you'll see that those within-
22 subject test and reference variances are still in the
23 numerator even when you're using population equivalence
24 approaches.

1 So, let's say I'm hypothetically in the NDA
2 phase and trying to develop a drug. If you use this
3 equation, you will always create the incentive for yourself
4 -- and maybe it's only for yourself. It has nothing to do
5 with the public health market access -- that allows you to
6 create better formulations.

7 I like to think that maybe your very first
8 formulation is a simple liquid formulation where you're
9 looking more at the variability of the drug substance as
10 opposed to the drug product. Ever after in your
11 development process, as you look at your formulation,
12 you're always trying to optimize it and make it better.
13 So, at the end of the day, this population equation serves
14 as a guide to a drug developer to create an optimal
15 formulation.

16 But I would argue it may not be a public health
17 issue so much. It doesn't relate necessarily to market
18 access. But the reward at the end of the day is that you
19 have a wonderful product that 15 years later will inhibit
20 generic substitution and make it harder for them.

21 DR. BRAZEAU: Roger, there is something I do
22 like about this equation, is that the idea that you can use
23 subjects that are more representative of the patient
24 population. I think that's also a key issue because some

1 of the things we've been talking about, variability in
2 patients versus normals, is an area that really needs to be
3 considered.

4 DR. WILLIAMS: I might point out to the
5 committee that -- I don't know where that is in the
6 document, Gayle.

7 DR. BRAZEAU: That was one thing that was said
8 in the talks.

9 DR. WILLIAMS: It's someplace in the document
10 where we refer to the patient population that should be
11 used now in bioequivalence studies and we move away from
12 the healthy male paradigm and say it should be done more in
13 the general population. But I might mention that that's a
14 compromise because some people have advocated actually
15 doing your bioequivalence study in the patient population
16 for which the drug is intended. But I thought I was in
17 enough trouble already and I didn't want to go that far.

18 (Laughter.)

19 DR. ZIMMERMAN: Other comments, questions?

20 Dr. Lamborn was saying earlier that we hadn't
21 had enough time to discuss the dermatopharmacokinetics, and
22 we have a few minutes. Did we want to go back to that
23 subject? I think probably the people who were involved
24 might have left. Oh, he's still here. Oh, good.

1 DR. BRAZEAU: I had one question.

2 DR. ZIMMERMAN: Would that be okay with the
3 committee, to go back to that? Because we felt like we
4 were behind time and needed to cut off the discussion.
5 Perhaps we can move back to that. Go for it, Gayle.

6 DR. BRAZEAU: I had one question about the skin
7 stripping method that to me is going to be a part of the
8 methodology, and that is the pressure to which these skin
9 strips are going to be put on and how are you going to
10 control that because that's going to impact upon your
11 sampling if you put something on lightly versus something
12 on with pressure. How do you control for that?

13 DR. SHAH: Instruments are available so that we
14 can apply more uniform pressure and do the skin stripping.
15 So, there is no problem on that. In the workshop we had
16 last year, experiments, data were presented where a
17 different amount of the pressure was applied and the skin
18 samples were analyzed.

19 DR. BRAZEAU: Is that pressure independent or
20 dependent upon the particular patient population?

21 DR. SHAH: On a particular patient, it is
22 pressure independent and it does not really make too much
23 of a difference whether more pressure is applied or not.
24 But if we want to quantitate it, then the pressure-

1 sensitive equipments are available for that. Uniform
2 pressure could be applied in the studies.

3 DR. LAMBORN: Could you clarify for me? It was
4 mentioned that the normal skin differs very much from skin
5 which has whatever the disease is that you're trying to
6 treat, and also unlike the situation, at least as I think
7 of it, of an oral dosage where usually the dissolution
8 component is being dealt with -- you know, they're normal
9 subjects but it's not necessarily related to the way the
10 drug is dispersed. Here you're directly talking about
11 permeability and how long it will stay there.

12 How are you dealing with that question in terms
13 of assuring that what represents bioequivalence in normal
14 skin will in fact translate into bioequivalence when they
15 actually have the disease?

16 DR. SHAH: Let me further explain. Maybe
17 people might have reviewed the article which was enclosed
18 in your background information, but for a simple
19 clarification so that we are all at the same wavelength,
20 let me review the procedure.

21 For taking the different samples, we had to
22 apply the different amounts at different sites. Each site
23 is yielding only one sample, one time point, like an area
24 under the curve, let's say if you are looking at eight time

1 points. I see that people are confused already.

2 DR. LAMBORN: No, I'm not because my question
3 is totally different. I'm talking about using a patient
4 who does not have the skin problem as distinct from looking
5 at a situation where the skin is actually affected, and how
6 do you know that bioequivalence will carry from one
7 environment to the other?

8 DR. SHAH: Stratum corneum -- the skin, the
9 normal skin -- is the one which is the hardest part through
10 which the drug has to go through, penetrate, and go deeper
11 inside the affected layers.

12 Now, in diseased patients where the skin is
13 affected, their stratum corneum is disrupted, and what
14 takes place or what is actually the amount of the drug that
15 is in the formulation itself which gets released and then
16 it gets straight to the site of action.

17 So, the three steps that gets involved with the
18 topical preparations are -- after the drug is applied to
19 the skin, the first step is the drug release from the
20 formulation, which we call that in vitro release or the
21 dissolution. The second step is the drug penetration
22 enters the stratum corneum, but that is the most difficult
23 and the barrier as far as the drug penetrations are
24 concerned. And the third one is the epidermis and where

1 the pharmacodynamic action takes place.

2 Now, in terms of the bioequivalency
3 determination, if we find that the DPK profiles are the
4 same between the test product and the reference product
5 going through the stratum corneum which is the main
6 barrier, then hopefully that would be reflecting the same
7 when it is being treated in the patients. So, that's an
8 assumption made, that once it crosses through the main
9 part, which is the main barrier, going through the stratum
10 corneum, everything would be the same. So, in the diseased
11 patients, the stratum corneum is disrupted and in that
12 particular case, the drug release is the predominant factor
13 which takes place.

14 Is it still more clarification?

15 DR. LAMBORN: If I understand it, you're saying
16 that you're assuming that if it goes through in normal
17 individuals, that it will work in --

18 DR. SHAH: It's the same principles that we use
19 for the bioequivalency studies for the oral products.

20 DR. LAMBORN: Except here where you're applying
21 it and where it has to be acting is right where the problem
22 is as distinct from an oral formulation where you assume
23 it's already dissolved, it's in the blood stream, and then
24 it goes to where the --

1 DR. SHAH: To the site of action.

2 DR. LAMBORN: Yes.

3 DR. SHAH: Here also, especially when we are
4 comparing the two products together, the test product and
5 the reference product, so long as they're both behaving in
6 the same manner, we are assuming that it will be the same
7 activity.

8 DR. ZIMMERMAN: Other comments or questions?
9 Dr. Williams?

10 DR. WILLIAMS: I want to say that I think we're
11 all sharing some concern about this approach that argues
12 for some further discussion and analysis. It's not that it
13 couldn't potentially be a very important approach, but I
14 think, Vinod, what you're hearing today is everybody is
15 saying there are some issues that we have to struggle with
16 still and I think we will struggle with them. It's not
17 that we don't intend to do that.

18 DR. ZIMMERMAN: Dr. Brazeau?

19 DR. BRAZEAU: There's one other issue that I've
20 been thinking about today. I sort of look at topicals
21 similar to pulmonary delivery. I sort of think of a
22 targeting ratio, that in the skin to which gets absorbed
23 systemically. And I haven't heard much about that.
24 Granted, some of these drugs are going to have some

1 systemic absorption, and I don't know if that's something
2 that you need to try to work in this process. Now,
3 certainly to determine bioequivalence would be reasonable,
4 but to look at a targeting ratio, what's going to stay on
5 the skin versus what gets absorbed, might be another area
6 you might want to consider.

7 DR. SHAH: Okay.

8 DR. ZIMMERMAN: Dr. Branch.

9 DR. BRANCH: I'll throw in a few more
10 variables.

11 Is there any way to standardize your
12 concentration based on amount of cells that you collect?
13 Because you're putting tape on people and just taking it
14 off and extracting drug and measuring it. So, do you have
15 an internal standard?

16 DR. SHAH: Not as an internal standard, but in
17 terms of the HPLC methodology and all, we have an internal
18 standard. But in terms of the amount, the area applied is
19 a standard tape, rounded tape which is exactly 1.5
20 centimeters in diameter, so the tapes of this area are
21 available. It's applied at the same spot and removed.

22 DR. BRANCH: I was thinking of, say, protein or
23 measure of DNA or some sort of way to normalize your data
24 for the number of cells that you're stripping off. With

1 respect to that, is there any difference in elderly? Is
2 there any difference in people on corticosteroids where you
3 know their skin is thin, the whole structure of skin is
4 changed?

5 It seems to me there are quite a lot of issues.
6 People on steroids very often do need other topical agents.
7 They're more susceptible to fungal infections, et cetera.
8 It seems it's a very interesting methodology.

9 DR. SHAH: That's true, but again going back to
10 the procedure, what we are using, Dr. Branch, is the test
11 and the reference, both the products are applied at the
12 same time in the same individual on two different arms.
13 So, whatever the variation is in existence, older people or
14 maybe the thick skin, thin skin, or whether the patient is
15 on a glucocorticoid or any other therapy, it will be the
16 same thing, and it will be affecting the same way both the
17 arms. So, the test and the reference application is at the
18 same time, which will again try to minimize the variability
19 that you may see due to the skin structure or the skin
20 effect.

21 DR. ZIMMERMAN: But are the people doing the
22 tape stripping -- it seems to me that there may be some
23 variability in how you actually take the sample, for
24 example.

1 DR. SHAH: Yes, that's true and all those will
2 be part of establishing the methodology itself, the
3 variability and all, how reproducible the system is and
4 all. That's the reason why we do recall that you do have
5 to have a good validated analytical method, and that
6 validation includes not only the analytical methodology of
7 the HPLC or any other method, but the whole, total
8 procedure. It needs to be validated.

9 Plus, we also indicate that you need to do two
10 studies, initially do the pilot study to get some more
11 estimate as to what kind of concentrations you'll be
12 getting, where it will be reaching the maximum time, and
13 when you need to start picking up the samples for
14 elimination. So, all those parts are part of the method
15 development and validations.

16 DR. ZIMMERMAN: I think Dr. Branch points out
17 that you may wish to normalize to something like protein
18 content. One could even weigh the tape before and after
19 you do the stripping so you know how much more tissue you
20 have or normalize to those sorts of things.

21 DR. SHAH: Yes. We had done that about six or
22 eight years ago, and that's part of our first publication
23 where we did it by the area and by weighing each tape.
24 Now, we need also to keep in mind that's a very hygroscopic

1 situation. The tapes are so hygroscopic it has to be done
2 in a very controlled area. In spite of that, if you wait
3 for two more minutes outside, the same tape again and weigh
4 it, it will be giving you different readings.

5 But under careful experimental conditions, we
6 have done that and we have found that either weighing the
7 tapes that way gives you the same results if we just do the
8 quantitation by the area itself, and that's the reason why
9 we finally concluded, in terms of standardization, that we
10 need to just go amount per square centimeter area.

11 DR. BRAZEAU: I have a very silly question.
12 Are there any differences between people, between the right
13 arm and the left arm? We're either right-handed or left-
14 handed, and does that impact upon the skin on those two
15 different arms?

16 DR. SHAH: Well, I'll say that there is no
17 difference between the right and the left arm, but there
18 will be definitely a difference between your arms and my
19 arms. We have done that. It's significantly different.
20 But within the individual, we have shown that there is no
21 difference.

22 DR. BRAZEAU: I guess I'm thinking simply often
23 I'm writing with this arm here. Now, this arm probably
24 doesn't get it.

1 DR. SHAH: But skin thickness is the same.
2 That's what I'm trying to say. As far as the DPK
3 measurements are concerned, drug concentrations in your two
4 arms are concerned, we get the same values. But, yes,
5 there is a difference between individual to individual skin
6 and all. The amount of the skin, the weight of the skin
7 that will be removed is different, but overall it turns out
8 to be the same.

9 Yes?

10 DR. STEWART: What about if one person is
11 hairier than another? What of the amount of hair? Does
12 that play in the effect?

13 DR. SHAH: Well, that is the area that you have
14 to be careful enough, so that you have to select the
15 patients so that he has wider arms and not too hairy,
16 otherwise he or she is disqualified to be in the study.
17 It's some of the criteria that you have to use.

18 DR. BRAZEAU: Does hair color play any
19 difference on the arm?

20 DR. SHAH: Hair color or skin color? Skin
21 color does not play any difference, no. That's what I
22 said. There is a difference in the amount of the drug that
23 will go in between your skin and my skin. We'll get a
24 different amount of the drug in the skin, but again when we

1 go back to using the test and the reference on the same
2 arm, it compensates for that.

3 DR. ZIMMERMAN: Dr. Williams.

4 DR. WILLIAMS: I'm delighted to listen to more
5 of the discussion, but I wanted to, before we close, draw
6 the committee's attention to a couple of things.

7 First of all, I thank the committee. It has
8 been an excellent discussion and very helpful.

9 I think you have seen in the course of the day
10 kind of three areas of focus, the Biopharm Classification
11 System, individual bioequivalence, and our attempts to deal
12 with these very problematic locally acting drugs. And the
13 committee knows they've been problematic for us with
14 metered dose inhalers and topical products, et cetera, et
15 cetera. They are a nightmarish category to show
16 bioavailability and bioequivalence.

17 But I think the committee also sees that we're
18 really dealing with some revolutionary approaches here.
19 The Biopharmaceutic Classification System I think is
20 revolutionary in its impact and will substantially reduce
21 regulatory burden. Now, I might argue that that's the
22 carrot.

23 The stick is individual bioequivalence which
24 will increase regulatory burden for a certain category of

1 drugs. But I might argue it makes sense to increase the
2 burden for that category of drugs because, by and large,
3 these will now be the lowly permeable and/or lowly soluble
4 drugs where you might expect more likely a subject-by-
5 formulation interaction to occur.

6 I think there's an emerging logic here that I
7 think is compelling, and I hope we can continue to work
8 together, I would say, on these three broad areas where
9 we're sort of struggling and debating.

10 DR. ZIMMERMAN: Other comments?

11 (No response.)

12 DR. ZIMMERMAN: With that, I think we'll close
13 for the day and hope to see you all back tomorrow.

14 (Whereupon, at 5:30 p.m., the committee was
15 recessed, to reconvene at 8:30 a.m., Friday, December 12,
16 1997.)

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