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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

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Thursday, October 22, 1998

8:40 a.m.

CDER Advisory Committee Conference Room
5630 Fishers Lane
Rockville, Maryland

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at

3

C O N T E N T S

Call to Order/Conflict of Interest 5

Overview and Objectives: Roger Williams, M.D. 7

Topics for a General BA/BE Guidance: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products

Statutory and Regulatory Basis: Don Hare 9

Science and Technical Concepts: Roger Williams, M.D. 18

Introduction to Guidance Topics: Vinod Shah, Ph.D. 31

Committee Questions/Discussion 38

Issues/Updates

Background: Roger Williams, M.D. 42

Criteria for Comparisons: Kathleen Lamborn, Ph.D. 48

Roger Williams, M.D. 52

Committee Discussion 61

Exposure Concepts: Mei-Ling Chen, Ph.D. 82

Committee Discussion 88

In Vitro Approaches (BCS): Azaz Hussain, Ph.D. 105

Committee Discussion 114

Open Public Hearing

Elizabeth Lane 121

Dr. Laszlo Endrenyi 123

Dr. Michael Spino 128

Special Topics

Need for Multiple Dose Studies

Presentation of Issue: Dale Conner, Ph.D. 134

Committee Discussion 145

C O N T E N T S(continued)**Biowaivers for Lower Strengths**

Presentation of Issue: Vinod Shah, Ph.D.	162
Committee Discussion	167

Metabolite Measurement

Presentation of Issue: Funmilayo Ajayi, Ph.D.	170
Committee Discussion	177

Chiral Drugs

Presentation of Issue: Chandra Sahajwalla, Ph.D.	196
Committee Discussion	200

Administrative Topics	213
------------------------------	-----

Adjournment	223
-------------	-----

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

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

8 Thank you.

9 DR. LAMBORN: Before we start on the agenda, I
10 thought that I would just ask the members of the committee
11 to briefly introduce yourselves and your affiliation for the
12 purpose of those in the audience.

13 DR. STEWART: Jim Stewart, College of Pharmacy,
14 University of Georgia.

15 DR. BRAZEAU: Gayle Brazeau, College of Pharmacy,
16 University of Florida.

17 DR. MAYERSOHN: Good morning. Michael Mayersohn,
18 College of Pharmacy, University of Arizona.

19 DR. LAMBORN: Kathleen Lamborn, University of
20 California, San Francisco.

21 DR. GOLDBERG: Arthur Goldberg, independent
22 consultant.

23 DR. BRANCH: Bob Branch, University of Pittsburgh,
24 Center for Clinical Pharmacology.

25 DR. LAMBORN: Roger, that brings us to the first

1 item on the agenda.

2 **Overview and Objectives**

3 DR. WILLIAMS: Good morning.

4 [Slide.]

5 Thank you very much, Lamborn. I will speak very
6 briefly because I know we want to get right into the topics
7 for discussion. My task is, first of all, to welcome the
8 committee. We are delighted to see you here and I am
9 delighted to be in this very fine new structure that makes
10 me think the agency has a lot more money than, in fact, it
11 really does.

12 I would like to speak very briefly, as I say, to
13 the committee about the topics for today and tomorrow. As
14 the committee knows, today is a meeting just for the
15 Advisory Committee for Pharmaceutical Science and tomorrow
16 is a joint committee meeting between the Dermatologic and
17 Ophthalmologic Drug Products Advisory Committee and the
18 Advisory Committee for Pharmaceutical Science.

19 I can say, on both days, we will be focussing on a
20 single topic which I will call biopharmaceutics or
21 bioavailability/bioequivalence to the exclusion of many
22 other topics that this advisory committee could consider and
23 has considered in the past.

24 So we are going to be very focused in these next
25 two days and I will show the committee some of the reason

1 for the focus in my talk at the next part of the session
2 which will be the session beginning at 9:00 today that will
3 focus on a guidance that we are working on within the
4 center. You will hear a lot about that guidance.

5 Tomorrow, we will focus on a different guidance.
6 The first guidance on here is directed toward orally
7 administered drug products which includes a broad array of
8 products that we regulate; immediate release, controlled
9 release, suspensions, solutions, et cetera.

10 Tomorrow will we focus on another category of
11 products that is intended for topical administration. This
12 leads to a point that I would like to make which is that
13 when we consider bioavailability and bioequivalence as
14 opposed to some of the other disciplines that we work with
15 in the center, we tend to focus on route of administration.
16 I will try to explain why that is the case in my next talk
17 that comes after this first opening statement.

18 So, tomorrow, if you look at the agenda, you will
19 see that we will be focussing on another guidance that deals
20 with the topic of bioavailability and bioequivalence but
21 focusing, as I say, on topical drug products.

22 I think, in the interest of time, I will save my
23 further remarks for my next talk which comes after the
24 opening of the discussion on the general guidance. I can
25 pause now if there are any questions for the committee and,

1 if there are none, Dr. Lamborn, I will be glad to introduce
2 the next speaker.

3 DR. LAMBORN: Please do.

4 DR. WILLIAMS: Our next speaker I am delighted to
5 introduce. Our next speaker is Don Hare. I am delighted to
6 introduce Don. I think many, many of you in the audience
7 know Don and know what his contributions are over many years
8 to bioavailability and bioequivalence concepts and, I might
9 say, specifically, to the implementation of the 1984 Hatch-
10 Waxman legislation.

11 Don, if it would help you, I would be delighted to
12 show your overheads.

13 MR. HARE: Fine.

14 DR. WILLIAMS: We could talk a lot about what Don
15 has done for the office but I will say, now, he works as a
16 special assistant to Doug Sporn who is the Director of the
17 Office of Generic Drugs. He has made signal contributions
18 over many years to all the things that we are going to be
19 discussing in the next two days.

20 At this point, I will turn it over to Don for his
21 presentation.

22 **Statutory and Regulatory Basis**

23 MR. HARE: Good morning.

24 [Slide.]

25 I think there is a well-worn statement that if you

1 know the history of an item, you can understand why a lot of
2 decisions were made and, also, it provides you the
3 opportunity of not repeating mistakes of the past.

4 [Slide.]

5 There is an awful lot of material in our slides
6 that I have prepared and I am not going to touch upon each
7 point. Roger specifically indicated fifteen minutes and
8 fifteen minutes alone. I might also just say, in starting,
9 that I think Roger is spreading the rumor that the reason
10 why he asked me to give this presentation is that I was
11 around in 1938 when the FD&C Act was passed.

12 That is not true. Close, but that is not true.
13 But I think one of the important things in 1938 is the fact
14 that, from that time on, a firm marketing a drug product had
15 to get prior approval. Also, drug products that were on the
16 market at that time were not required to gain an approval
17 from FDA.

18 They were grandfathered, so you have such drugs as
19 levathyroxin being on the market where you had no idea
20 whatsoever what the bioavailability or bioequivalence of
21 those drug products are. And that is true even today.
22 Then, in 1962, the FD&C Act was amended to require efficacy.
23 In '66, FDA contracted with the NAS/NRC to prepare study
24 panels to review those drug products that had been approved
25 for safety only between '38 and '62 to determine whether or

1 not they were effective.

2 In 1970, the ANDA process was started and then, in
3 1984, the Drug Price Competition and Patent Term Restoration
4 Act was passed. This gave us the statutory authority to
5 approve ANDAs for a drug product regardless of when it was
6 approved, whether it was prior to '62 or post-'62.

7 [Slide.]

8 These are some of the events. As I indicated, I
9 certainly don't have time to go over all of them. But when
10 a DESI product, a drug product that was approved between '38
11 and '62, was raised to the effective status, this was
12 announced in the Federal Register Notice. The Federal
13 Register Notice listed the conditions for marketing of that
14 abbreviated new drug application and, also, continued
15 marketing of the NDA.

16 For an NDA, at that point in time, there were
17 three types of bioavailability/bioequivalency that had to be
18 demonstrated. If it was self-evident, then we waived the
19 determination of bioavailability. It was a bio-problem
20 drug, and there was not methodology available, we would
21 defer the in vivo determination of bioequivalence and, at
22 some future time, they would have to perform that study.

23 And then there were those products in which
24 methodology was available in which the firm would have to do
25 an in vivo bioequivalency study. I might say that we have

1 come a long way since then because the first requirements of
2 a bioequivalency study was that the test product be within
3 plus or minus 20 percent of the reference product and there
4 should have been no statistical difference at any of the
5 sampling points.

6 That was it. I don't think you would want to look
7 at some of those early studies. I don't think you would
8 want to look at some of the clinical studies that were done
9 at that point in time.

10 Then, in 1972, there was a study that was done by
11 Dr. Lindenbaum who showed that products that met the USP
12 requirements for potency, content and uniformity were not
13 performing the same in vivo. Then, in 1974, the Office of
14 Technology Assessment Committee reviewed the
15 bioavailability/bioequivalency area. Also the
16 Biopharmaceutics Unit at that time started to develop the
17 criteria to determine bioproblem drugs as drug products
18 needed in vivo.

19 In 1975, the bioavailability/bioequivalency regs
20 were proposed. In '77, they were finalized. As indicated
21 in the slide, this gave us the regulatory authority to
22 require bioavailability of the innovator and bioequivalence
23 for the generic drug. At that point in time, we did not
24 have that authority so products such as dyazide, which was
25 approved, maybe, in 1967, was on the market and when the

1 generic drugs tried to copy this drug product, they found
2 that the bioavailability was 50 percent.

3 For example, the triamterine, which was
4 50 milligrams, actually produced 25. And the
5 hydrochlorothiazide, which was 25 milligrams, was producing
6 12.5. It really took a generic drug product to do a three-
7 way crossover study to be able to get approved where there
8 were two lots of the reference and their lot, and they were
9 able to show that their lot was not any different than the
10 two lots of the reference which were not meeting the
11 criteria.

12 [Slide.]

13 Then, in 1979, the Orange Book was proposed. This
14 was sort of a reflection of bioequivalence in that the
15 agency prepared this list of all the drug products that had
16 been approved and those drug products that were multiple
17 source. FDA went into their scientific database and made a
18 determination as to whether or not they were substitutable.

19 We were sued when we proposed this and so it took
20 us over a year to get the Orange Book established. Then, in
21 1981, the Paper NDA Policy was formulated. This was a
22 procedure that the agency had to approve a duplicate of a
23 post-62 NDA. Then, in '84, as we previously mentioned, the
24 Waxman-Hatch Amendments were passed and there were no more
25 deferrals of in vivo bioequivalence. This was not

1 permitted.

2 It also created a new type of application which
3 was called a 505(b)(2) which was very similar to a (j) in
4 some aspects and similar to an NDA in others. In 1986,
5 there was bioequivalence hearing that discussed the
6 procedures that we were using. Then, in 1988, the report of
7 this hearing was publicized. I might just indicate that you
8 are sitting here today because one of the recommendations of
9 that 1986 bioequivalence hearing was that the FDA
10 established an advisory committee to give them advice in
11 this area.

12 Even though, at that time, the government was
13 cutting back on advisory committees, the agency was able to
14 get that through. Then, in 1989, Waxman-Hatch regs were
15 proposed and they were finally finalized.

16 [Slide.]

17 As I mentioned on the previous slide, Dr.
18 Lindenbaum showed that there was a problem with the Lanoxin
19 tablets or digoxin tablets. The "A" represents the
20 innovator's product. The "B1" and "B2" are the same firm
21 with two different lots and the line "C" represents a third
22 company. That third company met all of the U.S.P.
23 requirements. But, as you can see there, no way are those
24 products interchangeable.

25 [Slide.]

1 Out of the Office of Technology Assessment, they
2 made eleven recommendations. But there were two that I
3 think are important for discussion and that is you do not
4 have to do an in vivo determination of bioequivalence on all
5 drug products. But there was enough information that was
6 available that would permit FDA to make this determination.

7 So in the case of the DESI effect of drug products
8 with the solid oral dosage forms, there were two universes
9 of drug products which were created, one universe where you
10 determine bioequivalence through in vitro methodology alone
11 and the other was where you determine bioequivalence through
12 in vivo methodology.

13 [Slide.]

14 As we indicated, in 1977, we had the regulatory
15 authority to require bioavailability of how the drug is
16 absorbed and excreted, metabolized and distributed, for an
17 NDA and also the requirement for an ANDA to have to perform
18 a bioequivalency study. Those are just some of the
19 important sections in that regulation.

20 [Slide.]

21 There are a number of ways, in that regulation,
22 that depict how you can determine bioequivalence. The
23 classical method of a systemically absorbed drug product
24 where you measure the active moiety or active metabolites as
25 the measurement of the function of time.

1 Urinary excretion is acceptable. For a non-
2 systemically absorbed drug product, you could do a PD study
3 or a comparative clinical trial or an in vitro method that
4 was acceptable to us--his is Roger's area--or any other
5 approach that is deemed adequate by FDA to determine
6 bioequivalence.

7 [Slide.]

8 This is found in that reg. This was the criteria
9 that was used by Dr. Cabana and his group to determine
10 whether or not an in vivo bioequivalency study was needed
11 for a solid oral dosage form or for a DESI drug product that
12 had been raised to the effective status.

13 [Slide.]

14 This relates to the Orange Book. As I indicated,
15 I think the Orange Book is a reflection of a lot of the
16 bioequivalency work that was done. But, for duplicates or
17 for pharmaceutically equivalent drug products, if they are
18 shown to be bioequivalent and meet all the CMC data and they
19 have been demonstrated to be bioequivalent, then FDA will
20 make a determination that the products are therapeutically
21 equivalent.

22 It is our position that products that have been
23 rated as therapeutically equivalent, you will not see any
24 difference between the safety profile and clinical
25 effectiveness if substitution is made. Our position is you

1 will not see any more difference between the test and
2 reference than you would between two lots of the reference
3 drug product.

4 [Slide.]

5 This is probably one of the most important pieces
6 of legislation that has been passed, the Waxman-Hatch
7 amendments, where it gave us the statutory authority for
8 generic drugs, for any NDA drug product that had been
9 approved for safety and effectiveness.

10 As I indicated, up until that time, we had
11 regulatory authority for pre-62s but no regulatory authority
12 for the post-'62s. So Congressman Waxman and Senator Hatch
13 gave us that. The main reason was to make high-quality,
14 low-cost generics which would reduce the healthcare cost to
15 the federal and state governments and to the consumer or to
16 the patient.

17 They eliminated costly and unnecessary duplicate
18 safety and efficacy studies. As I mentioned, in the case of
19 the paper NDAs, they did not have to repeat these studies
20 but they had to demonstrate that the product was effective
21 and safe through literature.

22 So, many times, there would be two indications.
23 If they could only demonstrate that one indication was
24 effective, then that is all they got. Or any of the
25 preclinical data; if some of the preclinical data could not

1 be supported through literature, then they would have to do
2 that, themselves. So, many times, these paper NDAs were a
3 combination of both literature and studies.

4 And then, in exchange, part of this compromise,
5 was the fact that an NDA holder could get up to five years
6 of patent extension not to exceed fourteen years from the
7 date of approval. That was the tradeoff.

8 [Slide.]

9 Also, Congress just pulled out of our 1977 regs
10 the definition for bioavailability and bioequivalence. We
11 were sued four times over this issue and one firm claimed
12 that the only way you could demonstrate bioequivalence was
13 through this definition that was in the statute not
14 realizing that this was only one definition of
15 bioequivalence but it was not complete. There were other
16 ways of demonstrating bioequivalence.

17 With that, I close. There is not much science in
18 this. I don't know whether you have any questions on the
19 historic regulatory aspect or not.

20 DR. LAMBORN: Thank you very much.

21 **Science and Technical Concepts**

22 DR. WILLIAMS: Dr. Lamborn and the committee, I am
23 delighted to follow Don.

24 [Slide.]

25 I will say that Don alluded, in his talk, to many,

1 many things that we are going to be discussing in the next
2 two days. I will also recall his comment something to the
3 effect that if you don't remember history, you might be
4 condemned to repeat it.

5 There are a lot of things that we will be
6 discussing that have been discussed many times in this
7 country before and that have been discussed specifically
8 before this advisory committee over the years of its
9 existence. I am delighted to say that because I think this
10 advisory committee has helped the center and the agency and
11 the Office of Pharmaceutical Science and the Office of
12 Generic Drugs in understanding the latest science and
13 technical approaches to achieve the societal intent.

14 The reality is these science and technical
15 approaches have continued to evolve. I will talk a little
16 bit about my own history. When I started doing some of this
17 work, the analytical methods for bioavailability and
18 bioequivalence were being developed by people at NIH with
19 the name of Bernard Brody. I am sure some of those names
20 ring bells with you, particularly to Dr. Stewart.

21 Some of the techniques available in the early
22 '60's and '70's were incredibly primitive compared to what
23 we have today in terms of looking at the performance of a
24 formulation.

25 [Slide.]

1 Don called our attention to the fact that the
2 science and technical understanding of statistics has
3 certainly evolved. Moving into what I would like to talk
4 about, and actually we are a little ahead of time--Don, you
5 did very well staying on track and you have got us ahead of
6 our schedule a little bit--what I would like to review with
7 the committee over the next two days, as I said, are two of
8 several guidances that the center is working on.

9 The first one is this guidance; a general
10 bioavailability and bioequivalence guidance for oral drug
11 products--for example, immediate release and modified
12 release--and, also, tomorrow, this guidance; locally acting
13 drug products for topical dermatologic products.

14 The first thing I would like to explain to the
15 committee is how do these guidances stand in relation to the
16 1977 regulations that Don alluded to. If you look at the
17 CFR at 21.320, you will see page after page of
18 recommendations and requirements regarding the performance
19 of bioavailability and bioequivalence studies.

20 So I would regard these guidances that I have on
21 this screen is more definitive "how to" recommendations, if
22 you will, that elaborate on how to achieve the intent of the
23 1977 regulations in terms of documenting bioavailability and
24 bioequivalence so that they are based on the most up-to-date
25 and modern science.

1 I think the framers of those 1977 regs, some of
2 whom are in this room, did an excellent job in allowing the
3 opportunity for science to always carry the day and to be
4 updated. So I would always argue that whatever we say here
5 regarding these guidances should stay in tune with the 1977
6 regulations and we'll be able to stay in tune with those
7 regulations because they were so well written to allow
8 science advancement.

9 As I say to the committee, I don't have to tell
10 you that the science investment is really remarkable.

11 In focussing on what we will be talking about
12 today, let me just say, generally, we are looking probably
13 at five general guidances that will come out from the center
14 over the next several years--I will pause to say that
15 developing these guidances is a very laborious process.
16 That will focus first on orally administered products and
17 then on a group of products that we call locally acting drug
18 products.

19 In that category are topicals, nasal inhalation
20 and oral inhalation. There is a reason for these products
21 being segregated out. The reason is quite simple. It is
22 because they do not produce a systemic exposure pattern that
23 we can rely on to document bioavailability and
24 bioequivalence. I will talk about that a little bit more.

25 But certainly, over the years, we have come to an

1 understanding that an orally administered product can
2 achieve a systemic exposure pattern that will allow us to
3 document bioavailability and bioequivalence. I will talk a
4 little bit more about that as well.

5 In the course of today, you will hear some updates
6 about key issues that this committee has considered many
7 times in the past. I am sure the committee looked at the
8 handout that had a long list of topics that will be
9 considered in this general guidance. In some of those
10 topics, I put beside them "issue updates."

11 Then we are going to introduce before the
12 committee today, and some of the subsequent presentations,
13 further issues for deliberation. I think there are three
14 issue updates that you will hear about shortly. And then,
15 in the afternoon, we will focus on these further issues.

16 I hope I am correct in saying that some of these
17 further issues that you see down here under "special
18 topics," will not take the intensity of public debate, if
19 you will, that has attached to some of our other issue
20 updates that we will talk about in the course of the
21 morning.

22 Before I leave this slide, I will say that there
23 are going to be some additional guidances beyond the four
24 major ones here. One of them is going to be a bioanalytical
25 methods guidance. There may be a pharmacodynamic guidance.

1 There is going to be a food-effects guidance. There will be
2 a special guidance for biopharmaceutic classification
3 system.

4 Then, as you all know, we have the draft December
5 guidance on population and individual bioequivalence which
6 relates to that particular criteria and acceptance criteria.
7 I would say you need to think, however, of these four
8 guidances as the core guidances. One of the ways to look at
9 them is a book on bioavailability and bioequivalence where
10 these are the chapters of the book. Some of the chapters
11 may have appendices or attachments.

12 As I say, we could talk a long time about all this
13 and I certainly don't want to do that before the committee.
14 But I can tell you that everything we talk about here is of
15 wide general interest, not only in the United States but in
16 the world at large. I hope to be able to come back to the
17 committee in the future to talk about some of the
18 globalization of these concepts which are quite powerful and
19 quite exciting.

20 I might mention that I think the United States and
21 its science and technical understanding of the issues is
22 leading the way in many parts of the world in terms of how
23 to document bioavailability and bioequivalence.

24 [Slide.]

25 Don already showed this slide and I won't belabor

1 it. But I will get a little deeper into the forest here by
2 saying that many times before this committee we have talked
3 about pharmaceutical equivalence. Pharmaceutical
4 equivalence, in my mind, is a hot topic. It was the hot
5 topic, the underscore, of the agency's decision on
6 conjugated estrogens.

7 It will come before this committee certainly in
8 the future, perhaps again with regard to conjugated
9 estrogens but certainly for complex drug substances such as
10 certain biotech products and botanicals. I regard many of
11 the issues here relating to analytical methodology and how
12 you can detect moieties within a complex mixture.

13 As I said before, our main topic today will be the
14 documentation of bioavailability and bioequivalence. As you
15 can see in this overhead that I am showing which, also, is
16 the same one that Don showed, we have many modalities
17 allowed to us in terms of documenting bioequivalence.

18 But I have a great mentor here at the agency,
19 namely Don, who always reminds me that we never waive the
20 documentation of bioavailability and bioequivalence. So
21 even, for example, if we are using an in vitro approach,
22 that doesn't mean we are waiving
23 bioavailability/bioequivalency documentation. It means we
24 are waiving in vivo documentation of bioavailability and
25 bioequivalence.

1 [Slide.]

2 Don also showed this slide and I would like to
3 descend into the trees of this particular forest a little
4 bit because we are now dealing with statutory definitions of
5 bioavailability and bioequivalence that--I will be frank,
6 and I always worry a little bit about being too frank--that
7 I would say, right now, in 1998, are not quite right.

8 The reality is these were framed 20 or more years
9 ago. Don probably could give the exact date. They focus on
10 rate and extent of absorption to the site of action. I will
11 pause and say, first of all, I think we are concluding that
12 we are not particularly interested in rate of absorption.

13 Even if we were particularly interested in rate of
14 absorption, I am not sure we could measure it. So I think
15 you will hear, in the course of our discussion today, a
16 transition from this particular wording and the thinking
17 behind this wording more into systemic exposures and metrics
18 of systemic exposure.

19 I am not standing here to tell you that I am going
20 to violate the Food, Drug and Cosmetic Act. I am saying
21 that we can create a modern understanding of rate and extent
22 of absorption based on systemic exposure metrics. As a
23 matter of fact, it is what we have been doing for many years
24 so I don't think I will be too much in violation of the FD&C
25 Act.

1 There is another aspect of this which is "becomes
2 available at the site of action." As many on the committee
3 know quite well, it is impossible, in most instances, to
4 measure this drug concentration at the site of action.
5 Again, from this particular perspective, it becomes a basis
6 for us focussing on systemic absorption measures and
7 parameters.

8 [Slide.]

9 This, of course, is what I have talked about and I
10 have shown this slide before the committee. Basically, in
11 the realm of product quality, we focus on the drug product.
12 We focus on the active moieties or moieties within that drug
13 product. We focus on the release of the active moieties
14 from that drug product according to a certain route of
15 administration.

16 That creates the concept of exposure expressed in
17 terms of dose and systemic exposure expressed in terms
18 usually of a pharmacokinetic measure or parameter. When I
19 talk about systemic exposure, I am talking about orally
20 administered drugs. Tomorrow, when we talk about exposure
21 and, perhaps, systemic exposure, it is going to be a
22 different perspective, perhaps focussing on the
23 dermatopharmacokinetic approach that the committee is aware
24 of.

25 So I would like to draw a distinction between our

1 understanding now that we can rely on concentration time
2 curves as a surrogate for both efficacy and toxicity. This
3 is a fundamental understanding. There is a lot of
4 discussion in the United States about surrogate markers. I
5 will say that I think concentration time curves, in some
6 ways, got there first.

7 We are very comfortable relying on concentration
8 time curves as a surrogate for safety and efficacy so that
9 if you achieve comparable concentration time curves between
10 two pharmaceutically equivalent formulations, the
11 expectation can be that they will yield the same therapeutic
12 effects under all conditions of use.

13 Some of the words that I just used there are drawn
14 from the Orange Book. They are not idle words. They are
15 hotly debated words, sometimes, and they appear in vigorous
16 debate in many locales across the country including this
17 locale, the Advisory Committee for Pharmaceutical Science.

18 I would say our challenge always is to come to the
19 most reasonable scientific approaches to assure that
20 interchangeability. As I say, we are going to focus today
21 on the systemic exposure patterns that are reflective of
22 rate and extent of absorption to the site of action.

23 [Slide.]

24 In one of my final overheads in this particular
25 section of the talk, you will hear the three questions that

1 I like to allude to frequently. I call them the
2 "Sheinerian" questions because they are drawn from some
3 comments of Louis Sheiner at the University of California in
4 San Francisco.

5 The first one is what is the question. The second
6 one is what are you willing to rely on. The third is how
7 confident do you need to be in the answer. But I would
8 argue that the first question relates to this particular
9 overhead.

10 I can tell you--you always like to think the
11 questions are easy--this is a tough question;
12 bioavailability and bioequivalence. We have actually had
13 some fairly intense debates back in the center recently on
14 just what is bioavailability and what is bioequivalence.

15 From a product-quality standpoint, I would like to
16 argue that bioavailability focuses on the release of the
17 drug substance from the drug product. But I might argue
18 that if you are a pharmaceutical scientist, you might say
19 that that is a fairly small fraction of the total
20 information connected with the concept of bioavailability.
21 I am certainly willing to admit that.

22 If you are speaking of human pharmacology and
23 clinical pharmacology, there is a lot beyond product quality
24 that would fall in the realm of bioavailability. I don't
25 need to remind the committee but just to review it briefly;

1 it is the release of the drug substance from the drug
2 product, the dissolution of that drug substance in the
3 gastrointestinal media, absorption across gastrointestinal
4 membranes where it may, perhaps, encounter transporters and
5 enzymes, entry into the portal circulation, entry into the
6 hepatic parenchyma, then entry into the systemic circulation
7 and movement to one or more sites of action.

8 So bioavailability has a lot of aspects to it.
9 But I would argue, in the discussions today and tomorrow, we
10 are focussing on the small fraction of bioavailability that
11 relates to product quality. That is what the intent of this
12 particular overhead is designed to show the committee and to
13 serve as a guide for the further discussions.

14 [Slide.]

15 I think these are my three questions. That is my
16 last overhead for this particular part. Just leave it up
17 for a minute. I have focussed on the first question; what
18 is bioavailability and bioequivalence and what do we want to
19 know when we talk about bioavailability and bioequivalence.

20 But, for the most part, our discussions in the
21 course of today and tomorrow and really going to focus on
22 the second question, what assumptions are we willing to
23 make, what are we willing to rely on to assure
24 bioavailability and relative bioavailability which is
25 bioequivalence.

1 You are going to get into a lot of very
2 interesting discussions today on concentration time curves,
3 metrics of concentration time curves, and statistical
4 criteria and other criteria to allow comparison of those
5 metrics.

6 You will also hear discussions about when we are
7 willing to not rely on concentration time curves and,
8 perhaps, are willing more to rely on in vitro dissolution in
9 some of the discussion today relative to the biopharm
10 classification system and, in the discussion tomorrow, when
11 we talk about dermatopharmacokinetics relying on the, if I
12 may say, stratum corneum exposure pattern as a means of
13 assuring comparable release of drug substance from the drug
14 product.

15 At this point in time, I will turn it back to the
16 chair. I am delighted to have these few minutes before the
17 committee and I will certainly take any questions.

18 DR. LAMBORN: Are there questions from the
19 committee members at this point? We have got a very clear
20 overview.

21 I guess we are moving on to the introduction of
22 the guidance topics.

23 DR. WILLIAMS: The next speaker I will be glad to
24 introduce, if the chair permits, is Dr. Vinod Shah. Vinod
25 has been with the agency also many years, just like Don, and

1 is now working as a senior research scientist in the Office
2 of Pharmaceutical Science in the Center for Drug Evaluation
3 and Research

4 **Introduction to Guidance Topics**

5 DR. SHAH: Good morning.

6 [Slide.]

7 I will be making the presentations on the various
8 topics for the general BA/BE guidance that Dr. Williams
9 alluded to in his previous presentations. These are all
10 going to be pertaining to the orally administered drug
11 product.

12 [Slide.]

13 As Roger indicated, we are in the process of
14 developing this new guidance which would be composed of all
15 types of orally administered drug products. This guidance
16 expands, clarifies and provides the "how to" information for
17 bioavailability/bioequivalency requirements and the
18 recommendations set forth in 21 CFR 320 for orally
19 administered drug products such as solutions, suspensions,
20 conventional-release and modified-release dosage forms.

21 This guidance would be applicable whenever certain
22 bioavailability and bioequivalency studies are planned
23 during preapproval of INDs, NDAs, ANDAs and post approval of
24 NDAs and ANDAs. The guidance will also be making reference
25 to several additional guidances that focus on the

1 methodological approaches and also the SUPACs.

2 It also updates and replaces several guidances and
3 ad hoc policies which have been set forth so far in the
4 Division of Bioequivalence and Biopharmaceutics area. The
5 purpose, again, here is to go back, review some of the old
6 guidances and try to bring changes into it. This guidance
7 would be replacing all those old guidances.

8 [Slide.]

9 The guidances will be focussing on the
10 methodological approaches, comparisons of the
11 bioavailability measures and the parameters, in vitro
12 dissolution studies, several types of the dosage forms,
13 under what conditions the biowaivers could be provided and,
14 also, some of the special topics and issues.

15 In some of these cases, we may be referring to the
16 guidances which will be published very soon such as the Food
17 Effects Studies Guidance and also the Biopharmaceutics
18 Classification System Guidance or the Biowaiver Guidance for
19 certain types of the dosage forms.

20 [Slide.]

21 The pharmacokinetic studies in this guidance will
22 be composed of the following sections of the chapters. The
23 first one will be talking about the general considerations
24 and the study conduct followed by the pilot studies and the
25 pivotal studies, the study designs. In some cases, it may

1 be a replicate design which will take into consideration the
2 individual bioequivalence approach.

3 In some cases, it may be the crossover design
4 where it will take into consideration the average
5 bioequivalency approach. It will be also talking about the
6 single-dose and the multiple-dose studies, when the
7 multiple-dose studies might be necessary and also different
8 pharmacokinetic parameters and the measures, and the new
9 concept that we are thinking about on the exposure concept.

10 So these are the different areas in the
11 pharmacokinetic studies which will be discussed in detail in
12 the guidance. The whole purpose is this guidance will be
13 trying to focus all the different issues at one point and
14 people would be very easily able to follow that.

15 [Slide.]

16 With respect to the in vitro studies, the guidance
17 should be focussing on how to set the dissolution
18 specifications. It will discuss, with respect to the
19 conventional-release products as well as modified-release
20 products. It is a very small section in this guidance, but
21 it connects back to the two very recent guidances on the
22 dissolution that the FDA has come out with in the last year
23 talking on the conventional-release as well as the modified-
24 release dosage forms and how to develop the in vitro/in vivo
25 correlations.

1 So these are the minor aspects that would be
2 presented here but, again, making the connections and trying
3 to bring out the most important key features.

4 [Slide.]

5 With respect to the dosage forms, it will be
6 talking on the solutions, suspensions, the conventional
7 relief dosage forms such as the single-dose for all the
8 strengths for the new drug applications because there is a
9 slight difference here with respect to the new drug
10 applications and the abbreviated new drug applications.

11 For the conventional-release or the immediate-
12 release dosage forms for the NDA applications, they do need
13 to perform the bioavailability studies on each and every
14 strength whereas for the abbreviated new drug applications
15 for the conventional-release dosage forms, a single dose
16 study is recommended on the highest strength and the lower
17 strengths would be provided the waivers, the biowaiver for
18 the lower strengths.

19 In certain cases, the food-effects studies might
20 be necessary with respect to the new drug applications or
21 the abbreviated new drug applications and these will be
22 discussed in the guidance.

23 Extended-release dosage forms; again, the single-
24 dose study is required for all the strengths, whether it is
25 the new drug application or the abbreviated new drug

1 application. Definitely, a multiple-dose study would be
2 required for the new drug applications but we are thinking
3 that maybe, under certain situations, the multiple-dose
4 study for the abbreviated new drug applications may not be
5 necessary.

6 This may be an unnecessary burden and with the
7 intent of lowering the regulatory requirements or regulatory
8 burden, we are thinking of eliminating the multiple-dose
9 studies under certain circumstances for the abbreviated new
10 drug applications.

11 The food-effects studies would be required at the
12 highest strength for both new drug applications as well as
13 abbreviated new drug applications. We also intend to cover
14 the other dosage forms such as occult products or sublingual
15 products, very rapidly dissolving products. All those would
16 be covered under the other dosage forms.

17 So all the different types of dosage forms which
18 are administered orally will be covered in this guidance.

19 [Slide.]

20 Under the special topics and the issues, we will
21 be covering the food-effects studies, under what types of
22 conditions, situations, the food studies should be
23 conducted. It will be, also, referring to some of the
24 sprinkle studies that need to be carried out. It will be
25 all referenced under the food-effects sections, food-effects

1 studies.

2 In certain cases, maybe we may have to measure the
3 different moieties in the blood. It may not be the actual
4 drug. In some cases, it may be the metabolites, under what
5 conditions the metabolites should be measured, how many
6 metabolites should be measured and what should be the
7 criteria. That would be covered under the section of
8 metabolites.

9 In the section of the enantiomers and the
10 racemates, the conditions will be laid out as to when each
11 enantiomer has to be measured or under what circumstances we
12 don't need to measure the enantiomers and racemates. The
13 mixture measure would be completely acceptable.

14 The guidance is also going to refer with what to
15 do and how we should measure the complex mixtures. It will
16 be also be referring to long-half-life drugs, the first
17 point Cmax. In certain cases, we have seen that when you
18 measure the first blood-plasma sample, that turns out to be
19 the maximum concentration. So, what to do under those
20 conditions will be also referred into this guidance.

21 Also, referring to the endogenous drugs, how to
22 measure that; orally administered drugs which are intended
23 for local action since these are orally administered but,
24 because of the internal, local activity, we do not expect it
25 to be absorbed into the blood stream so how to measure the

1 bioequivalency of these types of products. It will be also
2 referring to the drugs with the narrow therapeutic ratios.

3 [Slide.]

4 So that is the general outline of what the
5 guidance will be covering. Today, as Dr. Williams indicated
6 earlier, we will be referring to only a few topics such as
7 the issues and the updates. There are three areas. One
8 would be the criteria for the comparison which will be
9 presented by Dr. Kathleen Lamborn.

10 This will be followed by the exposure concepts,
11 discussions on that to be presented by Dr. Mei-Ling Chen,
12 and in vitro approaches, or the biopharmaceutics
13 classification system, will be presented by Dr. Ajaz
14 Hussain. These are the topics which have been discussed
15 before in front of this advisory committee but, today, we
16 will be bringing updates on these three different issues.

17 Then we will be talking about four other issues
18 which would be special topics. The first one will be the
19 need or multiple-dose studies. That will be presented by
20 Dr. Dale Conner. I will be coming back again in front of
21 you to discuss about the biowaivers for the lower strengths.

22 Dr. Funmi Ajayi will be presenting on the
23 metabolite measurements and Dr. Chandra Sahajwalla will be
24 presenting the chiral drugs and what needs to be measured.
25 So this is a brief outline for the discussions today on the

1 general BA/BE issues.

2 I will be happy to answer any general questions
3 you have on these topics.

4 DR. LAMBORN: Thank you.

5 **Committee Questions/Discussion**

6 DR. LAMBORN: I have a feeling that the question
7 numbers are going to be increasing substantially as we get
8 into the individual issues. Are there some specific
9 questions right now?

10 I just had one. You speak of this as a single
11 guidance but I assume that you will be finalizing portions
12 of this guidance at different times. Is that correct, or is
13 the intent to hold the whole thing to a single guidance.

14 DR. SHAH: No. The intent is to have a single
15 guidance, so it will be one guidance. It will be finalized
16 data. Again, as you know, we cannot say exactly the time
17 when it would be ready, but our goal is to have it ready as
18 a draft guidance, level 1, for public comment sometime in
19 1999.

20 That is what I was trying to indicate that, even
21 though it will be a single guidance, it will be making cross
22 references to the other guidances which are already on the
23 outside, on the Internet, which is available, like the
24 biopharmaceutics classifications or the dissolutions,
25 individual bioequivalence.

1 It will be making cross references to all those
2 guidances. But, with this single guidance, people or the
3 sponsor who are interested to do the bioavailability or
4 bioequivalence studies would be able to come back and say,
5 "Okay; I need to go back and pull out that guidance.
6 Otherwise I can just have everything addressed in the same
7 guidance."

8 DR. LAMBORN: Roger, did you have anything in
9 particular that you wanted us to discuss, or particular
10 issues that you wanted to make sure that we were aware of at
11 this point as distinct from moving on to the specific
12 issues?

13 DR. WILLIAMS: Kathleen, we certainly gave the
14 committee a chance to ask questions about all the
15 introductory material at this point in time before the
16 break. I did want to draw the committee's attention to one
17 thing because it is illustrative of a point that I was
18 trying to make.

19 Don, maybe you could show the committee that one
20 where we had studies needed for a conventional release and a
21 modified release. It was about three back in Vinod's talk;
22 not in my talk. But if the committee doesn't have any
23 detailed questions at this point, we can take our break and
24 then move right into the specific updates.

25 [Slide.]

1 But, in the way of maybe pointing out an
2 observation as well as maybe stimulating a little
3 discussion, I will say that this particular overhead gets to
4 some of the issues that I was talking about in terms of
5 bioavailability and bioequivalence. It also relates to a
6 distinction that we sometimes draw about the studies needed
7 for a pioneer product versus a generic.

8 Let me just make some points and then, if the
9 committee wishes to comment, I would certainly be interested
10 in hearing it. You can see there that, for an ANDA, we
11 don't ask for in vivo bioequivalence for all strengths
12 because we are willing to rely--the second question--"under
13 certain circumstances, on in vitro dissolution to show
14 equivalence for lower strengths."

15 This has been a practice in the United States for
16 many years. I think we are comfortable with it but I am
17 drawing a distinction for the committee that, for an ANDA
18 and also for a post-approval change and for an pioneer and
19 an abbreviated application, we will sometimes only look in
20 vivo at the highest strength and then waive down, based on
21 in vitro dissolution studies. It is the second question in
22 action, if you will.

23 I would also like to draw the distinction, then,
24 between bioavailability and bioequivalence because you could
25 argue why do we ask, for the pioneer, that they perform an

1 in vivo study on all strengths. The answer to that, I
2 think, relates to the distinction between bioavailability
3 and bioequivalence.

4 We are asking the pioneer to show bioavailability
5 for all those strengths and, in the course of doing that,
6 they can show dose proportionality not only for the drug
7 substance but for the performance of the drug substance in
8 the product.

9 So it is with a dose-proportionality
10 bioavailability study you can begin to look at both
11 linearity or non-linearity in absorption of the drug
12 substance and the drug product. I would say that
13 distinction that we have drawn there with our approaches
14 attends to the distinction between bioavailability and
15 bioequivalence.

16 DR. LAMBORN: Thank you. I am sort of torn. We
17 just started an hour ago. . . It seems early to take a break.
18 On the other hand, there may be people who were sort of--do
19 we have a guideline?

20 MS. TOPPER: It is your call.

21 DR. LAMBORN: As my call, I guess, I think it
22 makes more sense to just continue a little longer. I think,
23 technically, I am up next but I am deferring to Dr. Williams
24 to give a background on this.

25

Issues/Updates

1 **Background**

2 DR. WILLIAMS: I am going to, again, speak very
3 briefly. I have two overheads that speak to the first
4 update we would like to present to the committee.

5 [Slide.]

6 This update relates to the committee's
7 deliberations and the deliberations of many other people
8 regarding criteria for comparison of bioavailability
9 measures or parameters. The committee, I am sure,
10 understands I am choosing my words carefully.

11 In the past, as the committee knows, we have
12 relied on the criterion that we call average bioequivalence.
13 Over many years, I would say at least six years in the
14 center, we have worked very intently to consider the
15 regulatory approach, adjusting our regulatory approach, to
16 compare these measures or parameters using new criteria that
17 are called either population or individual bioequivalence
18 criteria.

19 There are many things we could say about this but
20 one of the things I could say first of all, as the committee
21 has already heard, the agency is always willing to update
22 its approaches based on the latest science. You heard this
23 morning from Don that in the very early years of comparison
24 of bioavailability measures' parameters, we relied on point
25 estimates as well as comparison of concentrations at

1 individual times.

2 I think we would all recognize that that is not
3 adequate. There was, then, the period when we went into the
4 statistical frequentest approach where we looked at
5 significant difference with the p-value. I think we all
6 felt that that was not appropriate and we moved to an
7 equivalence approach.

8 There was, also, intruded into our thinking in the
9 mid to late '80's, the concept of individual bioequivalence
10 as reflected by an old rule that many of you recall called
11 the 75/125 rule which was rejected because of lack of
12 statistical rigor, as I understand it.

13 We came to our current approach, average
14 equivalence, in the two/one-sided t-test based on some very
15 fine work from an agency statistician named Don Sherman and
16 others, and we have been using that method for the last
17 several years to compare bioavailability metrics. In the
18 late '80's and early '90's, some of the new approaches begin
19 to appear in the literature and the agency began to consider
20 them very carefully in a very deliberative process that I
21 look forward to coming to a conclusion in the next several
22 months or year or so.

23 This particular overhead gives you information
24 about the process. There is nothing in this particular
25 overhead that talks about science and technical aspects of

1 the new criteria but it does talk about the process and it
2 doesn't talk about the process that preceded November of
3 1997.

4 The process, as shown in this overhead, begins in
5 November, 1997 where I would say we had a very healthy,
6 vigorous discussion at an AAPS meeting in Boston. I might
7 say we are about at the anniversary of that meeting. At
8 that meeting, there was a clear consensus from the public at
9 large and the pharmaceutical industry that we needed a very
10 careful further discussion of these new approaches I think
11 for a very simple reason; they increase regulatory burden.

12 Nobody in this current day and age is interested
13 in doing anything that doesn't have a solid justification
14 when it comes to increasing regulatory burden. I might also
15 add that many of the other topics that we will be talking
16 about in the course of the meeting today and tomorrow tend
17 to reduce regulatory burden.

18 I think, as Dr. Shah alluded to, this one doesn't
19 quite move in that direction. However, it does offer some
20 opportunities for reduction in regulatory burden that the
21 committee knows about for highly variable drugs.

22 Now, the deliberative process that we embarked on
23 after the AAPS meeting in Boston was, first of all, to
24 publish as a preliminary draft a guidance that delineates
25 the individual and population bioequivalence approaches.

1 Preliminary draft--all these words are carefully chosen--
2 means that it is not even ready to be draft.

3 It certainly shouldn't be used by the industry now
4 in any way to compare bioavailability metrics. It was more
5 an attempt to get the document out in front of the public to
6 let people know what the agency was thinking. This was very
7 carefully stated in the preamble to the Federal Register
8 Notice.

9 There was also a call for us to share, as we
10 could, our data publicly and the agency has done that. We
11 also had a workshop in March of this year that focussed on
12 the topic and a workshop report of that meeting is expected.
13 There was also a call to form an expert committee and that
14 expert committee was formed. Its membership is available to
15 the committee. It is chaired by Dr. Les Bennett at the
16 University of California in San Francisco.

17 It has had three meetings. The first two are
18 indicated there, March 16 and 18, in connection with the
19 AAPS workshop. It had a further telephone conference
20 meeting on October 9. It has been a very useful exercise to
21 have this expert panel. It has been a highly valuable
22 exercise and there have been many points of discussion with
23 recommendations from the expert panel for further work by
24 the internal FDA working group which is co-chaired by Dr.
25 Mei-Ling Chen and Dr. Rabi Patnaik.

1 Some of that further work is in progress and I
2 will comment on it.

3 I will say two things about the expert panel. I
4 am delighted to say that a link to this committee, the
5 advisory committee, and the expert panel is provided by our
6 chair today, Dr. Kathleen Lamborn, who, in a few minutes
7 will speak to you about her view of the deliberations that
8 occurred on October 9 and some of the earlier ones, as well,
9 as she wishes.

10 I will also talk a little bit, too, about some of
11 those deliberations in terms of what the internal agency
12 working group is doing in the general matter.

13 The other thing I would like to say is that we
14 shared with the expert panel draft work of our responses to
15 the public responses that came in in the December 1997
16 Guideline. The December 1997 Guideline stimulated, as you
17 would expect, a lot of interest from the community, the
18 United States community, and there were many comments.

19 The internal agency working group worked hard to
20 provide responses to the expert panel to give them some
21 understanding of what our thinking was to the public
22 comments. We will continue to provide written comments to
23 the expert panel about some of their issues as well.

24 There is every intent to share all this publicly
25 at the right moment with the industry and with public

1 constituencies. So even though some material now is going
2 before the expert panel, I have every expectation that the
3 deliberations of the panel, as well as the material provided
4 to the panel by the internal agency working group, will be
5 shared publicly.

6 I would say at this point in time it is not
7 possible to say exactly what the next steps are. There
8 needs to be some further work that you will hear about from
9 Dr. Lamborn and myself, but I think there is the intent to
10 provide a reproposal of the December guidance which will now
11 be in draft for comment, not preliminary draft.

12 So we will take another round of comments from the
13 public on the guidance after it has been updated once in
14 response to the first round of public comments and then
15 there will be an implementation strategy, I can imagine,
16 although no final decisions have been made.

17 Dr. Shah alluded to the fact that some of that
18 implementation strategy may be presented in this general
19 BA/BE guidance that we are talking about today.

20 When will all this happen? I don't think I can
21 quite say but I think our intent is to move forward with
22 vigor. We have deliberated a long time about this and I
23 think we wanted to come to some conclusion about it so I
24 think we are looking at some action in 1999 based on the
25 further discussions and deliberations.

1 With that, I will go to the next overhead which, I
2 think, sets the stage for some of the comments of Dr.
3 Lamborn.

4 Criteria For Comparison

5 [Slide.]

6 DR. LAMBORN: Basically, I would like to start by
7 commenting on how impressive it is, someone coming in just
8 periodically and seeing how much progress the working group
9 has been working, the fact that we had a presentation last
10 December. That there is substantial new information to be
11 provided now I think is a good sign.

12 I think the other thing I would like to comment
13 on--I am sort of the liaison to the expert panel. I don't,
14 by any means, claim to be an expert on this particular area
15 and I think that the one thing that should be an assurance
16 to everyone is that the balance on the expert panel--I think
17 we have people representing the full range of views that you
18 all saw in the comments from the--when the call went out for
19 public comment.

20 So I think we have got all the perspectives
21 represented which gives us a chance, as part of the expert
22 panel, to really be looking all of the components of the
23 issue. Then, I think that what is written here is to try to
24 sort of summarize some of key concerns on the statistical
25 ius as they were presented.

1 One is there was a lot of concern, particularly
2 with the individual bioequivalence component on the method
3 of estimation that was initially proposed and, since the
4 last time we heard about this and the preliminary draft,
5 there has been a move away from the maximum-likelihood
6 estimation method to a method of moments which, I think, has
7 resolved a lot of the concerns that were present with regard
8 to the biases. There is continual exploration in that area.

9 Another concern was that the methodology for
10 creating the confidence interval was based on a bootstrap
11 technology which included a random component. Now, with the
12 method of moments and with some alternative information that
13 has been evolved, it looks like there is an ability to move
14 away from that method to something that is simpler.

15 The issue of discontinuity--this has to do with
16 the fact, as you will recall, that when the variance is
17 small, you use a constant denominator. When the variance
18 becomes large, it becomes scaled according to the
19 variability of the reference and, at the break point between
20 the two, there was an apparent situation where, if you had
21 slightly larger variance, it was easier to pass than when
22 you went below to the constant.

23 The current proposal that the working group has
24 presented was to use, in a sense, a "play the winner" rule
25 which is, if you were right near that cutpoint, you could

1 use whichever of them, whether it was the scaled or the
2 constant, that seemed most beneficial in terms of passing a
3 product and that the work was ongoing to verify that this
4 did not, in fact, substantially change the operating
5 characteristics in terms of the likelihood of success or
6 failure overall. But I think that that will be further
7 described as the working group proceeds.

8 A major concern was the concept of what is called
9 here aggregate versus disaggregate. This has to do with the
10 fact that the criteria, as you see at the top of that
11 transparency, includes both a component that relates to the
12 equivalence of the average and also to the differences in
13 the variability.

14 It allowed the situation where, if you improved
15 the variability for the test product, you could be in a
16 situation where you could have a difference consistently in
17 the mean. I think the sense of the expert panel was that
18 there can be an argument that is made that the metric that
19 you really care about is whatever is going to move the
20 patient from one place to another, whether that is
21 variability or whether that is because the average has
22 moved.

23 One way or another, the key thing is that
24 distance. Therefore, it is logical not to split that up.
25 On the other hand, there was a concern about perception and

1 whether it would really be well accepted if you had a
2 circumstance where the means were substantially different.

3 I think the sense was that the working group was
4 going to be asked to come back with a modified criteria that
5 would put some bound on the estimate difference in the
6 means. Of course, if that bound is put in, there will,
7 then, be a need to relook at the criteria and its
8 characteristics in terms, again, of the likelihood of
9 acceptance and rejection of the test product depending on
10 its characteristics.

11 So I think that is one of the areas where the
12 working group is going to have to invest more effort. The
13 other is the outlier analysis. Of course, there has always
14 been the issue of what do you do with outliers. This was
15 true even with average bioequivalence. The concern is,
16 particularly when you are working with variance components,
17 the outliers may have even more effect.

18 I think the working group recognizes that there
19 has to be more information provided on how that would be
20 addressed. So I think that the sense of the panel, as they
21 discussed this in the conference call, was that a lot of
22 progress was being made on the statistical issues. However,
23 there were some specific areas that had not yet been fully
24 worked out that, if you look at the summary of the proposed
25 next steps that were in there, there was a place in there

1 where it suggested that there might be an interim period
2 where it could be sort of a choice as to whether the
3 individual population bioequivalence or the current standard
4 was used.

5 I think the feeling was we weren't ready yet to
6 say that we knew enough about these characteristics with
7 these modifications to be saying that it was ready to be
8 used as an alternative approach to demonstrating
9 bioequivalence but that, as far as the statistical issues
10 are concerned, it is making excellent progress.

11 I think that there continues to be a question of
12 where are the concerns of most criticality in terms of
13 individual bioequivalence, the issue of the narrow
14 therapeutic-index drugs, also the problem with the highly
15 variable drugs and an ability to focus on where there is
16 most likely to be a problem that we really needed to be
17 addressing further.

18 What I would like to do now is ask Roger to come
19 back and speak from the agency perspective on the second
20 half and then both of us would be available to answer
21 questions on where we think the expert panel is.

22 DR. WILLIAMS: Thank you, Kathleen.

23 Kathleen has spoken to you about the statistical
24 issues. I would like to talk a little bit more about the
25 criterion which you see at the top of the page and some of

1 the public-health justification for considering this
2 criterion.

3 As the committee well knows, we think that there
4 are three aspects of it that merit consideration. One is
5 the possibility of scaling to the reference. That is based
6 on the denominator term, sigma within reference which would
7 allow a reduction, a widening of the confidence interval for
8 certain drugs that are highly variable and, hence, would
9 make it easier to pass a comparison test of bioavailability
10 metrics.

11 That particular aspect of the criterion is
12 informed by the fundamental thesis of it which says that the
13 distance between the tests and the reference should be about
14 the same as the distance between the reference compared to
15 itself. As I say that, I always feel that there is a deep
16 fundamental logic to the criterion that I find compelling.

17 That is one aspect of the criterion. The other
18 aspect of the criterion appears in the numerator and it is
19 the comparison of variance terms in the parentheses to the
20 right in the numerator, the sigma within test and the sigma
21 within reference. That is the term that allows a reward for
22 reduction in variance.

23 Again, I find that a compelling public-health
24 objective that we would always encourage, both for pioneers
25 and generics, less variable, more optimally formulated

1 products.

2 In some ways, those are things that might benefit
3 a producer and, in some ways, reduce the producer risk of
4 doing bioequivalence studies. Of course, by producer, I
5 mean sponsors, both pioneer and generics, who have to ask
6 the bioequivalence question and compare bioavailability
7 metrics

8 There is another aspect of the criterion which is
9 sigma D. That is the middle variance term in the numerator.
10 I would say that is the public-health core argument for the
11 criterion and it relates to the subject-by-formulation
12 interaction.

13 Now, without belaboring the subject-by-formulation
14 interaction, which I think the committee well understands,
15 it is the concept that there may be a subset of patients or
16 individuals within bioequivalence studies who are not
17 bioequivalent. In that respect, it harkens back to the
18 75/125 rule of about ten years ago.

19 Of course, the public-health question arises, is
20 there, in fact, a subject-by-formulation interaction that
21 would occur with any public-health frequency in
22 bioequivalence studies or in the marketplace when patients
23 are switched. I think the argument of switchability relates
24 to the fact that if there were a significant subject-by-
25 formulation interaction, if there were a subset of people

1 who were displaying bioinequivalence, our public-health goal
2 of assuring switchability would be reduced.

3 We could argue that there are many aspects of this
4 question. In fact, there are, and many aspects of this
5 question have been posed by the committee in a very useful
6 way in some of the prior deliberations.

7 There are many questions that we could talk about
8 but I will just review them briefly. One is what would be
9 the clinical relevance of a subject-by-formulation
10 interaction. Many people have asked this question of the
11 working group within the agency. It certainly is true that,
12 for some drugs, that if you saw a subject-by-formulation
13 interaction, that they had flat dose-response curves and
14 they were otherwise safe drugs, you might not be too
15 concerned about them.

16 I will give a perspective from the working group
17 which is that if we say we are willing to rely on
18 bioavailability metrics using systemic exposure, to judge
19 bioequivalence, why would we not be willing to rely on those
20 same measures to say that when we see a subset showing
21 bioinequivalence, it wouldn't be a manifestation of some
22 concern.

23 That is one argument. I am sure there are other
24 arguments that we could talk about of the clinical relevance
25 or lack thereof of a subject-by-formulation interaction. I

1 do look forward to bringing this topic and others as well
2 back before the committee hopefully in its next meeting as
3 we resolve some of the issues that Dr. Lamborn talked about.

4 There is another aspect of the subject-by-
5 formulation interaction which is what is the evidence for
6 it. I think there are kind of three lines of thinking in
7 that regard. One is looking at retrospective datasets that
8 exist within the agency. Those are the datasets that we
9 made public that I talked about in my earlier slide.

10 A retrospective view is always a little bit
11 problematic because people have argued, I think with
12 justification, that the need to do replicate studies in the
13 first place might have biased the study group in some ways
14 so that you would be picking up subject-by-formulation
15 interaction. That is an argument not to rely on those
16 datasets that we have showed the committee before.

17 However, we did see some subject-by-formulation
18 interactions that appeared to have an interesting magnitude
19 and, in some cases, perhaps, even a statistically
20 significant magnitude. We have chosen, as a magnitude of
21 interest, 0.15 and that can be justified before the
22 committee at the right time.

23 Then the counter-argument to not relying on those
24 data is to say you saw something there even in mostly
25 healthy subjects where you wouldn't expect to find anything,

1 so there is kind of a counter-argument to the initial
2 argument.

3 There was also some concern, as Dr. Lamborn
4 alluded to, that the bias of the estimation approach that we
5 were using, the REML approach, was creating a bias in our
6 detection of subject-by-formulation interaction. I think I
7 can say that, even with the new approach, the method of
8 moments, that we are still seeing some interesting subject-
9 by-formulation interactions in the FDA datasets that are of
10 a magnitude that attracts our interest.

11 However, when all is said and done, and I think
12 that we have received this comment from the advisory
13 committee that the reliance on retrospective datasets within
14 the agency were probably insufficient to justify the public-
15 health argument to move forward and use the individual
16 bioequivalence requirement.

17 So we were left with, then, B) and C). B) was
18 discussed by the advisory committee in its August 1996
19 meeting where there was a suggestion to look to the
20 marketplace for evidence of significant subject-by-
21 formulation interaction. Perhaps, by surveying HMO records
22 or doing specific prospective studies--and many of you on
23 the committee are aware of that discussion.

24 I think the FDA working group is considering a
25 different approach which we are willing to discuss before

1 the committee and that is to consider a public experiment,
2 if you will, where, for a specified period of time, we look
3 at information from replicate studies to understand, based
4 on our exposure metrics, whether significant subject-by-
5 formulation interactions are or are not occurring.

6 That was the proposal that appeared in the packet
7 of the advisory committee that accompanied our responses to
8 the public comments.

9 Now there are reasons for choosing this other
10 route. First of all, we think it can be done without
11 substantial, if any, significant regulatory burden for those
12 conducting the bioequivalence studies. Second of all, we
13 think there would be, perhaps, greater accuracy in the data
14 rather than relying on what I might call a noisy set of data
15 which would be the marketplace.

16 As I say, further discussion at this point needs
17 to occur but it was that basis that brought us to that set
18 of recommendations that appeared in the package of the
19 advisory committee.

20 I think the idea behind all this would be that
21 there would be some period of public study, perhaps two or
22 three years, at the end of which time the agency would have
23 a reasonably reliable dataset to make a case or not make a
24 case for use of the criterion to find significant, important
25 subject-by-formulation interactions.

1 That would be based on a finding that they, in
2 fact, occurred with some frequency. We could also argue
3 that if they didn't occur with any frequency, we could drop
4 that term out of the equation or go back to average with
5 scaling. I think you could even imagine an argument that it
6 would expand the opportunities to rely on the in vitro
7 studies.

8 I say that very carefully now because, as you will
9 hear on our subsequent update, we are going to talk about
10 reliance on in vitro studies to document bioavailability and
11 bioequivalence in certain very carefully defined settings.
12 One of the concerns about that reliance is that we would be
13 missing a subject-by-formulation interaction because you
14 wouldn't pick it up without doing clinical studies.

15 You have to have the subjects to find the subject-
16 by-formulation interaction. So if--and this is all becoming
17 increasing hypothetical as it gets out in time--but, if at
18 the end of this public experiment, we did not see
19 significant subject-by-formulation interactions, it might
20 become a further argument to expand the category of drug
21 products, probably immediate-release drug products, which
22 could be assessed in terms of their bioavailability and
23 bioequivalence primarily based on in vitro approaches.

24 I want to say one more thing, but I might say,
25 there might be some pain here but, at the end of the day, in

1 terms of reduction of regulatory burden, there could be
2 substantial gain.

3 One other thing I want to say about retrospective
4 data. There was one point that eluded me and I want to come
5 back to it which is there has also been the claim of relying
6 on retrospective data in terms of looking at all the agency
7 datasets which are based on non-replicate study designs, for
8 the most part, test and reference, and looking at total
9 variance with the thought that if total variance is low,
10 then, necessarily the subject-by-formulation-interaction
11 variance is low.

12 I think that is a reasonable approach. Again, I
13 will give a perspective from the working group which is that
14 it concerns me in that most of those studies were done in
15 healthy volunteers. Again, if you were going to pick up a
16 subject-by-formulation interaction, you would probably not
17 pick it up and so your finding of a low total variance and,
18 hence, a low subject-by-formulation-variance, would have
19 less meaning than if the studies had been conducted in a
20 population more representative of the patient population or
21 general population for which the drug products were
22 intended.

23 We have certainly thrown a lot before the
24 committee and I think both Kathleen and I are willing to
25 take a lot of questions. But I will say this, that what you

1 have heard so far is what I would call a progress report and
2 that a more definitive discussion of the matter could occur
3 before the advisory committee once some of this further
4 effort is done at its next meeting.

5 So, thanks very much.

6 **Committee Questions/Discussion**

7 DR. LAMBORN: Are there questions? Why don't I
8 just ask if there are questions, comment.

9 DR. BRANCH: I have been following this discussion
10 with interest of the evolution of ideas. I think, in terms
11 of looking back on the historical perspective, it was
12 interesting that major changes took place when there was a
13 database to be able to provide convincing evidence of
14 bioinequivalence.

15 The digoxin data that was presented here; one
16 picture made a very compelling argument. Dr. Lamborn, you
17 made the comment that there has been a lot of data actually
18 reviewed as a result of the discussions that took place a
19 year ago.

20 It would really help the cause of this evolution
21 of ideas if there was one really clear dataset where the
22 issue of this particular drug-by-subject interaction was
23 clearly demonstrated and the case could be made that this
24 was of clinical relevance and importance.

25 One good story can take this a long, long way. Is

1 there such a good story? Is there one dataset that can be
2 taken out and said, this is a drug for which there is a
3 public-health issue.

4 DR. LAMBORN: Roger? There have been datasets
5 looked at, but I don't know, is there any case where it has
6 been demonstrated how the clinical--

7 DR. WILLIAMS: Those datasets have been presented
8 to the committee before, Bob, and they expressed in terms of
9 the exposure metrics that we say we care about. As the
10 committee knows, we have had our nomenclature for this. We
11 call that the "smoking gun" set of data.

12 Data from the marketplace is much more difficult
13 to come by and much less compelling. There are certainly
14 anecdotal reports of switching causing a problem. But are
15 you willing to rely, the second question, on that kind of
16 data to come to a public-health conclusion?

17 I might mention, too, as I say this, this is not a
18 generic issue or a pioneer issue. It is an issue for all
19 manufacturers in the presence of post-approval change.
20 There is a lot of switching that goes on for a pioneer. Are
21 there problems in the marketplace associated with that?

22 We don't know because we don't--the point at which
23 the switch occurs is not as well defined as it is for the
24 generic.

25 As always, I would be delighted to hear from the

1 committee how you would design the experiment based on the
2 marketplace experience. But, speaking personally, I always
3 have a lot of reluctance, in terms of relying on that data.
4 I prefer the greater precision associated with the kinds of
5 studies we can do in a more controlled way.

6 Let me ask this question maybe as a countervailing
7 view. We are very interested in drug-drug interaction
8 studies. Would we be happy to rely on marketplace
9 experience to tell us about those drug-drug interaction
10 studies or would you prefer to see a discrete study based on
11 exposure measures. It is a general question and I am very
12 interested in it.

13 DR. BRANCH: When we were discussing this last
14 year, the missing link was replicate study design or
15 experience where you have got replicate studies. And that
16 is sort of what you are asking for now on a systematic
17 basis. That is the same issue that happens with drug
18 interactions, to say there is no drug interaction, what
19 happens in the replicate-study design.

20 I know that you were looking actively for
21 replicate-study designs. Did you have anything in your
22 portfolio that, by chance, somebody had done that sort of
23 thing. So the question is, out of that review, have you
24 come up with the sort of study design that you really would
25 like and are advocating in this proposal that has already

1 been done but it happened to be done by chance.

2 Even if it is a small number of examples, they
3 could be very illustrative.

4 DR. LAMBORN: Roger, the set--is it fourteen now,
5 of datasets--twelve?

6 DR. WILLIAMS: Rabi is the one who marshalls our
7 understanding of that dataset. Would it be all right if he
8 spoke to that for a little bit?

9 DR. LAMBORN: Yes; please. We have got a little
10 extra time.

11 DR. PATNAIK: We analyzed twelve studies,
12 datasets, comprising of 34 analytes. We saw, both for AUC
13 and Cmax, about 50 percent of the drugs showing high
14 subject-by-formulation interactions. In some drugs, about
15 two drugs, the studies failed primarily by subject-by-
16 formulation interactions with a low difference in the mean
17 difference as well as in the variability difference.

18 But the subject by formulation was so high that it
19 failed individual bioequivalence while passing average
20 bioequivalence.

21 DR. MAYERSOHN: Rabi, could you characterize those
22 drugs in terms of their characteristics? Were they
23 insoluble drugs?

24 DR. PATNAIK: One was the estrogenic drugs and
25 another one is the calcium channel blockers.

1 DR. MAYERSOHN: Can you tell me anything about
2 their properties, physical-chemical properties, solubility,
3 permeability? Do they fall into any specific category?

4 DR. PATNAIK: Estrogenic drugs are a complex
5 mixture. It is a salt. The calcium channel block, I think,
6 is a weak base and it is quite soluble.

7 DR. MAYERSOHN: But they have permeability
8 limitations. That is two drugs.

9 DR. PATNAIK: I cannot offhand tell the
10 permeability of that drug, the characteristics of that drug.

11 DR. MAYERSOHN: So of the half, there are six, you
12 are saying--you are saying half of these twelve studies, six
13 drugs, different drugs--

14 DR. PATNAIK: Yes; when you combine both AUC and
15 Cmax.

16 DR. MAYERSOHN: Where there was significant
17 formulation/subject interaction.

18 DR. PATNAIK: Yes.

19 DR. LAMBORN: This is with the revised analysis.

20 DR. PATNAIK: The revised analysis excluded two
21 drugs because they were done in three-period design.

22 DR. LAMBORN: I'm sorry. I guess the issue is
23 that we had the REML which seemed to identify number and
24 then it was redone with method of moments.

25 DR. PATNAIK: Yes; but two drugs which were done

1 by REML method, they are three-period design. So they have
2 not yet been analyzed by method of moments.

3 But the other drugs which have got completely
4 full-period replicate design, the drugs which showed high
5 subject-by-formulation interaction by the REML method also
6 showed very high subject-by-formulation interaction by the
7 method of moments.

8 That is what Dr. Williams alluded to earlier.

9 DR. MAYERSOHN: I think this is very important
10 because I had the same concern, Roger, you know as Bob just
11 voiced that there should be some clear data indicating at
12 least the existence of a problem. You are saying it exists.

13 DR. PATNAIK: That is what the working group
14 observed.

15 DR. MAYERSOHN: Have you formed any conclusion as
16 to the clinical pertinence or ramifications of these
17 differences? I will accept the statistical difference.

18 DR. PATNAIK: Yes; the working group has to look
19 into the drug. We are now proceeding toward that end. We
20 are also receiving some more replicate designs and we will
21 be looking at that, too.

22 DR. MAYERSOHN: Roger, in terms of the issue of
23 marketplace information, I would have thought that the
24 sparse data analysis, the non-MEM-type approach, might pick
25 up in phase III some formulation by subject interactions.

1 Is that possible? Have they looked at that?

2 DR. WILLIAMS: I'm sure they haven't looked at it,
3 Mike, but I would be glad to entertain a thought or a
4 proposal.

5 DR. MAYERSOHN: But I assume it is information you
6 can pull out of a sparse data analysis, I would think. Is
7 that right, Kathleen? The sparse data analysis, using non-
8 MEM or any other program, applied to phase III studies
9 during which there have been changes in formulations, can
10 you factor out formulation-by-subject interactions?

11 DR. LAMBORN: I would have to defer to somebody
12 who has done more work in that. I suspect there is somebody
13 in the audience, if we really want to get into it.

14 DR. WILLIAMS: But, Mike, just a question. I am
15 not sure I understand your experimental design because, in
16 phase 3, people usually aren't switched from one to the
17 other.

18 DR. MAYERSOHN: I am assuming that there are
19 changes in formulation. I would have to encompass, from
20 beginning, phase 1, 2 and 3. But all that information
21 should be available.

22 DR. BYRN: Do we have any information on the
23 mechanism of the subject-by-formulation interaction? That
24 is, do we have any evidence about biochemical changes the
25 formulation is inducing that might cause this, because if we

1 could get some information like that, we could start to
2 design, like Roger says, a controlled experience that would
3 make different formulations and just test them.

4 DR. PATNAIK: The working group hasn't come up
5 with any kind of explanation yet.

6 DR. BYRN: So right now, to design and experiment,
7 it would be totally empirical. We make a number of
8 different formulations and try and do a test and measure
9 blood levels, I guess.

10 DR. WILLIAMS: I think you could do that. Dr.
11 Lesko at the March meeting talked about some mechanistic
12 bases for subject-by-formulation interaction. That was
13 certainly a very interesting talk. I think you could design
14 a lot of prospective studies where you would try to identify
15 a mechanistic basis for a subject-by-formulation
16 interaction.

17 But they would have to be done in the right study
18 populations. It is not just the formulation understanding.
19 You have to pick patient populations and study populations
20 that would pick up the interaction should it exist. But it
21 certainly worth a discussion.

22 I think there are many approaches to getting the
23 necessary information. I might mention that I think Azaz is
24 planning a sorbitol study at Tennessee that, in essence,
25 looks at the possibility of sorbitol creating a subject-by-

1 formulation interaction.

2 DR. LAMBORN: Other comments? Questions?

3 DR. BRAZEAU: One of the attachments you provided
4 to us was a summary of pertinent parameters from 34
5 datasets. Could somebody walk me through that? It was
6 attachment 13. I think it was related to some of the
7 statistical--

8 DR. WILLIAMS: Rabi, I think Gayle is referring to
9 your 34 datasets.

10 DR. BRAZEAU: It is tab C.

11 DR. WILLIAMS: Gayle, if I understand what you are
12 looking at, I don't think this is real data.

13 DR. PATNAIK: This table shows a summary of the
14 various parameters. We go over AUC, eight analytes out of
15 34 had within-subject variability higher than 0.2. That is
16 more than 20 percent variability. So 24 percent of the
17 analytes had higher variability.

18 The next one is the ratio of the test within-
19 subject variability to the reference within-subject
20 variability varied between 50 percent to 200 percent. That
21 was 0.5 to 2.0. The third column, subject-by-formulation
22 interaction, as Dr. Williams mentioned, this value which is
23 higher than 0.15, we considered it as significant. The same
24 thing--eight analytes out of 34 analytes--so the value is
25 higher than 0.15. That is for AUC.

1 For Cmax, 18 analytes out of 34, which is
2 53 percent, the within-subject variability of the reference
3 product was more than 20 percent. The test reference ratio
4 for within-subject variability for Cmax varied between
5 60 percent to 170 percent. That means some of this test
6 product had very high variability compared to the reference
7 product and some of the analytes shows lower variability,
8 significantly lower variability, compared to the reference
9 variability.

10 Then, with respect to subject-by-formulation
11 interaction, ten analytes out of 34, which is about
12 30 percent, had subject-by-formulation-interaction value
13 higher than 0.15 which we consider significant.

14 DR. LAMBORN: Again, this is the reanalysis?

15 DR. PATNAIK: No; this is by the original
16 analysis. We have not completed that yet.

17 DR. LAMBORN: I think you need to see the revised
18 analysis with the revised estimation methodology because it
19 is recognized that the original methodology overestimated
20 the sigma D.

21 DR. BRAZEAU: So how does this compare with what
22 he was just telling us that 50 percent of the samples showed
23 a subject-by-formulation variability? Is that because of
24 the new datasets or exclusion of some datasets based on the
25 new--

1 DR. PATNAIK: The new dataset showed that the
2 subject-by-formulation-interaction value which was lower
3 became still lower by the method-of-moments analysis. But
4 those values which were higher--that means higher than 0.15-
5 -remain as high.

6 So I don't think, if we compute it again the same
7 way, this is going to change significantly this number with
8 respect to subject-by-formulation interaction.

9 DR. BRAZEAU: So, basically what I am saying is,
10 in this particular dataset, about 25 to 30 percent are what
11 showed a subject-by-formulation effect; is that right?

12 DR. PATNAIK: Yes; that's correct.

13 DR. BRAZEAU: So that is one out of four to one
14 out of three drugs. And I go back to Robert's question; the
15 clinical significance of this issue. I think that you need
16 to have well-defined studies to show that this is, indeed, a
17 problem. There may be anecdotal evidence, but is it causing
18 a problem in the care of patients?

19 DR. BRANCH: I would ask another question in terms
20 of the studies that you have analyzed. One of the
21 implications that Roger brought out was this interaction
22 between subject and formulation is likely to be more
23 clinically relevant in the patient populations than when you
24 study normal subjects.

25 So the first part of the discussion says, "Well,

1 we are going to double the number of studies you need in
2 order to be able to measure this variable, so you have got
3 an extra burden coming there." But is the next step, the
4 next logical step, suddenly to turn around and say, "Well,
5 you need to do the studies in the patient populations as
6 opposed to normal people because that is going to be not
7 necessarily a greater number of studies but they are going
8 to be much more difficult studies to do because you have got
9 to go and find your target population and do a
10 bioequivalence study, and how do you take people off drugs
11 and put them back on?"

12 It comes back to is this the right step to make.
13 Right now, you are using average variance. You are taking a
14 very simplistic approach and you are not breaking down and
15 trying to attribute the variance to individual components.
16 Now you are starting to take the science that is available
17 to go down to the individual component.

18 I really think you have got to make a case that
19 there is a public-health need for that to pursue that line.
20 I think if you can make a good argument for the public-
21 health need, that is not statistical, it is the magnitude of
22 the change that is potentially of clinical relevance.

23 It is a relevance issue more than a statistical
24 argument, I think, that needs to be brought out in the near
25 future.

1 DR. LAMBORN: Roger, you alluded earlier to the
2 fact that the sigma D criteria of 0.15, at some time you
3 would explain it to the committee. Can either you or Rabi
4 give a two-sentence explanation? First of all, you have to
5 remember, this is the estimate that was more than 0.15, not
6 the actual demonstration that it was over 0.15.

7 Or do you feel that it would be inappropriate now
8 and you would just as soon say this is very preliminary and
9 we will come back with that justification later? That is
10 fine, too.

11 DR. WILLIAMS: Just a comment, Kathleen. First of
12 all, I think all these comments are very good. We are
13 considering them all very carefully and a lot of the
14 questions the committee is asking, we will present, as I
15 say, at the next meeting.

16 Your particular question, our consultant, Dr.
17 Hauck, has given us that information. The 0.15 number is a
18 surprisingly conservative value to use to say when you have
19 a sigma D of some importance. I am drawing a distinction
20 between a statistically significant observation and an
21 important observation.

22 But, unfortunately, I just don't have those
23 numbers in front of me, Kathleen. Rather than give them to
24 committee now and guess, it is probably better to give them
25 to you late on and accurately.

1 DR. LAMBORN: The piece that I remember about it
2 is simply that it was related to what would be considered to
3 be an important mean difference and a tradeoff about the
4 implication of the shift that would occur in the dose
5 received based on if you had a formulation interaction that
6 would similarly potentially shift what the patient received.

7 So, in broad terms, that is the portion of it that
8 I recall hearing. The specifics, I can't provide unless
9 somebody else can.

10 DR. MAYERSOHN: I have got two questions, Rabi.
11 With the dataset we just went through, is it fair to say
12 that of the ten under Cmax, eight of those are the ones that
13 had the problem with the AUC? They are the same eight
14 products? Do you recall?

15 DR. PATNAIK: The dataset which we saw, the
16 working group saw, some of these analytes are metabolites
17 within the same studies for the same drug product. One drug
18 product we absorb, there are a large number of analytes
19 within that drug which showed subject-by-formulation
20 interaction.

21 DR. MAYERSOHN: What I am asking, though, is of
22 the ten where there was an interaction under Cmax, were
23 eight of those the same ones where there was an interaction
24 for AUC? Do you recall?

25 DR. PATNAIK: No.

1 DR. MAYERSOHN: They were not.

2 DR. PATNAIK: No, not the same. The question is
3 whether you saw the same interaction in high values for both
4 AUC and Cmax within the same drug?

5 DR. MAYERSOHN: Yes.

6 DR. PATNAIK: No; I don't think so.

7 DR. MAYERSOHN: Finally, these were all
8 bioequivalent?

9 DR. PATNAIK: Studies; yes.

10 DR. MAYERSOHN: These were bioequivalent products.
11 All these products, using the traditional definitions that
12 we use now, were bioequivalent.

13 DR. PATNAIK: Some of them were bioequivalent with
14 an average bioequivalence criteria. Some of them were not.
15 But if the committee wants, I can get much more detail in
16 the afternoon.

17 DR. MAYERSOHN: I would be curious; of those that
18 were not bioequivalent, by average values, how many of those
19 also showed subject-by-formulation interaction? In other
20 words, are we being redundant here? Are we seeing the same
21 kind of problem with a product that you would identify as a
22 problem using average bioequivalence?

23 DR. PATNAIK: It is hard to say like that. But,
24 again, if the committee wants, I can give you a complete
25 analysis of the--

1 DR. LAMBORN: I think what we need to do at the
2 moment is to define the types of questions that would need
3 to be addressed when the formal presentation would be
4 provided. The things that I am hearing are, we would need
5 to be clear on which of these were equivalent and which were
6 not, any information about the nature of the products where
7 this was seen.

8 There is a continued concern, I believe I am
9 hearing, that we also need to be able better translate what
10 the implication of sigma D--even if it is there, is there a
11 demonstrated clinical relevance in terms of impact on the
12 patients.

13 DR. BRAZEAU: I just would like to ask Roger for a
14 clarification. In our packet, you have a section called
15 "proposed next steps." So, at this meeting, are you asking
16 for us to not comment on those particular items, or did you
17 want us to wait on those?

18 DR. WILLIAMS: What we provided to the committee
19 was the background material to the expert panel. I think
20 what we are working with the expert panel on is to look at
21 some implementation strategies, get their final view and
22 then bring that final view before the advisory committee for
23 further discussion.

24 DR. BRAZEAU: I guess what I am hearing here is
25 that, from what I read, I think what the agency needs to do

1 is it needs to design the appropriate studies and partner
2 with someone to demonstrate that this technique can
3 demonstrate inequivalence to products that were shown to be
4 bioequivalent through the standard methods and that this
5 could be related to this subject-by-formulation difference
6 and that, likewise, the other way, that it has got the
7 greater sensitivity to show us a potential problem.

8 Until you can get us one or two clearly defined
9 studies that show that this method can actually document
10 important differences--and choose your drugs correctly,
11 drugs that may have a clinical significance--then it is
12 going to be hard for us to understand it.

13 Using retrospective datasets doesn't provide that
14 information. This needs to be clearly defined studies. And
15 I don't see asking for studies to be conducted over a two-
16 year time frame to do it will necessarily address it. I
17 think you will go a lot further by one or two carefully
18 designed studies that attempt to answer the questions you
19 are trying to ask here.

20 DR. WILLIAMS: Maybe we can do both in parallel.

21 DR. BYRN: Just briefly, just to add to the
22 questions, and this is just going on with this discussion,
23 it was mentioned that we have anecdotal information about
24 problems with switching. We have two compounds that showed
25 the largest sigma D. That was the estrogenic drug and the

1 calcium channel blocker.

2 Can we correlate that in any way with anecdotal
3 reports of problems with switching? Do we know whether
4 those two drugs have--there have been significant reports of
5 problems with switching? Do you see what I am saying?

6 DR. PATNAIK: Could you please repeat the
7 question, please.

8 DR. BYRN: What I am trying to do is ask a
9 question that will help us understand the clinical relevance
10 of this. We know we have anecdotal reports of people that
11 switch from one product to another and, apparently, had a
12 different therapeutic response.

13 And we also know that this study showed that there
14 were two drugs that had the highest sigma D, an estrogenic
15 drug and a calcium channel blocker. Is there any
16 correlation; that is, do we have significant, whatever that
17 means, anecdotal reports on those drugs?

18 DR. PATNAIK: No, but the drugs are not approved
19 yet. The estrogenic drug is not approved yet.

20 DR. BYRN: So we can't ask that question.

21 DR. PATNAIK: It is difficult to say.

22 DR. BYRN: I guess a second way to approach this
23 would be to take the drugs where we have a lot of anecdotal
24 reports and go in and do a study on datasets and see if we
25 have large sigma Ds for those.

1 DR. PATNAIK: What Dr. Williams was telling was
2 that the working group, when they analyzed the data with the
3 new approach, the working group observed this phenomenon
4 which had not been looked at earlier. Secondly, as Dr.
5 Williams alluded to the fact that, in this experimental
6 period, if one does a replicate-design study, not with a
7 very controlled population but in the general population,
8 general healthy population, the chances of observing
9 subject-by-formulation interaction, if there is, would be
10 much more enhanced.

11 DR. LAMBORN: I think, Roger, that the message
12 that you heard from the last two speakers links to the fact
13 that if you take a situation where there appears to be a
14 subject-by-formulation interaction, if the agency was
15 willing to coordinate and sponsor a specific trial, to then
16 apply this methodology and to demonstrate that, in fact,
17 this problem exists, that that might--to look for a problem
18 situation as distinct from just taking whatever came
19 through, many products of which will be the type that you do
20 not expect to see a problem so that your ability to detect
21 the sensitivity of this and the clinical relevance may be
22 small even with a large number of datasets.

23 I think that was Gayle's point a minute ago, so
24 just to clarify what I think the committee is trying to
25 suggest.

1 DR. MAYERSOHN: Kathleen, if I can just comment,
2 and this is from an historical perspective--Roger, you
3 probably remember this very well--when this whole issue of
4 bioequivalence came about, twenty-some odd years ago,
5 clinical relevance or clinical proof of relevance of
6 bioequivalence was raised as a red herring.

7 It was slapped around to essentially minimize the
8 significance of bioequivalence testing. Clearly, that is a
9 non-issue. The agency has moved ahead considerably since
10 then and it is well-accepted as being an important aspect of
11 testing.

12 This issue of clinical relevancy being raised here
13 is not to that same purpose. I think this is being raised
14 in a genuine concern to public health, the same concern that
15 you have, and asking are we going to potentially seek types
16 of problems that we clearly know bioinequivalent products
17 would lead to.

18 Did I make myself clear? It is not being used as
19 a red herring. It is a reflection, I think, of the real
20 concern of the committee members.

21 DR. PATNAIK: I just wanted to make the point here
22 to the committee here. As I said earlier, 50 percent of the
23 studies for both AUC and Cmax combined, we saw subject-by-
24 formulation interaction more than 0.15. But they were
25 comprised of not only two but more than two drug products.

1 That is what I wanted to emphasize.

2 DR. BYRN: I was just suggesting that we pick the
3 worst ones to start with.

4 DR. LAMBORN: Yes; that's what I understood that
5 you were saying.

6 DR. GOLDBERG: The 50 percent figure you just gave
7 included some products that were bioinequivalent, I believe,
8 by average bioequivalence as well?

9 DR. PATNAIK: Some of them were bioequivalent by
10 individual bioequivalence while the same drug was
11 bioinequivalent for average bioequivalence.

12 DR. GOLDBERG: Also that included some metabolites
13 as well as parent drug?

14 DR. PATNAIK: Yes, one or two drugs. I can't
15 recall the exact number but some examples are there.

16 DR. GOLDBERG: So that 50 percent really
17 encompasses a lot of things that we really don't know too
18 much about right at this point.

19 DR. PATNAIK: The origin of subject-by-
20 formulation, I don't think the working group has looked at
21 it for that detail.

22 DR. GOLDBERG: Thank you.

23 DR. LAMBORN: I think that we are ready for our
24 break now. If we take our fifteen-minute break, we will be
25 right about where we were supposed to have been according to

1 the original schedule.

2 [Break.]

3 DR. TAYLOR: Let's reconvene for the remainder of
4 the morning session for the Advisory Committee on
5 Pharmaceutical Sciences. As you can see, there have been
6 some changes at the table. I am Dr. Robert Taylor. I am
7 the chairman of the committee. I am from Howard University
8 where I am an academic physician as well as Chair of the
9 Department of Pharmacology.

10 We also have my colleague, Dr. Steve Byrn. Dr.
11 Byrn, would you introduce yourself.

12 DR. BYRN: Yes. Good morning, everyone. I am a
13 professor and head of the Industry and Physical Pharmacy
14 Department at Purdue University.

15 DR. TAYLOR: My alma mater.

16 DR. BYRN: And we are very proud of our graduate
17 who is chairing the committee, I might add.

18 DR. TAYLOR: That will cost me, I'm sure. I will
19 hear from the dean next week.

20 What we would like to do is continue with the
21 morning session, the issues and updates portion of that
22 session of the agenda. We will proceed right into the
23 agenda. Dr. Mei-Ling Chen will discuss exposure concepts.

24 **Exposure Concepts**

25 [Slide.]

1 DR. CHEN: Good morning, everyone.

2 [Slide.]

3 As some of you may recall, in the last advisory
4 committee meeting in June, we discussed the agency's
5 proposal on reviews of exposure concepts for assessment of
6 bioavailability and bioequivalence. Specifically, we talked
7 about the general concerns for attempting to find an optimal
8 measure for rate of absorption in bioequivalence when, in
9 fact, rate is not a single number and it is a continuous
10 varying function with time.

11 So, since the objective of bioequivalence testing
12 is to demonstrate comparable exposure between the test and
13 the reference product, we have proposed to use systemic
14 exposure for characterizing the plasma profiles. The three
15 descriptors of systemic exposure for concentration-time
16 profiles proposed are total exposure, peak exposure and
17 early exposure.

18 The total exposure of the drug is readily obtained
19 by the AUC, area under the curve from time 0 to infinity or
20 from time 0 to the last quantifiable concentration. The
21 peak exposure can be estimated by Cmax. We talk about the
22 early exposure. There could be measures by estimating the
23 partial AUC at a suitable cutoff at early time after dosing.

24 [Slide.]

25 So, what we would like to discuss today is the

1 continuation of this topic in refining the approaches for
2 incorporating the exposure concept in the assessment of
3 bioavailability and bioequivalence studies.

4 In general, we all agree that total exposure is
5 essential for demonstration of bioavailability and
6 bioequivalence. So, for simplicity, our discussion today
7 will be focussing on the peak exposure and early exposure.
8 The general principle is, then, to ask these two questions
9 in sequence. First, is there a need for assessment of peak
10 exposure or is peak exposure a concern for safety and
11 efficacy of the drug product.

12 So the same question could be asked for early
13 exposure, is there a need for assessment of early exposure
14 or is early exposure a concern for the safety and efficacy
15 of the drug product.

16 [Slide.]

17 This decision tree illustrates our current
18 thinking process for identifying the appropriate measures
19 for oral immediate-release or conventional-release products.
20 If you start from the left-hand side on the top, according
21 to the biopharmaceutics classification system, if the drug
22 product belongs to BCS, class 1, that has high solubility
23 and high permeability and the drug product is rapidly
24 dissolving, then we don't need to do in vivo bioavailability
25 and bioequivalence studies.

1 Otherwise, you will go down and say, a
2 bioavailability study will be required. So, if a study
3 needs to be done then we could start thinking what kind of
4 measures we would need for assessment of bioavailability and
5 bioequivalence.

6 First of all, for a conventional IR, immediate-
7 release product, we would ask the question of whether there
8 is a relationship between the peak concentration and the
9 effect. Since the dosage form is designed to release the
10 drug regularly for immediate release, most of the time I
11 think we are interested in the peak exposure.

12 I would envision that only in rare cases where
13 there is absolutely no relationship between peak
14 concentration and effect could we ignore the peak exposure
15 and assess total exposure only.

16 So if the answer to that question is yes, then we
17 can move to the right. And the next question would be do we
18 need early exposure for assessment of safety and efficacy.
19 From a clinical perspective, I could envision two situations
20 arise where we may have to look at early exposure. One
21 scenario is where there is a rapid onset of action, if a
22 rapid onset is needed for the therapeutic effect of the drug
23 such as an analgesic or an anti-inflammatory drug for
24 indication of pain relief or fever reduction.

25 The other scenario is when a slower onset of

1 action or rate of input is required for prevention of an
2 adverse reaction. So, under either condition, it seems to
3 be beneficial to assess early exposure.

4 So, if the answer is positive to the question of
5 early exposure, then we have three metrics. If the answer
6 is negative, we fall back to two metrics.

7 [Slide.]

8 So, in essence, there are two questions if we want
9 to use early exposure for assessment of bioavailability and
10 bioequivalence. First, when do we need early exposure and,
11 second, who should determine or who can decide if early
12 exposure is essential for bioavailability and
13 bioequivalence.

14 For the first question, we have just talked about
15 two scenarios. For the second question, there might be no
16 easy answers. Prospectively, a pioneer may design or
17 manufacture an immediate-release product that is faster or
18 slower than the conventional-release or dosage forms. In
19 this case, I could envision that the innovator may want to
20 consider to conduct some comparative clinical trials or
21 collect some clinical information to demonstrate that it
22 makes a difference in the efficacy and/or safety profile
23 when you change the input rate.

24 This will provide good evidence that a measure of
25 early exposure is important for assessment of

1 bioavailability and bioequivalence. Retrospectively, the
2 decision may be up to the regulatory agencies to decide
3 whether an early exposure is needed for assessment.

4 [Slide.]

5 In the case of modified release, the current
6 thinking of the Metrics Working Group in the FDA is early
7 exposure may be more important than peak exposure. We can
8 use early exposure to safeguard against dose dumping and
9 assess comparability of profiles if bioequivalence is the
10 objective of the study.

11 The dosage form is designed to release the drug in
12 a slow fashion and so Cmax may not be critical. So, under
13 such circumstances, the Metrics Working Group is in favor of
14 using early exposure for characterizing plasma profiles of
15 modified-release drug products.

16 The working group actually considers early
17 exposure a more meaningful measure than peak exposure for
18 these kind of dosage forms.

19 [Slide.]

20 There is another descriptor of systemic exposure
21 that the Metrics Working Group is actually pondering at this
22 time and that is the late exposure after a single dose of
23 modified-release dosage forms. This measure was proposed
24 for certain drugs in modified-release dosage forms where
25 concerns have often been raised regarding the maintenance of

1 adequate trough concentrations at that end of the dosing
2 interval after chronic administration.

3 This is exemplified by those drugs that have
4 clear, well-defined therapeutic ranges such as
5 antiepileptics, antihistamines, antivirals and others. So
6 one way to assure adequate trough concentrations is, of
7 course, to conduct steady-state studies and monitor the C_{min}
8 levels.

9 Alternatively, we can do a single-dose study and
10 assess the late exposure of the drug product because, unlike
11 immediate release, the input rate of a drug in modified
12 release is not always faster than the elimination rate and
13 so late exposure is product related and that could reflect
14 the release characteristics of the dosage form.

15 I think this is my last slide, and that concludes
16 my talk. Thank you for your attention.

17 **Committee Discussion**

18 DR. TAYLOR: Thank you. The presentation is now
19 open for discussion by the committee.

20 DR. MAYERSOHN: Mei-Ling, do you anticipate the
21 need to alter study design, sampling protocols and
22 strategies depending upon how you define which metric you
23 are interested in?

24 DR. CHEN: Yes. I could actually envision that if
25 we are interested in early exposure, especially for

1 immediate-release, conventional-release, dosage forms, we
2 would probably like to have more sampling points before the
3 peak. That would give us a better estimation for partial
4 areas.

5 And for modified release, it is not that critical
6 because Tmax usually is later than immediate release.

7 DR. MAYERSOHN: Have you done any retrospective
8 analysis as to how this would--the implications of this
9 approach?

10 DR. CHEN: Yes. Actually, the working group is
11 currently looking at some of the data in-house to see how
12 this proposal is workable and feasible in terms of the
13 variance cutoff for early exposure measurement.

14 DR. MAYERSOHN: Thank you.

15 DR. TAYLOR: Any other discussion by the
16 committee?

17 DR. GOLDBERG: I had a question and that is do you
18 have to look at late exposure of the terminal plot of plasma
19 versus concentration is equivalent to the elimination rate
20 from an immediate-release dosage form, for example?

21 DR. CHEN: Yes. The proposal of late exposure is
22 in the context of single-dose studies immediate release. So
23 we were saying that if there is a concern with respect to
24 the Cmin levels, then, perhaps, we could look at the single-
25 dose studies and assess late exposure later than conducting

1 multiple-dose studies for bioequivalence assessment.

2 DR. GOLDBERG: Thank you.

3 DR. BRAZEAU: I was thinking about most of these
4 studies you design are for a single dose; is that correct?
5 You are talking about single dose here.

6 DR. CHEN: Yes.

7 DR. BRAZEAU: It seems to me that--I sort of
8 question that because most drugs are not taken as a single
9 dose. They are taken as multiple doses and we talk about
10 the concepts of getting up to steady state. I guess the
11 general assumption is when it takes four to five half-lives
12 to get to a steady-state level; is that correct?

13 So it seems to me that this early-exposure concept
14 might be more critical for those drugs that have longer
15 half-lives. They are going to take longer to get to steady
16 state and where there might be a patient's difference in how
17 well they are getting the desired effect.

18 I don't know if you have thoughts about how the
19 half-life of drugs could play into some of these
20 phenomenons.

21 DR. CHEN: The proposal for early exposure is
22 actually meant to address the question on the input rate.
23 If you are talking about long half-life drugs, I think we
24 are actually talking about the total exposure. So, in a
25 way, I think the working group is in a position that,

1 because most of time we will be interested in the total
2 exposure for assessment of bioequivalence unless the half-
3 life of the drug is so long that that prevents us to do
4 crossover studies.

5 Then we could use parallel designs to conduct
6 bioequivalence studies for these kinds of drugs. That is
7 the current thinking.

8 DR. TAYLOR: Does that answer your question?

9 DR. BRAZEAU: I guess I am just sort of thinking
10 of this from a perspective--say that I have a drug that has
11 got a very short half-life and I am going to be taking it
12 four times a day. I will get my, I will say, Cmax at
13 fifteen minutes versus thirty minutes so that there may be a
14 difference in that.

15 But is the patient going to perceive a difference?
16 I don't know. Compared to a drug that I take once a day
17 where I may not see my Cmax one hour versus three hours;
18 that might be a more significant relationship because I am
19 not sure that the early exposure is going to apply to all
20 drugs.

21 DR. CHEN: You are correct. We were saying that
22 you have to go through the decision tree and decide whether
23 this exposure should be used for this specific drug product
24 or drug substance. That is why, for a modified-release
25 product, we are proposing early exposure and total exposure

1 will be the two key measures. We will be interested in peak
2 exposure.

3 DR. BRAZEAU: I guess that I would suggest that,
4 somewhere in your decision tree, you have to look at what is
5 going to be the half-life of the drug and the dosing
6 frequency of it, to some extent. Maybe that will play an
7 impact in your decision tree.

8 DR. CHEN: Okay.

9 DR. MAYERSOHN: Mei-Ling, which metrics are you
10 pursuing other than area? Are you looking at moments as
11 well?

12 DR. CHEN: For total exposure, of course, it is
13 AUC. We already know. For peak exposure, we would use
14 Cmax. It is commonly used and clinicians like the notion of
15 Cmax. I think we will still keep a Cmax for peak exposure.
16 For early exposure, the working group actually has conducted
17 simulations in collaboration with Dr. Tozer and Dr.
18 Endrenyi.

19 We have looked at a number of possible measures
20 for early exposure. Ajaz, maybe you could show one of my
21 slide that I didn't--

22 DR. TAYLOR: Are you holding out on us, Mei-Ling?

23 [Slide.]

24 DR. CHEN: That is the measure for early exposure.
25 I sort of thought that the question would come up. The

1 general principle is we will truncate at an early time point
2 of the plasma-concentration-time profile. The simulations
3 have been done for all the potential measures, this variance
4 cutoff.

5 Those four are the potential candidates for early
6 exposure measurement. Of the four, I would say that the
7 simulation results actually reveal that early Tmax as the
8 cutoff would be the most powerful and most effective measure
9 for early exposure, and that is in the context of immediate
10 release.

11 But, as you can see, the earlier cutoff, the more
12 sensitive the measure and the tighter we can meet the
13 current confidence-incidence criteria. So, in some ways,
14 the working group is looking at modifications. We may say
15 that we may have to either use point estimates or widen the
16 confidence intervals for this measure in reality.

17 If replicate-design studies can be used, then we
18 could rely on the confidence intervals with scaling to
19 reference variability. But if we don't have the replicate-
20 design studies, the working group is planning to conduct
21 further simulations and to refine the confidence interval,
22 the bioequivalence limits, for the measure.

23 DR. MAYERSOHN: Just a couple of comments. I
24 suspect, and I can't verify this, that early times following
25 oral dosing, there are greater measurement errors in both

1 concentration and the X axis, and in time as well, which we
2 usually ignore. That is an issue. If you are going to do
3 simulation analyses, you want to make sure you throw in some
4 error analysis and variability.

5 Are you combining your models, the kinetic models,
6 with any dynamic issues, effect-concentration relationships,
7 that are steeper in some cases, less steep in others? You
8 are doing the kinetic analysis independent of any
9 pharmacodynamics.

10 DR. CHEN: Yes. Right now, we are only focussing
11 on the pharmacokinetic aspect of the drug.

12 DR. MAYERSOHN: So you have eliminated mean
13 absorption time as a possible useful approach?

14 DR. CHEN: See, that was the early study of this
15 working group. We have looked at the mean absorption time
16 but the approach was rejected because we see there are a lot
17 of problems with estimation of mean absorption time.

18 DR. MAYERSOHN: Numerical problems?

19 DR. CHEN: Yes; technical problems. Sometimes,
20 you will get negative numbers if you have a drug with a long
21 half-life.

22 DR. MAYERSOHN: That is a problem.

23 DR. CHEN: Yes. And when you use the moment
24 analysis, inevitably, you will get into some difficulties
25 for estimation of the elimination-rate constant and the area

1 under the curve. So it is another hurdle. So it was
2 rejected by the working group early on.

3 DR. MAYERSOHN: In the same way, would you not do
4 deconvolution?

5 DR. CHEN: Deconvolution?

6 DR. MAYERSOHN: You would not.

7 DR. CHEN: No. It is a very complicated procedure
8 and people don't like it at all.

9 DR. MAYERSOHN: I guess my suggestion is the
10 committee should just--I am probably stating the obvious--
11 should just keep its mind open to as many possible
12 parameters and metrics that you can come up with that are
13 being developed with time to help resolve this issue.

14 DR. CHEN: Yes.

15 DR. TAYLOR: Any other questions? Dr. Williams?

16 DR. WILLIAMS: I don't want to interrupt the
17 committee discussion but it seems like you were concluding
18 your comments here and I did want to make a few closing
19 statements if it is time.

20 DR. TAYLOR: That's fine.

21 DR. WILLIAMS: I wanted to talk about process and
22 motivation. One of the things that is happening at this
23 meeting is we are having this deliberation before the
24 committee as we write this guidance. So probably the next
25 step that would happen for the public is to see words in the

1 guidance, this general guidance that we have been talking
2 about, that say what Mei-Ling just said in a series of
3 overheads.

4 That would go out for public comment. We would
5 presumably get some or, perhaps, a lot of public comment and
6 then we would try to summarize those comments and bring them
7 back before the committee. So there would be a chance to
8 not only see some further internal deliberations but also
9 see the public comment.

10 With that process statement out of the way, let me
11 just say what I see as a motivation going on here. I think
12 there is a public-health motivation, if you will, to say
13 that under certain circumstances, patient needs would be
14 served by products that control the rate of input a little
15 more carefully.

16 Now, I will speak mostly about conventional-
17 release products. For example, an analgesic, you might want
18 to see a rapid upstroke in the concentration-time curve to
19 relieve pain more quickly. Conversely, with some products
20 where a rapid upstroke is associated with some kind of
21 toxicity, you might slow it a little bit.

22 I will remind the committee that I think, in some
23 ways, that was a motivation for the slowed release of
24 phenytoin. But I do want to emphasize that I think that
25 this should be based on good data and there is sort of no

1 free lunch here. I would be up to the pioneer to show
2 compelling evidence to the agency to justify either the more
3 rapid input or the slowed input compared to a conventional
4 release and that should be reflected in the labeling.

5 This is my hope about all this. Furthermore, the
6 burden, then, should be to control the manufacturer of the
7 product so it reliably does what the labeling says it should
8 do. In that context, I think we can move to these
9 additional metrics that Mei-Ling is talking about and make
10 them apply to all instances where bioequivalence is to be
11 performed.

12 I think that is the motivation that we are getting
13 here. I guess I would conclude this motivation by saying I
14 am going to be fairly reluctant to say we should go to these
15 metrics without that compelling dataset. I would not want
16 somebody to come in with a bizarre exposure pattern and say,
17 "Let's duplicate this," without some data to justify why it
18 should be duplicated.

19 DR. LAMBORN: Could I just make sure I am
20 understanding. What you are really saying is that you
21 envision in the future where an indication for an innovator
22 product would indicate that the timing of the exposure,
23 either early or late, would be relevant to the clinical
24 activity, that, under those circumstances, you would like to
25 have in place a guidance that would say what metrics must be

1 met in order to demonstrate that changes or a generic was,
2 in fact, equivalent for those circumstances.

3 DR. WILLIAMS: Exactly. I think we might imagine
4 these instances wouldn't be all that frequent when you think
5 about it.

6 DR. TAYLOR: That was my next question, how often
7 you would say, looking at products that are currently
8 marketed--what percent of the time would you think they
9 would apply? Would you maybe lump them by 10 percent,
10 20 percent, 30 percent?

11 DR. WILLIAMS: I think we are talking in the
12 10 percent range, Dr. Taylor. But I don't know. The
13 reality is we don't control most of our products this way
14 and everybody is perfectly happy. So it gets back to your
15 clinical "people in the streets" argument, if you will.

16 DR. BRAZEAU: But I think we have got the
17 potential for this to be more interesting as we develop new
18 excipients and new components that are going to go into
19 particular oral-dosage forms that could have impact on some
20 of these properties. So I think it is something to at least
21 keep a finger on as we have all different types of things--
22 we are talking about complexing drugs with all different
23 types of molecules to try to change absorption profiles.

24 DR. TAYLOR: I recall at our last meeting we
25 talked about comparing some of these newer metrics with

1 older metrics for the various categories of drugs. I guess
2 I am curious as to what sort of concordance was there
3 between the old and the new. You probably didn't bring that
4 data but could you give me some general comment.

5 Is a tendency for an immediate-release drug to
6 have less concordance when we look at early exposure or less
7 concordance and what would be the situation for the modified
8 release. In other words, how often would the current
9 metrics mislead us into thinking that we had a safer
10 effective product and would justify the need to change it.

11 DR. CHEN: I presented this example at the last
12 advisory committee meeting, and that is ibuprofen. In the
13 way that we didn't look at the early exposure and we only
14 looked at Cmax and AUC. Those two products have identical
15 AUCs and identical Cmax's. Yet, the test product is
16 absorbed consistently slower than the reference product in
17 most of the individual subjects.

18 That is where, retrospectively, now, looking at
19 the data, we think we really need to have some type of
20 measure to safeguard that phenomenon. That is where we
21 think early exposure would be important. I don't know,
22 looking at in-house data that we have, how many drugs would
23 fall into that category. I have no idea.

24 DR. TAYLOR: I think I was alluding to the
25 ibuprofen study that you reported last time. So the major

1 modification in the whole exposure issue is really an early-
2 exposure metric; is that correct?

3 DR. CHEN: For immediate release.

4 DR. TAYLOR: For immediate release; yes. That is
5 the major twist in your proposal.

6 DR. CHEN: But also for modified release. If you
7 recall that the working group now is actually more
8 interested in early exposure for modified release--

9 DR. TAYLOR: For safety issues.

10 DR. CHEN: Yes; for safety issues. And also
11 people would like to see comparable profiles between the two
12 modified-release dosage forms especially in the presence of
13 different release mechanisms. In lieu of peak exposure, we
14 may be more interested in early exposure and use that as a
15 tool to compare two profiles.

16 DR. TAYLOR: I think, in the long run, the value
17 of the new early-exposure metric will be born out by what
18 impact it has on safety and efficacy review in the agency
19 over some period of time. I think that we have to keep that
20 in mind that there may be some other metric that is
21 available that we can devise that would give us even greater
22 information.

23 But that is something we have to find out by
24 testing it.

25 DR. BYRN: Something Roger said raised a question

1 for me. This would be, at least I think, and I am thinking
2 about how this would be implemented, I would be implemented,
3 I think, from the way Roger discussed, on NDAs and through
4 packaging or would there be a way to retroactively--it seems
5 it would be more difficult to retroactively implement it.

6 DR. WILLIAMS: I think I agree. As I say, the
7 driver for this, and I think I am echoing what Dr. Taylor
8 said, too, is safety and efficacy data that justifies the
9 need for it. I think, looking retrospectively, it would be
10 hard to find that.

11 DR. BYRN: So the way this might happen is an NDA
12 would come in, it would use these metrics, and it would
13 include on the labeling and the package insert a description
14 of the reason they were used and the importance of them and
15 then an ANDA, later, would have to meet those methods, then.

16 DR. WILLIAMS: If I could just add; I think the
17 motivation is slightly different for controlled release. I
18 will echo what I think Mei-Ling was saying which is usually
19 the way it works for controlled release is that people like
20 to go from immediate release to controlled release and not
21 adjust the therapeutic indications.

22 So the primary motivation in that circumstance is
23 just the reduced dosing frequency which can help compliance
24 or otherwise argues for the utilization of the drug,
25 although I could imagine a controlled release where, if you

1 smooth out those peaks and troughs, you would have a better
2 tolerated product.

3 So, in some ways, I don't think we are doing
4 anything different than we have done before for controlled
5 release. I think what Mei-Ling is suggesting where you go
6 from immediate release to controlled release--unless you
7 provide data to show that that change in peak affects the
8 safety or efficacy profile, the presumption is the peak
9 isn't very important.

10 For that reason, the focus should switch to either
11 early or late metrics. I am looking at Mei-Ling to see if
12 she is nodding her head here. The early-exposure metric is
13 to focus a little bit more on input, comparing two different
14 controlled-release products. The focus on the late exposure
15 is the assure comparability in Cmin at steady state.

16 So I would argue the motivation for immediate
17 release and controlled release is different.

18 DR. CHEN: Correct.

19 DR. MAYERSOHN: Roger, if my memory serves me
20 properly, nitrofurantoin fell into this category. I think
21 the release was slow to avoid the incidence of nausea and
22 vomiting. You probably have lots of nitrofurantoin data in
23 your files. It is one of the earlier drugs where the
24 generics were created, I believe. I don't know if this will
25 help you any.

1 DR. CHEN: We will back to look at--

2 DR. MAYERSOHN: You don't have already have enough
3 to do.

4 DR. BRAZEAU: Roger, let me ask a question. I
5 heard someone say here that--talked about NDAs and ANDAs. I
6 assume with some of the other guidances you are developing,
7 some of these would or would not be applied to SUPAC or
8 post-approval changes; is that correct--because you would
9 try to go according to some of the other guidances you are
10 developing?

11 DR. WILLIAMS: Yes. I think you are right, Gayle,
12 that if we do go this approach and it can be documented
13 based on clinical safety and efficacy data, then I think it
14 should intrude into the world of SUPAC, as well, when you
15 have to redocument in vivo bioequivalence in the presence of
16 some post-approval change.

17 DR. BRAZEAU: But I thought you were also trying
18 to develop some guidances where you could for some of these
19 modified and controlled release. Aren't you trying to do
20 some in vitro work for that, too; is that correct or not?

21 DR. WILLIAMS: We are coming to that discussion
22 from modified release and maybe we could hold it until we
23 get there.

24 If I may, one other comment you made was long
25 half-life drugs. I would tend to think this would be more

1 pertinent for a short half-life drug in terms of early
2 exposure on the same argument as a modified release because
3 a long half-life drug is sort of like a modified release.

4 If you think of a drug like piroxicam, where Cmax
5 is fairly insensitive to rate of input--you know, we get all
6 those simulations that showed that. I would argue that I
7 don't see this approach being particularly suitable for a
8 long half-life drug. I don't know. I am interested and we
9 could have further discussion on that at some point in time.

10 DR. TAYLOR: What about narrow therapeutic-index
11 drugs? How would it impact on that category of drugs?

12 DR. WILLIAMS: I think it could be pertinent. You
13 might, in terms of toxicity, take a drug that would be more
14 problematic and slow its release so that patients would
15 tolerate it better. In that case, it might be suitable for
16 these metrics.

17 DR. TAYLOR: And then you would be concerned about
18 the Cmin issues as well.

19 DR. WILLIAMS: You mean in terms of loss of
20 efficacy.

21 DR. TAYLOR: Yes.

22 DR. WILLIAMS: Yes; perhaps.

23 DR. TAYLOR: I think we have had a good
24 discussion. If there are no other questions from the
25 committee, I would like to proceed to the next presentation.

1 It is Dr. Ajaz Hussain, in vitro approaches.

2 **In Vitro Approaches**

3 DR. HUSSAIN: Thank you, Dr. Taylor.

4 [Slide.]

5 I have prepared by presentation to be very brief,
6 without data. I did provide to the advisory committee our
7 thoughts and some information on issues related to the
8 guidance in the handout packet so I will not be repeating
9 some of that but go straight to sort of an overview.

10 [Slide.]

11 What I would like to do today is briefly overview
12 how the agency looks at biopharmaceutics classification
13 systems. The regular questions that we ask, and this is
14 following up on what Dr. Williams showed you, the three
15 questions, I would briefly summarize for you the public
16 discussions we have had on BCS, then go on to the highlights
17 of the draft-guidance document, talk about the class
18 boundaries, methods for permeability determination and
19 applications, and summarize two issues for you to consider.

20 [Slide.]

21 Just to summarize, the key elements that are
22 involved in the biopharm classification system include two
23 properties or characteristics of the drug substance, namely
24 solubility and intestinal permeability, and the product
25 characteristics of interest is product dissolution.

1 We have classified drugs into high solubility or
2 low solubility; similarly for permeability as high and low
3 permeability. Product dissolution, the criteria for saying
4 a product is rapidly dissolving is that the immediate-
5 release solid oral dosage form has a high likelihood of
6 behaving as a solution when given orally.

7 Not rapid; the same product may have significantly
8 different exposure or Cmax compared to, say, a solution
9 dosage form. Again, the biopharm classification system is
10 being applied only to wide therapeutic-window drugs.

11 That is sort of a summary I wanted to present
12 before I go on.

13 [Slide.]

14 From the regulatory perspective, the scope of this
15 classification system is limited to immediate-release solid
16 oral dosage form. These are conventional tablets and
17 capsules, mainly. We looked at BCS as a tool for minimizing
18 in vivo bioequivalence tests when such tests will not
19 provide additional new information by showing or improving
20 product quality.

21 It is a tool that helps us build confidence in the
22 dissolution test and, in the working group's opinion, you
23 actually can improve the quality of products on the market
24 using this tool. It continues to be an active research area
25 because we believe the scope of this classification system

1 can be significantly enhanced.

2 [Slide.]

3 The three questions that were posed by Dr.
4 Williams with respect to biopharmaceutics are; what do we
5 want to know. Does a change in the manufacturing process
6 alter the safety and efficacy profile? The manufacturing
7 process could change dramatically going from one
8 manufacturer to the other manufacturer and so forth.

9 What assumptions are we willing to make prior to
10 this biopharm classification system? Our assumptions were
11 in vivo bioavailability--that is, the rate and extent of
12 absorption--is a surrogate for safety and efficacy.

13 How sure do we want to be? We use bioequivalence
14 testing when products meet certain criteria. They have to
15 be pharmaceutically equivalent. They have to be
16 manufactured under GMP conditions. They have to meet
17 stability and all of the chemistry requirements.

18 In addition to that, the in vivo bioequivalence
19 criteria has been set and has been used for several years
20 now, the 90 percent confidence interval for Cmax and AUC.
21 However, we have allowed the waiver of in vivo
22 bioavailability and bioequivalence under several situations.
23 Don Hare summarized some of this earlier.

24 For example, currently, for oral-solution dosage
25 forms such as elixirs and syrups, we have the provision for

1 biowaiver. For solid oral dosage forms when you document in
2 vitro/in vivo correlation. Also, non-bioproblem DESI drugs
3 and in other situations such as lower strengths.

4 [Slide.]

5 These same questions could be looked upon
6 differently under the biopharm classification system. The
7 first question remains the same and what assumptions we are
8 willing to make now are different. With this biopharm
9 classification guidance that the working group has proposed,
10 for IR products containing highly soluble and highly
11 permeable drugs, not including narrow-therapeutic index
12 drugs, we are willing to assume that pharmaceutically
13 equivalent IR products that exhibit rapid in vitro
14 dissolution may be considered to be bioequivalent to each
15 other.

16 Inherent in that assumption is another assumption,
17 that conventional excipients, or inactive ingredients, that
18 are used in immediate-release solid dosage forms do not
19 affect bioavailability.

20 How sure do we want to be? Obviously, validation,
21 GMP, stability, all chemistry requirements, have to be
22 satisfied, same as before. And all so well-characterized
23 excipients. In addition to that, the criteria of rapid
24 dissolution, that being 85 percent in 30 minutes in a media
25 of pH 1.0, 4.5 and 6.8, is being recommended.

1 A similar dissolution profile using the profile
2 comparison technique that has already been in practice of an
3 f2 value of greater than 50 or equal to 50 when dissolution
4 is not 85 percent in 15 minutes. That is the criteria of
5 how sure we would like to be if we move in this direction.

6 [Slide.]

7 The biopharm classification system has been in
8 practice in SUPAC IR and also in the guidance on immediate
9 dissolution. The underlying scientific principles have been
10 discussed at the advisory committee, the predecessor of this
11 one, the Generic Drug Advisory Committee, and at this
12 committee on several occasions.

13 In addition, we have discussed our thoughts at
14 national and international meetings and workshops. What we
15 have learned from this discussion is, in general, many--in
16 fact most--pharmaceutical scientists consider the proposed
17 class boundaries and regulatory applications to be
18 conservative. I probably could have said too conservative.

19 At the same time, there have been concerns
20 expressed that the potential-impact excipients may have on
21 gastrointestinal physiology and, thereby, bioavailability
22 needs always be constant.

23 [Slide.]

24 The draft guidance--I was hoping that I would have
25 this out before this advisory committee meeting. That did

1 not happen. It is currently under review by the regulatory
2 policy staff of CDER and we hope that it will be out soon.
3 The guidance has been approved by the Biopharmaceutics
4 Coordinating Committee so, in a sense, the steps have been
5 taken to get this guidance out for public comment.

6 The guidance addresses the following: it defines
7 class boundaries. With respect to solubility and
8 permeability, the class boundaries have not changed. They
9 are the same as in the SUPAC IR. It does define a rapid
10 dissolution class boundary, which is different. It defines
11 methods suitable for classifying a drug, focussing mainly on
12 permeability methods.

13 Instead of defining in detail the experimental
14 procedure, we adopted an approach of defining data-
15 acceptance criteria instead of defining these are the
16 experimental conditions that need to be used.

17 Also the applications that are included are for
18 biowaivers under certain situations.

19 [Slide.]

20 I would like to focus on the dissolution class
21 boundary because this is new. Rapid dissolution is being
22 defined as in vitro dissolution rate of not less than 85
23 percent in 30 minutes in aqueous media, 900 ml or less of pH
24 1.0, 4.5 and 6.8 using USP apparatus I at 100 RPM or
25 apparatus II at 50 RPM.

1 The criteria of similar profile is being
2 recommended when dissolution in the three media is slower
3 than 85 percent in fifteen minutes. And the test and
4 reference product should exhibit a similar dissolution
5 profile.

6 [Slide.]

7 I would like to just summarize the permeability
8 methods that are included in the guidance, pharmacokinetic
9 methods that include mass balance or absolute
10 bioavailability; in addition, intestinal perfusion methods
11 in vivo in humans, in vivo in situ perfusion methods in
12 animals, in vivo methods using appropriate membranes such as
13 excised intestinal tissue or monolayers of functional
14 cultured human intestinal cells.

15 In addition to permeability, stability in GI fluid
16 needs to be documented and, also, we are requesting
17 supportive data to, for example, optimal water-quality
18 coefficient and other information that can help suggest the
19 permeability characteristics of the drug.

20 [Slide.]

21 As I mentioned earlier, we have tried not to
22 include experimental details in the guidance. In a sense,
23 we are defining method-suitability criteria which suggest
24 that using 20 or more model drugs, a form needs to document
25 a relationship between measured permeability in the direct

1 experimental system and the extent of absorption of drugs in
2 humans.

3 The relationship must permit classification
4 correctly of the selected model drugs. We also recommend
5 use of internal standards. Once a method has been found to
6 be suitable for subsequent experiments, the inclusion of a
7 high- and a low-permeability internal standard is
8 recommended to keep track of variability as time goes by and
9 also to aid in the classification.

10 In addition, for in vitro systems, we have some
11 concerns that expression of certain transporters and efflux
12 systems would need to be characterized and we would like to
13 use in vitro systems when absorption is via passive transfer
14 or when a linear relationship between those and
15 bioavailability has been documented.

16 [Slide.]

17 In terms of application, requests for biowaivers
18 under this guidance would happen when the drug is a wide-
19 therapeutic-window drug. That definition, we are waiting
20 for a separate group to define narrow-therapeutic- or wide-
21 therapeutic-window drugs. But, from a biopharm
22 classification perspective, the drug needs to meet the
23 criteria of high solubility and high permeability and the
24 product needs to meet the rapid-dissolution criteria.

25 So when all these four criteria are satisfied, the

1 guidance recommends a biowaiver.

2 [Slide.]

3 These biowaivers will occur preapproval as well as
4 postapproval. Having defined or introduced in vitro methods
5 for classifying a drug based on its permeability
6 characteristics, we feel that, tentatively, the class
7 membership of a drug could be achieved or determined quite
8 early from in the preclinical phase now.

9 As clinical data starts coming in and the product
10 already meets the specification, dissolution specification,
11 and the class membership will be confirmed as dose is
12 formed--the highest dose strength has been defined--then
13 waivers would start right in the preapproval phase and,
14 also, will continue in the post-approval phase for SUPAC-
15 related changes where currently SUPAC level-3 changes
16 require biostudies.

17 In addition, introduction of multisource products
18 would also occur based on dissolution and, subsequently,
19 postapproval changes through this multisource product would
20 follow the same line.

21 [Slide.]

22 To summarize, the working group feels the proposed
23 BCS applications are based on a mechanistic understanding of
24 oral drug absorption. I would like to hear from the
25 advisory committee are these applications appropriate.

1 The second issue is the proposed guidance
2 identifies methods that may be used to classify a drug
3 according to BCS and outlines method suitability and data-
4 acceptance criteria. Should this list of methods for
5 permeability determination be expanded to include extent of
6 absorption in animal models, I have provided to advisory
7 committee some information saying that that may be possible.

8 I would like to seek your advise on that point,
9 and also are the method-validation criteria for intestinal
10 perfusion methods appropriate. The reason I am asking this
11 question to the advisory committee is, at the AAPS workshop
12 that was held in August, the recommendations from that
13 workshop appear to be very liberal compared to what this
14 guidance is recommended.

15 There is a difference between what the guidance
16 recommends and what the workshop is recommending. The
17 difference mainly lies in requiring 20 drugs to be tested to
18 define method suitability and is 20 really too much or is it
19 necessary to include that. So that is my third question to
20 the advisory committee.

21 I will stop with that.

22 DR. TAYLOR: Thank you.

23 **Committee Discussion**

24 DR. TAYLOR: The presentation is now open for
25 discussion by the committee.

1 DR. MAYERSOHN: Ajaz, it is probably diabolical
2 that the one group of compounds, high-soluble, high-
3 permeability drugs, we all agree concerning the waiver for
4 bioequivalence are probably the drugs that the industry no
5 longer produces. They are all called "grease balls." They
6 all have high clearances. They are problematic drugs.

7 So I think, while we all agree with the thinking
8 and the science behind this, I suspect that this may cover
9 very few drugs that are being developed. Do you agree with
10 that?

11 DR. HUSSAIN: Yes.

12 DR. MAYERSOHN: In terms of the methods to
13 characterize permeability, I think the more the better. We
14 are learning more about the issues at a gut level, if you
15 will pardon the expression, using a variety of different
16 approaches.

17 The paper by Chiou is very compelling. I was
18 really very surprised. Prior to that, Amidon's relationship
19 between bioavailability and permeability measurements were
20 also very supportive of the fact that you have some
21 reasonably valid procedures. Is 20 enough? It is probably
22 not enough. If you can get 100, so much the better and the
23 more faith you have in the procedure that you are using to
24 validate.

25 Is 10 enough? I don't know. I can't answer that

1 question. I think the answer is the more the better. And
2 there is probably a lot of data in the literature and I
3 encourage people to go back to the literature and see if
4 they can't cull from the literature these types of
5 correlations.

6 DR. TAYLOR: Looking back on that slide where you
7 showed drug solubility, drug permeability and product
8 dissolution, recognizing that each of those items are
9 continuous sorts of measurements, in your table you actually
10 had high and low suggesting that you are going to set, or
11 the committee or somebody was going to set, a cutoff that
12 meant high or meant low.

13 You did that for product dissolution. You
14 presented that today.

15 DR. HUSSAIN: Correct.

16 DR. TAYLOR: But for drug permeability and
17 solubility, I didn't hear that.

18 DR. HUSSAIN: No. I did not present that because
19 the cutoff remains unchanged. You have that in your
20 handout. The cutoff for solubility is the highest dose
21 strength should be soluble in 250 ml of water across a pH
22 range of 1.0 to 8.0 So that cutoff remains unchanged for
23 permeability. Extent of absorption needs to be good in 90
24 percent. Again, that cutoff remains the same.

25 DR. TAYLOR: So that clarifies that. The other

1 issue I had that you were going to use some internal
2 standards. Would the draft guidance define what those were
3 or what the innovator selects and justify the selection of
4 those?

5 DR. HUSSAIN: The guidance includes a list of
6 drugs where permeability has been determined and classified
7 those model drugs as high and low and encourages the sponsor
8 to use as many of those as possible and also identifies
9 potential internal standards. I did not provide the list to
10 you.

11 DR. TAYLOR: The other item that I had a question
12 about had to do with issues of drug permeability, drug
13 elimination, that were sort of tied together that resulted
14 in basic clearance issues, I guess, because you need to talk
15 about them together. I didn't understand how in vitro
16 testing would get to the issue of things like p-
17 glycoprotein, for example, where the p-glycoprotein may be
18 used as an elimination or a drug-extrusion technique.

19 I didn't understand. Now, you did suggest that
20 there may be some animal models, but I didn't see how that
21 was going to translate into something we could use
22 clinically.

23 DR. HUSSAIN: I get your point. Since p-
24 glycoprotein or other efflux systems in the gut can serve an
25 elimination when the drug has been absorbed systemically but

1 also they serve as a barrier for absorption. So, in a
2 sense, a drug subject to efflux by certain systems will have
3 a lower permeability than we anticipated.

4 That is the reason why, when we recommend in vitro
5 methods such as CACO-2, generally, so far, what we have seen
6 is the expression of PGP tends to be higher or overly
7 expressed in these systems. So we would like the systems to
8 be characterized for the degree of expression of such
9 systems.

10 The way we intend to do that is through model
11 drugs. For example, verapamil is a substrate for PGP. If
12 it can be documented that, in a given system, the apical or
13 brush border to the basal lateral transport and, vice versa,
14 from basal lateral to apical transport--if the ratios are
15 similar for a drug like verapamil, then that will suggest
16 that the expression is nonexistent or is not there.

17 But if the ratio is high, then that would suggest
18 some degree of expression in your in vitro system. So that
19 sort of experimental evidence would need to be gathered when
20 you look at in vitro systems which have or may not have
21 these efflux systems.

22 DR. TAYLOR: Would these be in animal models or
23 would these be human culture cells.

24 DR. HUSSAIN: I think the concern is more with the
25 cell cultures, human cell cultures.

1 DR. TAYLOR: Human gastrointestinal epithelial
2 cells.

3 DR. HUSSAIN: Right.

4 DR. WILLIAMS: Just a quick clarifying question to
5 Ajaz. I think your intent, Azaj, was not to ask every
6 sponsor to do all those 20 drugs but that would like of like
7 be a preexisting standard curve? What was your thinking on
8 that.

9 DR. HUSSAIN: The guidance, as has gone forward,
10 would require every sponsor or every site where these
11 studies have been done to do those 20 drugs.

12 DR. GOLDBERG: If the class I categorization of
13 rapidly soluble, or highly soluble, highly permeable drugs
14 are sufficient for WTI, wide-therapeutic-index drugs, what
15 is the basis for excluding narrow-therapeutic-index drugs?

16 DR. HUSSAIN: Again, I think the working group
17 debated that issue and we felt it was more prudent to take a
18 more conservative and cautious step in this direction. I
19 think once we get a sense of--gather more information,
20 probably we will have to reexamine that question.

21 DR. GOLDBERG: Thank you.

22 DR. TAYLOR: Any additional comments by the
23 committee? Dr. Williams, would you like to summarize these
24 comments?

25 DR. WILLIAMS: Just very briefly. I think the

1 intent is to let this guidance go into the public arena,
2 have comments made to it and we will try to bring those
3 comments back to the committee.

4 Thank you.

5 DR. TAYLOR: We are back on time, I think,
6 slightly. We have one-and-a-half hours for lunch. It is
7 now 12 o'clock, so we will begin our committee deliberations.
8 promptly at 1:30, and we will begin with the open public
9 hearing phase of the committee's meeting. The morning
10 session now stands adjourned.

11 [Whereupon, at 12 o'clock p.m., the proceedings
12 were recessed to be resumed at 1:30 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:35 p.m.]

Open Public Hearing

DR. TAYLOR: The afternoon session is designed from the public to provide comments relative to the agenda that we are discussing today. We have identified three individuals who have indicated that they would like to make public comments.

Each of these individuals are either representing themselves or other organizations. As you make your presentation, I would like for you to identify yourself and the organization that you are representing. You will have ten minutes to give your presentation. We are going to try to stick to that schedule.

The first presentation is by Elizabeth Lane representing Pharmakinetix Laboratories.

MS. LANE: Thank you. Good afternoon. I am employed by Pharmakinetix Laboratories. What you are hearing today is my opinion. I thank you for the opportunity.

I am very interested in the development of these possible new metrics for comparing drug products in bioequivalence comparisons. I was thinking about that. We have AUC zero to infinity. This explicitly represents extent of absorption. In comparative bioavailability

1 studies, we allow that day-to-day subject variability in
2 oral clearance may muddy the comparison of AUCs but it still
3 is a fair representation of the relative fraction absorbed
4 or extent of absorption.

5 The other metric we have been concerned with,
6 Cmax, has been examined for its strengths and weaknesses as
7 a representation of rate or rate constant of absorption. It
8 has been found wanting. But this finding has been based on
9 explicit model-based relationships. Maximum concentration
10 depends on extent of absorption and elimination-rate
11 constant as well as absorption-rate constant.

12 Now, a new metric has been discussed. Partial AUC
13 is proposed for early exposure. I have a few questions
14 about that metric really based on the same way we have been
15 able to think about Cmax and AUC zero to infinity. How does
16 this partial AUC explicitly represent characteristics of the
17 formulation? How does day-to-day variability in subject
18 biochemistry and physiology affect our ability to make a
19 product comparison with this proposed metric? Just what do
20 relative partial areas test when a comparison of two
21 products is being made?

22 DR. TAYLOR: Thank you for those comments.

23 The next presentation is by Laszlo Endrenyi who is
24 representing himself. If that is not correct, you can
25 correct me.

1 DR. ENDRENYI: The program and the details of this
2 meeting have changed from what was posted on the Internet so
3 I have also modified my presentation.

4 [Slide.]

5 First, I would like to talk somewhat about
6 exposure. It has been a controversial issue that
7 bioequivalence metrics are representatives of therapeutic
8 surrogates which serve as measures of pharmaceutical quality
9 control. In representing therapeutic surrogates, what is
10 important is the clinical relevance, that the study be
11 performed on a target population and under clinically
12 relevant conditions.

13 If it is a quality-control measure they would be
14 interested in, then they are interested in sensitivity, high
15 statistical power. For these reasons, they would like to
16 conduct the study in healthy subjects under sensitive
17 conditions. But this is a difficult issue, controversial
18 and there is wide disagreement about it at almost every
19 meeting.

20 But bioequivalence, or not, this is coming up. It
21 is an issue for clinical trials and not just for
22 bioequivalence.

23 [Slide.]

24 In the case of bioequivalence, there are various
25 measures, various procedures, which are on one side or the

1 other. For example, multiple dosing is more relevant
2 clinically whereas single drug administration is more
3 sensitive. Using a target population is clinically
4 relevant. Healthy subjects are used because of higher
5 sensitivity that can be achieved.

6 Similarly, the discussion of exposure versus rate,
7 or Cmax versus AUC as measures are, again, two sides of the
8 coin. I think what I would like to emphasize here is that
9 those starred items are essentially preferred by FDA; a
10 single administration, the use of healthy subjects, the use
11 of exposure and Cmax.

12 What I would like to urge is a need for
13 consistency on one side or the other.

14 [Slide.]

15 For example, a case can be made for quality
16 control because this being the only occasion, bioequivalence
17 testing when the new drug formulations are being approved.
18 On the other hand, Dr. Gerhard Levy consistently argued for
19 the clinically relevant viewpoint. So I urge consistency.

20 On the matter of early exposure, partial AUC has
21 been recommended. On the other hand, there have been other
22 procedures presented, described, and some of these, such as
23 suggested by Macheras, are more powerful. This comparison
24 has been described in a recent paper in Pharmaceutical
25 Research so, perhaps, there is room for other

1 considerations.

2 [Slide.]

3 Turning, now, to individual bioequivalence. We
4 simulated crossover studies on the assumption of complete
5 bioequivalence including no interactions, sigma being zero.

6 [Slide.]

7 Here is the comparison of the simulated results on
8 top and those are the FDA data. In this case, the
9 estimation was by the old-fashioned REML, the maximum
10 likelihood procedure. But what I would like to draw your
11 attention to--first of all, the similarity of the patterns.
12 Secondly, indeed the outcome is, in both cases, biased. But
13 you notice the pattern of the estimated interaction with the
14 estimated intrasubject variation.

15 Therefore, we believe that it is very difficult to
16 say that a single value such as 0.15 would represent excess
17 or high subject-formulation interactions.

18 [Slide.]

19 But these are just simulations. On the top, the
20 fixed intrasubject variation. You notice that the spread
21 increases. At the top, you notice the true intrasubject
22 variation is presented. On the bottom, the estimated
23 intrasubject variation is shown.

24 But, in both cases, you see--especially on the
25 bottom--that the 0.15 level is easily penetrated at higher

1 variations.

2 [Slide.]

3 These are still warm. These are simulations with
4 the method of moments. In this case, the estimates of the
5 interaction are almost unbiased. On the other hand, there
6 is still the increasing spread.

7 [Slide.]

8 Here is stated for the average being close to
9 zero. Now, they used the method of moments but the spread
10 rises with increasing intrasubject variation and fairly
11 dramatically so.

12 [Slide.]

13 So, conclusions--our conclusions, at least--about
14 the interaction component, that if we estimate it by the
15 maximum-likelihood procedure, then it is biased. Both the
16 bias and dispersion--and I emphasize--rise in proportion to
17 the intrasubject variation.

18 In the case of estimation by the method of
19 moments, the dispersion, again, rises in proportion with the
20 intrasubject variation. Therefore, at least we conclude
21 that a constant level of sigma D such as 0.15 cannot
22 indicate the substantial subject-by-formulation interaction.

23 [Slide.]

24 Now, the other observation was the similarity of
25 the simulations and the FDA data, the patterns. Therefore,

1 we conclude that the FDA dataset is, in fact, compatible
2 with the hypothesis of no interaction. Now, this is based
3 on the maximum likelihood estimation.

4 Actually, at present, at least, there is no real
5 evidence for the high prevalence of the high interaction
6 and, therefore, the concern calling for the study of
7 individual bioequivalence is, at present, not supported.
8 Therefore, we raise the question whether widespread
9 prospective studies are justified in the absence of any
10 evidence.

11 [Slide.]

12 In terms of the experimental design, I would like
13 to focus on the high-variability drugs. We recognize, I
14 think, in practically all of them, that scaling is at least
15 one procedure that you can have. Scaling is based, in
16 principle, on the estimated sigma WR. That is the
17 intrasubject variation of the reference formation.

18 But, in practice, the procedure that could be
19 applied by two-period ANOVAs is interaction is not important
20 and there are questions about the prevalence in identifying
21 different intrasubject variance when they are estimated. It
22 is not a trivial question.

23 So, in practice, we believe that this procedure,
24 scaling, should be urgently applied in any of its forms
25 because it would have both the agency and industry. This is

1 a crying need at present. And it doesn't matter which
2 procedure is applied. For an interim period, it will help.
3 The procedure can be modified later.

4 Thank you.

5 DR. TAYLOR: Thank you for your comments.

6 The next presenter is Michael Spino from Apotex.

7 DR. SPINO: Thank you, Mr. Chairman. I appreciate
8 the opportunity to address the committee.

9 [Slide.]

10 The stated basis for individual bioequivalence
11 relates to switchability. It was based on the theory that
12 the absorption in some subjects of one brand may, in fact,
13 differ from what is found in another brand even though
14 average bioequivalence says that the products are
15 bioequivalent.

16 The basis of establishing that this was a problem,
17 we were told, was the detection of subject-by-formulation
18 interactions in the FDA studies. I, and I guess a number of
19 others, have had substantial criteria concerns. One of the
20 questions was already raised this morning in the committee
21 and that is what is the scientific basis for choosing the
22 value of 0.15.

23 Laszlo, I think, just pointed out that, perhaps,
24 that is seriously up for question based on his modeling
25 approach. With a high within-reference or a high within-

1 test variability, could this so-called subject-by-
2 formulation interaction of sigma D 0.15 not occur by chance
3 alone?

4 On a scientific basis, I submit that the dataset
5 proposed by the FDA, which are presented as support of
6 individual bioequivalence, are unconvincing at the very
7 least. In fact, based on data analysis that I will show you
8 in a minute, it appears that the apparent subject-by-
9 formulation interactions are due to drug, not product,
10 formulation variability or due to chance alone.

11 On March 2, FDA did release their original dataset
12 from which they drafted the IBE guidelines, the basis for
13 it, and this was reviewed immediately by one of our
14 scientists at Apotex. At that time, there were twenty-one
15 datasets from nine studies. We have heard today that there
16 are twelve now.

17 The large subject-by-formulation interactions were
18 reported for AUC for eight datasets and five studies but, in
19 fact, when we analyzed this, we found that none of them were
20 significant for AUCT; that is, none were less than 0.15 for
21 the p-value.

22 There were large subject-by-formulation
23 interactions indicated for Cmax but, once again, there were
24 no Cmax interactions that were significant.

25 [Slide.]

1 I shared this with the main statistician
2 supporting FDA on this and the response was that studies
3 were not designed to test this. Therefore, they didn't have
4 a large enough "n" and, therefore, may not, necessarily,
5 have a significant subject-by-formulation interaction.

6 My question is, we are dealing with a statistical
7 process and we do not have to prove, on a statistical basis,
8 that it is significant. Justification for IBE was raised in
9 the June DIA meeting of 1997. It was suggested to establish
10 that there is a need to change the current methodology.

11 One should be able to demonstrate, as has been
12 said in this committee meeting, that a problem exists in
13 switching generic products using current methods. But the
14 current dataset does not satisfy this requirement as an
15 apparent subject-by-formulation interaction could be due to
16 the variability of disposition of the drug, itself, or by
17 chance alone, as we have already said.

18 [Slide.]

19 There seems to be a fundamental failure to
20 appreciate that the brand is not identical in the same
21 individual on different occasions. This has already been
22 demonstrated very often. It is predictable
23 pharmaceutically.

24 [Slide.]

25 Today, we heard that this issue for some of the

1 datasets proposed by FDA were related to estrogens--I
2 assume, conjugated estrogens--and calcium channel blockers.

3 We have done a number of studies with a brand on
4 the same subject on different occasions under very highly
5 controlled conditions. We revealed a high level of day-to-
6 day variation with the same brand in the same subjects on
7 different occasions.

8 This suggests that maybe that lots of the brands
9 adverse effect not switchable with itself if we apply the
10 concept that has been proposed for IBE.

11 [Slide.]

12 Just to summarize those data on subjects who were
13 studied with the brand on more than three occasions. We had
14 fifteen subjects in the fasting condition and the ratios for
15 those individuals for the AUCs, the total amount of drug
16 absorbed up to time T which, I believe, in this case was
17 24 hours, the ratios were 1 to 1.88.

18 In the fed situation, it was 1.12 to 2.05. When
19 you combine the fasting and fed, there were eleven subjects
20 and that was 1.03 to 3.29. Clearly not reproducible.

21 [Slide.]

22 The relevance of all of this is, should we move
23 from the current average bioequivalence to individual
24 bioequivalence and have to do replicate designs, our
25 estimate of the in-house cost--and these are Canadian pesos,

1 not American dollars--we would be dealing with, roughly, a
2 doubling of the cost of conducting a study in the same
3 number of subjects.

4 [Slide.]

5 This is on the basis of what I believe is a
6 failure to demonstrate a significant difference between the
7 two methods or at least the one is the more sensitive than
8 the other. To Apotex, that would translate into an
9 additional \$10 million to \$12 million per year.

10 [Slide.]

11 Resource conclusions? The individual
12 bioequivalence approach to bioequivalence studies will
13 result in a massive increase in cost and much greater
14 complexity leading to failure due to non-formulated-related
15 issues--that is, will fail by chance increasingly. And, as
16 a result of a longer time, there will be fewer ANDAs
17 submitted impacting the American public in their costs.

18 [Slide.]

19 Regulatory decisions, I believe, should be based
20 on scientific validity and include a cost/benefit
21 consideration. Since the case demonstrating the need for
22 IBE is weak, at best, and since the current approach seems
23 to have some critical flaws including a lower degree of
24 confidence in the bioequivalence decision--that was
25 presented at another time, not today--then the current

1 projected costs and business ramifications, in my opinion,
2 cannot be justified.

3 [Slide.]

4 Today, we were presented with two important
5 concepts by Dr. Williams. The first was that regulatory
6 decisions should be driven by good science. Secondly, we
7 should try to decrease the regulatory burden where possible.
8 But, the scientific analysis of these very data submitted
9 fail to support the need for the IBE concept and the IBE
10 approach, as I have indicated, would double the regulatory
11 burden.

12 [Slide.]

13 I propose that we terminate further resource
14 expenditure on the attempts to further justify individual
15 bioequivalence or, if for some reason, that is
16 inappropriate, then I suggest that the FDA, if they are
17 still convinced of the need for IBE on the basis of
18 anecdotal evidence, then they need to conduct a study to
19 demonstrate that the new method is justified and has
20 increased sensitivity without the loss of selectivity.

21 Any method must provide evidence to demonstrate
22 equivalence of truly bioequivalent products which contain
23 highly variable drugs without requiring the use of even more
24 subjects.

25 Thank you.

1 DR. TAYLOR: Thank you for your comments.

2 To the committee, are there any comments you would
3 like to make at this time relative to the comments that we
4 have heard?

5 If not, then we will proceed with the special
6 topics according to the agenda. Issue No. 1 is the need for
7 multiple-dose studies. Dale Connor will be making that
8 presentation.

9 **Special Topics**

10 **Need for Multiple-Dose Studies**

11 DR. CONNOR: Good afternoon.

12 [Slide.]

13 I think this is among the many very exciting
14 topics. This is one that is quite exciting to me and is
15 likely to be quite controversial. It is likely to make me
16 both many friends and many enemies when I kind of present
17 this.

18 But I have titled this with a question; are
19 multiple-dose BE studies really needed. It is something
20 that many of us have been pondering for a good while in that
21 we, in certain circumstances which I will go into in a
22 second, tend to do multiple-dose bioequivalence studies on
23 certain types of products.

24 The real question that we have to examine every
25 once in a while is is what we are doing necessary because

1 these are extra studies that sponsors have to perform and we
2 really need to critically evaluate are these things
3 fulfilling a need.

4 [Slide.]

5 Just a brief regulatory history. This is, by no
6 means--I can't compete with Don about the length of time
7 that I have been at the FDA, but this is more than a
8 history. It is kind of a couple of references that are
9 important in this.

10 The first and foremost laid out what we understand
11 today as the current policy as far as doing types of studies
12 for BA and BE is the 1984 Division of Pharmaceutics
13 Guideline--then they were called guidelines--of the
14 evaluation of controlled released drug products.

15 This is a document that mainly referred to the NDA
16 world and kind of laid out, for everyone, what the
17 expectations were for establishing BA for the NDAs.
18 Subsequently, in 1993, and you could look at this both as a
19 separate document and, also, as an extension or expansion of
20 the original document, a document was produced, the oral-
21 extended or controlled-release dosage forms, in vivo
22 bioequivalence testing and in vitro dissolution testing.

23 This, among other things, laid out what was
24 expected for BE studies for the ANDA, or generic world.

25 [Slide.]

1 Just to quickly go over something I'm sure most
2 people are aware of, for modified-release products, the
3 current studies that we ask for and expect from ANDA
4 applicants--and remember, this is generic or the ANDA world
5 I am talking primarily about now--is a single-dose fasted
6 study.

7 I think we rightly consider this the most
8 discriminating test. Other people who have spoken today
9 have kind of alluded to that. For other reasons, we ask for
10 a single-dose fed study to make sure that the effects of
11 food on the proposed formulation is the same as the
12 reference listed drug.

13 Finally, what we are here to talk about today, a
14 multiple-dose or steady-state study.

15 [Slide.]

16 What I have in this slide and the next one is kind
17 of a grab-bag of possible reasons for doing a multiple-dose
18 study. This comes from a variety of different sources
19 including the CFR as well as what I would jokingly consider
20 the current wisdom. By that, I mean that I went around to
21 people that have been doing bioequivalence reviews or
22 setting policy for a long time and I said, "Give me all the
23 reasons you can think of, even if they are kind of shaky,
24 about why we do these studies."

25 So you go from reasons that are kind of quickly

1 dismissed to, perhaps, ones that are not so easily
2 dismissed. Not really in order, but I tend to have the
3 easily dismissed ones up at the front.

4 The first one that I was given was kind of an
5 interesting one. They said, "Well, we need to see if there
6 is dose-dumping at steady state." If you really consider
7 the phenomenon of dose-dumping where the formulation
8 unexpectedly--a modified-release formulation which has,
9 relatively speaking, a lot of drug in it that is supposed to
10 be released gradually over a large period of time, if it
11 dumps its dose all at once, that is, generally, considered a
12 bad thing.

13 However, when this happens, generally, it is when
14 the dosage form is stressed--say, when it is given with
15 food--or it is isolated events. So it is hard to think
16 that--again, people may disagree with this--it is hard to
17 think of these as a function of steady-state dosing since
18 this phenomenon would probably be kind of isolated events
19 likely to happen at every dose or at a single dose, equally
20 likely.

21 So, this one I kind of dismissed and, of course,
22 people may disagree with me on that, but I see this dose-
23 dumping as isolated events that are not--it is hard for me
24 to see how chronic dosing would affect that.

25 The second one was kind of almost--I wouldn't

1 quite say it was silly, but almost silly. What someone gave
2 me, "Well, an immediate-release is not only the input
3 change; there is a different apparent half-life." As a
4 pharmacokineticist, that seems a little silly to me because
5 what you are really referring to there is, in some cases
6 where the input rate of the process--and pharmacokineticists
7 are well aware of this--is close to or slower than the
8 output.

9 You get something that pharmacokineticist calls a
10 flip-flop model so that what we usually look at as the
11 terminal elimination rate is actually, because of, really, a
12 pharmacokinetic artifact, a representative of the input rate
13 instead of the output. This is more or less a
14 pharmacokinetic output not a real reason to do multiple-dose
15 studies.

16 A very pragmatic one that is always brought up is
17 there are certain cases where the assay technology is not up
18 to snuff as far as measuring the appropriate sensitivity of
19 plasma concentrations that one gets from a single-dose
20 study.

21 This is actually pretty pragmatic. Sometimes it
22 is difficult. This is, I think, even more true in the NDA
23 world where we are dealing with a relatively new compound
24 and assay development hasn't progressed to be able to
25 measure that.

1 So one of the ways of dealing with inadequate
2 assay sensitivity is you just give the drug up to steady
3 state and, of course, the plasma concentrations are higher
4 and so they are easier to measure.

5 I think this can be dealt with in other ways,
6 perhaps using single-dose studies with multiple dosage
7 units, higher doses and, often, if they exceed the
8 recommended label dose, those might have to be done under an
9 IND. But it still doesn't say that the only answer to this
10 is to do a multiple-dose study.

11 Another one is better measures of drug-level
12 fluctuation between the two products. Again, that refers to
13 the C_{min} issue that has been talked about. Even though we
14 could possibly predict from a single-dose level what the
15 C_{max} is because we measure it and, certainly, with a linear
16 drug we can extrapolate to that, how sure are we that the
17 minimum concentration at steady state is also going to be
18 equivalent between two products.

19 That sounds good but I will show you a simulation
20 later on that may cast some doubt on that.

21 [Slide.]

22 Here is what I consider a mostly theoretical, but
23 it would probably be a compelling, reason to do multiple-
24 dose studies. It was brought up that excipients that exist
25 in one product but not in the other might affect the

1 absorption and/or the subsequent disposition over time

2 I put over time at the end because it is
3 conceivable--Ajaz has been doing quite a bit of work on
4 this--we could conceivably find an excipient that would
5 affect the absorption or disposition of a product. But if
6 it was an acute effect, the single-dose study would likely
7 pick that up.

8 So the only compelling--and I think it is a
9 current theoretical--is that if that excipient had really
10 required multiple dosing to see the effect. So that would
11 cut a very low-incidence event down to an even small one and
12 that excipients that affected it acutely probably would show
13 up in the single-dose.

14 Finally, one of the most frequently cited reasons
15 for doing multiple-dose studies is if we have non-linear
16 pharmacokinetics so that we might see a very different
17 answer, as far as bioequivalence goes, when the plasma
18 concentrations increase and the product is dosed at steady
19 state versus a single dose.

20 This is, I think, one of the harder things to
21 argue against, at least on the face. But I think one has to
22 consider there are several types of nonlinearity and I have
23 simply broken them down into two. There is input
24 nonlinearity and there is elimination nonlinearity which may
25 have very different effects.

1 So this is, on the face of it, the hardest thing
2 to argue against but I think if you really think carefully
3 about it, even if this were true, there may be other ways to
4 control this. The way I think about this is when you reach
5 a nonlinear range, the difference between products,
6 difference in release, the effect would be magnified in some
7 way.

8 So one can either control it by actually studying
9 at steady state or, if you really believe that is going to
10 happen, an alternative view might be to do a single-dose
11 study and just have a tighter criteria to control for that
12 kind of increased difference or apparent difference in
13 products.

14 So this is probably the most interesting to
15 discuss in this area.

16 [Slide.]

17 Why do we not want to do multiple-dose studies or
18 what are the things that I think are probably bad about it.
19 Obviously, they are expensive. They are time-consuming.
20 They may unnecessarily expose subjects to drug testing.

21 If we, as a regulatory agency, become eventually
22 convinced that a test is unnecessary, then we really cannot,
23 in good conscience, expose subjects to increased testing
24 that we have come to the firm conclusion that it is
25 unnecessary.

1 Finally, in most cases, my contention or working
2 hypothesis is these studies are insensitive to differences
3 in products. I think that is quite true for linear
4 pharmacokinetic drugs and still arguable for nonlinear
5 drugs.

6 [Slide.]

7 I am going to show you a few graphs based on
8 simulations. I thank Dr. Tom Tozer for providing these.
9 These are all based on drugs with linear pharmacokinetics so
10 it is the simplest possible case. Since I have limited
11 time, I didn't really try and do the much more complicated
12 case of nonlinear.

13 But just to give you an idea. These simulations
14 are modified-release-dosage-form linear pharmacokinetics.
15 We see here he has displayed--on the X axis, we look at the
16 theoretical input of two products, the T being test and R
17 being reference and a factor of 10 on either side, one being
18 that the products are identical. The left side of the test
19 product is one-tenth of the input rate, so the furthest to
20 the right is ten times the input rate. So that is quite a
21 wide range of difference between the products.

22 As you will see, the simulation that he has done
23 shows that the multiple-dose study which is shown on the
24 dotted line really doesn't vary all that much over this
25 quite range of difference. The conclusion one might draw

1 from that is that it is somewhat insensitive over the range
2 of very large differences to show those differences.

3 In the single-dose study, which is the solid line,
4 compared to the multiple-dose study, you see quite a change
5 over this large difference. Of course, at X equals 1, they
6 should, if everything is working correctly--the ratio should
7 be 1 as well. You see that, apparently, is so on the graph.

8 So this is simply a simple illustration of a
9 simple case to illustrate the fact that multiple-dose
10 studies, at least for linear drugs, are insensitive to
11 showing differences and may, indeed, call two very different
12 products the same whereas single doses are less likely to
13 make that error.

14 [Slide.]

15 Again, a somewhat similar slide, showing T_{max}.
16 Again, I think it is known, at least for linear drugs, that
17 T_{max} is sometimes kind of compressed or blunted when you
18 give drugs to steady state or in multiple doses. Yet here
19 you see where I have the T_{max} varies over that same scale
20 from very small to very large.

21 As you see, the single dose changes quite a bit
22 over that range where the multiple-dose comparator leaves
23 almost a straight line across showing a lack of sensitivity
24 to determine differences in T_{max} is you believe T_{max} is an
25 indicator of rate.

1 [Slide.]

2 Finally, quickly, this is one he did to attempt to
3 answer the question of what about C_{max} and C_{min} , how much
4 sensitivity, or apparently sensitivity, do you get by doing
5 a steady-state study where products are really different.

6 Again, you have seen the C_{max} --not seen them side-
7 by-side, but this is the same curve you saw before for C_{max}
8 and now he has plotted, also, C_{min} . Only in very large
9 differences do you see any real sensitivity. The curves
10 don't really change that much at multiple dose.

11 So the conclusion of all these, and, again,
12 remember that this is a simple case, a linear drug, is that
13 you really see the multiple dose compared to the single dose
14 shows very little sensitivity to look at differences and may
15 do what is bad for me as a bioequivalence person--may
16 actually tell us that two products are equivalent when they
17 are truly not.

18 [Slide.]

19 So, for discussion, I will restate the question,
20 are multiple-dose bioequivalence studies needed for
21 modified-release products. Just a list of possible answers;
22 our conclusion, after all this discussion, is yes, it is
23 probably a good idea to do multiple-dose studies for all of
24 these products which is, essentially, what we do now, with
25 some exceptions.

1 The other extreme is no, they are completely
 2 unnecessary, I don't see any reason for it. And there is
 3 the middle ground where no, we can probably get rid of some
 4 of the types of studies but there are some cases or types of
 5 products or types of situations where we would really want
 6 to have that multiple-dose study.

7 So I look forward to your discussion, although we
 8 don't actually have that much time for it. But we will
 9 probably be discussing this again.

10 Thank you.

11 DR. TAYLOR: Thank you.

12 **Committee Discussion**

13 DR. TAYLOR: The committee now can discuss this
 14 presentation.

15 DR. BRANCH: In the non-linear kinetic part of the
 16 discussion, you raised this as a potential area of interest.
 17 Is there any evidence to support the idea that your measures
 18 of bioequivalence actually change if you are in different
 19 parts of a nonlinear curve?

20 DR. CONNOR: I am not sure that I am answering
 21 your question, but the way I conceive of--and now I am
 22 talking mainly about nonlinearity of elimination, which the
 23 case may be different if you are talking about nonlinear
 24 absorption.

25 The way I conceptualize it, and people that are

1 more intelligent about these things, like Dr. Endrenyi, may
2 want to correct me, but the way I look at it is, as you
3 reach the nonlinear portion of the kinetics, as
4 concentration increases, that small changes which, in a
5 linear drug would be linear all the way through the
6 concentration rates, now appear much larger than they would
7 if it were a linear drug.

8 So it kind of amplifies the difference. That is
9 important because that will also result in--usually, drugs
10 are used under those conditions or used at those
11 concentration ranges. So it is an important thing to know.
12 Even though there is an expansion of the difference, that is
13 an important thing to know because that may lead to true
14 inequivalence of nonswitchability of products in their
15 method of us.

16 So it is important to account for that. But the
17 question is is a single-dose study sufficient, even in those
18 situations, with proper controls on it, to predict that and
19 to account for that blowup, if you will, of difference of
20 that magnification of difference.

21 That is just how I conceptualize it which is, I
22 think, kind of a simplistic way. So one of the alternatives
23 to just doing the multiple-dose study and studying the
24 phenomenon, if you know it is a nonlinear drug, you could
25 simply do a single-dose study and tighten up the criteria to

1 account for this, to control the difference.

2 DR. BRANCH: But if you take the point that these
3 are cumbersome studies to do, if a single-dose study will
4 suffice, it is a heck of a lot easier to do that.

5 DR. CONNOR: yes.

6 DR. BRANCH: Presumably, you do have some points
7 of comparison of data already in hand to be able to say, are
8 you adding value by going to multiple dose.

9 DR. CONNOR: Yes.

10 DR. BRANCH: The best way of evaluating that is to
11 be able to say what actually helped in making the decision.

12 DR. CONNOR: We haven't done it in probably as
13 organized a fashion as we should have, but, obviously, we
14 have a lot of data in our files where, since we have been
15 asking for most products for quite a few years, I think what
16 we probably should do is put together--go through our files
17 and look at how many of these studies actually contributed
18 anything that we wouldn't have known if we didn't do the
19 study.

20 My sense is, from the ones that I have looked at,
21 that, in very, very few cases, does a multiple-dose study
22 add anything different, or different insight, than what we
23 have seen from the single-dose study. That doesn't mean
24 there aren't isolated cases where somebody failed the
25 multiple-dose and passed the single-dose. I am sure we

1 could find cases of that but they are in a very small
2 minority.

3 DR. LAMBORN: You have presented, sort of, some
4 questions, but what are your specific next steps that you
5 are planning to take. For example, it was just asked if
6 there had been a systematic look at the datasets.
7 Obviously, there is the potential here in your choice which
8 is maybe we need them for some and not for other classes.

9 DR. CONNOR: Right.

10 DR. LAMBORN: So how are you specifically going to
11 be trying to hone in these to come up with a recommendation.

12 DR. CONNOR: We have been doing and need to
13 probably do more of the simulation work which I have shown
14 you just the start of. People have done already some
15 simulations but it needs to be brought over in a consistent
16 fashion, more of the same, especially for nonlinear drugs.
17 I really have little doubt at all that, for linear drugs,
18 simple modified-release dosage forms, that multiple-dose
19 studies are not needed.

20 I believe, although I don't have as much in my
21 hands to prove it, that probably most of the time nonlinear
22 drugs don't need multiple-dose studies as well. But I
23 probably need to pursue both simulations and actual data in
24 our files and put together a package that either confirms
25 that or says that there are some, probably, limited types of

1 drugs or products that we need to do it in.

2 So that is pretty much the next step, I think.
3 But it really was important to get out as a point of
4 discussion to get some input from you.

5 DR. BRAZEAU: One are the other possible reasons,
6 you said, would be excipients that could change the
7 absorption or disposition over time. Do you have any
8 particular excipients that you are thinking about?

9 DR. CONNOR: Ajaz is hiding behind Doug Sporn, but
10 most of that work is being done under the direction of Ajaz
11 Hussain. That is one of his major areas of interest right
12 now is excipients and especially how excipients affect
13 products and disposition--

14 DR. BRAZEAU: So you are talking about, like,
15 surfactants which could change GI permeability and things
16 like that we might see.

17 DR. CONNOR: Right. Again, for this particular
18 topic, to stress again, it is not only enough to find an
19 excipient that affects, say, absorption but if it affects it
20 acutely, all it has to do is be there at all, in one dose.
21 You really don't need the multiple-dose study.

22 The multiple-dose study would only be for
23 excipients that might have an effect, or where you would
24 only see the effect, after multiple dosing, say generating
25 enzymes or proteins or taking some time to come to some

1 steady state to actually see an effect.

2 That would be even a small subset of excipients
3 which might have an effect. So I think it is theoretically
4 possible and we may actually find one, but to fit that
5 criteria, I don't know of any right and--Ajaz can correct
6 me, but I don't think we have found any that fit that
7 criteria.

8 DR. STEWART: In those single-dose steadies where
9 assay sensitivity is a problem, what are people doing to
10 over come that?

11 DR. CONNOR: A variety of different things.
12 Obviously, it is very easy to say, well, just go back to the
13 lab and develop a better assay. But that is not always
14 easy. Most of the time--you know, I have also been involved
15 with the new drugs area, new drugs review, and I saw this
16 much more frequently, I think, where you have a new chemical
17 entity. It has probably only existed for a couple of years
18 at most and it may be difficult to measure.

19 For NDAs, sometimes sponsors will come in and say,
20 "Look; I have done everything I possibly can. I can't
21 measure it. So there is a bit more flexibility to get the
22 kind of bioavailability information that one requires for an
23 NDA by altering the doses or things like that.

24 Most of the time, when we see a drug in generics,
25 the drug has been out for quite a few years and people have

1 had time to work on assays. So it is not as much of a
2 problem for ANDAs although there are still some drugs with
3 assay sensitivity problems.

4 But the possibilities are to somehow get the
5 plasma concentrations up higher so you can measure a
6 complete profile. Now, you can do that by giving steady-
7 state concentrations which, if it is a drug that
8 accumulates, it will be higher, or just giving higher single
9 doses. It is a question of--the only limitation on that I
10 mentioned is if you say, "I am going to do a single dose
11 study but I am going to give much higher levels of dose than
12 are accepted in the labeling," then I have to come in under
13 an IND.

14 So that is an additional administrative hoop that
15 has to be gone through. But that is an alternative to doing
16 a multiple-dose study.

17 DR. TAYLOR: Dr. Desmar Walkes, who is our
18 consumer representative, has a question.

19 DR. WALKES: I just had a question about what you
20 were saying. I wasn't quite clear about the notion that it
21 wasn't important to know what happened when people ate as
22 far as dose-dumping goes?

23 DR. CONNOR: No; actually is it quite important.

24 DR. WALKES: Are you basing that on the fact that
25 you are working with a generic and the parent compound has

1 been out for a while?

2 DR. CONNOR: You are talking about food studies;
3 right?

4 DR. WALKES: Right.

5 DR. CONNOR: No. Dose-dumping is extremely
6 important. But the things that tend to cause dose-dumping--
7 and we have had some historical--for example, a few years
8 ago, there was a theophylline product that delivered 24
9 hours worth of theophylline in one dose. It was quite an
10 interesting thing that some university investigators--I know
11 them all personally so I got some of the story--decided that
12 they were going to prove that the bioavailability was
13 decreased when you gave it with food.

14 So they did what is now common, to be very close,
15 just by luck, almost, they came to do what is now the FDA
16 Food Study. Instead of decreasing, it dumped all its dose
17 all at once and caused all of these normal volunteers--they
18 were all fellows and students--to be extremely ill.

19 So, especially for drugs like that, it is
20 extremely important. However, the thing that most causes
21 dose-dumping is putting these modified-release dosage forms
22 in stressful situations. For some types, it is high-fat
23 meals or other types of food or conditions that are out of
24 the ordinary for where it is tested under a fairly
25 controlled environment, like an empty stomach.

1 So it is an extremely important topic but the only
2 reason I brought it up here was that when it dumps its dose,
3 the likelihood of dumping a dose isn't necessarily related
4 to the next dose. It is really kind of an isolated event.

5 So if something is going to dose-dumped with food,
6 it is either going to do it all the time or, if it is a
7 random event, it is randomly likely to happen during any
8 dose. The fact that you got a dose previously doesn't
9 necessarily impact the likelihood of it happening with the
10 next dose.

11 DR. BYRN: One of the possible answers was no
12 except in limited cases. Do we know ahead of time what
13 those limited cases are?

14 DR. CONNOR: No; that is part of the discussion,
15 actually.

16 DR. BYRN: So, from a public-health standpoint,
17 that would almost require it to be done in all cases if
18 there isn't a way that we know it ahead of time.

19 DR. CONNOR: I think that we can, both with what
20 we know about product quality and we know about
21 pharmacokinetics and what we can pull out of the literature
22 and out of our own files, I think we have a body of
23 knowledge where we can make a judgment.

24 However, what we are likely to do is, if we get
25 away from the, "Yes, we require it in all studies," closer

1 to the, "No, we don't require it," a lot of people are going
2 to come in with opinions based on the available data and
3 say, "No. I think you are kind of right but I think, in
4 this situation, you should do it." So those are the types
5 of situations.

6 For example, nonlinear pharmacokinetics; a lot of
7 people, now, still believe, rightly or wrongly, that if a
8 drug is nonlinear, you are going to need a multiple-dose
9 study. So, even if they were to accept our contention,
10 "Well, a linear dose, you don't need it," but, as soon as
11 you had a nonlinear pharmacokinetics, there is a certain
12 percentage of people that really believe that you need the
13 multiple-dose study to show that.

14 DR. BYRN: One of the possible next steps might be
15 to get a decision tree that sort of walked you through all
16 this?

17 DR. CONNOR: My working decision tree is, "No."
18 That is my own belief now. What I am looking for is people
19 to come, in this committee or other ways, saying, "Well,
20 wait a minute. There is this case here, this situation,
21 where you really need it." So we are asking you to modify
22 your extreme view and to be consistent with what we believe
23 is compelling data.

24 DR. BYRN: What I am interested, just to restate,
25 is there might be an answer, "Well, yes; but just in some

1 cases."

2 DR. CONNOR: Yes.

3 DR. BYRN: But then, if we don't know what those
4 cases are ahead of time and we don't have any scientific
5 basis to select those cases, and it is a major public-health
6 issue, then we are going to say, "Yes; we have to do it all
7 the time."

8 DR. CONNOR: I guess it really is a cost-benefit
9 thing. For example, if we come to the conclusion that there
10 is a tiny chance that an excipient is going to fall into
11 this category and maybe we even have one case of it, or one
12 alleged case, and it covers maybe one out of a thousand of
13 the products that we look at.

14 Now, to catch a one-in-a-thousand case, are we
15 going to make everyone else do a very expensive, time-
16 consuming study, and expose a lot of normal volunteers, and
17 sometimes patients, to extra drug testing just simply so
18 that we can catch a one-in-a-thousand or one-in-ten-thousand
19 case. It is the tradeoff of how important you think it is.

20 DR. WILLIAMS: I think the committee really has
21 the sense of this issue but I thought I could say a few
22 words that would amplify how I think the committee might
23 help us. A couple of points. First of all, I would like to
24 thank Dr. Endrenyi for really focussing us in a very
25 interesting way on this issue between the therapist's

1 approach to this issue versus the quality-product approach
2 to this issue.

3 I can tell you, in the agency, we are always
4 struggling with this. I have a feeling probably the
5 committee struggles with it as well, too, periodically.

6 If I were to give one boundary of that, I might
7 say that, in the presence of any change, for both the
8 pioneer and, certainly, a new generic, we would ask for
9 comparative clinical studies. That is kind of that
10 boundary. We all recognize that that is not necessary, for
11 many reasons, although I might say, in the world of complex
12 drug substances, because we are unsure about the impact of
13 the change, that that frequently happens, that the agency
14 says that.

15 So it is not like it is totally off the wall. It
16 actually happens, now, in another environment that I might
17 say is related to pharmaceutical equivalence. So, over the
18 years, based on a lot of good science understanding and our
19 experience and our willingness to rely--we have moved more
20 and more to what I would call the formulator hat or the
21 product-quality hat.

22 I guess if I were to try to answer Dr. Endrenyi, I
23 would say I am always trying to move in that direction
24 because it sort of makes sense. We are willing to rely on
25 systemic exposure patterns. We are willing to rely, maybe,

1 on in vitro in certain settings, et cetera, et cetera.

2 Now, the core issue here, I think, having made
3 those general comments, first of all relates to conventional
4 release. Let me talk about that for a minute. Some of what
5 I am saying you will see in the wording of the draft
6 guidance so we are not only going to search internally in
7 our own records, we can ask the public to comment on some of
8 these specific issues.

9 One of the things I might ask the advisory
10 committee is what should we ask the public to do for us in
11 responding to the proposal in the guidance. But I think we
12 are going to say something like this; for conventional-
13 release products, we distinctly prefer single-dose studies
14 to address the question of bioequivalence.

15 That is sort of our posture, anyway, but I would
16 not want a sponsor to rely on a steady-state study to show
17 bioequivalence for a conventional-release because of the
18 simulations that Dale showed, that it is insensitive to the
19 question that we care about.

20 But I think we are pretty comfortable with that,
21 although I think we could always be swayed by some other
22 argument. But I think the argument would come from the
23 clinician who says, "This drug will be dosed to steady
24 state. Why not dose it to steady state and show equivalence
25 at steady state?"

1 Probably the more pertinent area of focus that we
2 will ask the public for, and maybe we are asking you for as
3 well, is the issue of dropping the steady-state study for an
4 extended-release product in the area of bioequivalence.

5 As the committee well knows, in some ways,
6 everything we do here makes people unhappy. You have heard
7 a lot of unhappiness already about the subject-by-
8 formulation and individual bioequivalence. If we were to
9 drop the steady-state study for modified-release products,
10 we would tend to create concern on the part of the people
11 who sort of wear the therapeutic hats all the time.

12 "You may be satisfied, Roger," they might say to
13 me, "that you tested the question with adequate sensitivity
14 in a single-dose study but I will need to see that extra
15 measure of assurance at steady state to assure
16 interchangeability."

17 I think where that will come up particularly is
18 for drugs that exhibit nonlinear kinetics. We had this
19 debate very vigorously in the center with regard to
20 phenytoin where, in a single-dose study, we saw something
21 like a 5 to 8 percent difference in the measures of
22 absorption and disposition, Cmax and AUC.

23 Of course, then the question became, what would
24 happen to that 5 to 8 percent difference at steady state in
25 people exhibiting nonlinear kinetics. As Dale already

1 pointed out, it could be magnified and so, all of a sudden,
2 you have something that shows equivalence at single dose'
3 and, perhaps, inequivalence at steady state.

4 But, again, I think we can argue that maybe the
5 way to address that problem, as Dale alluded to, is to do
6 single-dose studies and, perhaps, narrow the confidence
7 intervals to disallow substantial differences in means. So
8 it depends on how you want to approach the question to
9 address the public-health concern.

10 What I might argue to the committee, the way you
11 could help us, is help us think of reasons why we would need
12 a steady-state study for a modified extended-release
13 product. If we drop that, what would be our public-health
14 statement to say why were we willing to reduce the
15 regulatory burden?

16 I think that is our question to you.

17 DR. TAYLOR: Any further comments to Dr. Connor's
18 presentation? Then we can move to Dr. Williams' request.

19 DR. BRANCH: Just as a comment, in response to
20 that, I was thinking of one instance where I could imagine
21 that a very small difference in bioequivalence could be
22 magnified, and that is drugs that undergo autoinduction. 4-
23 transretinoic acid is able to induce its metabolism to a
24 very substantial extent.

25 I could imagine a situation where baseline

1 parameters are not necessarily pertinent to what is
2 happening under steady-state conditions.

3 DR. CONNOR: That is possible, but just remember
4 that we are doing bioequivalence. The assumption is that if
5 I have two products that are either identical or very close
6 in their performance, which means the way they release drug,
7 their active substance, from each other, that all the rest
8 down the line will be the same.

9 So if we have two identical products, every
10 strange pharmacokinetic phenomenon that occurs later on will
11 be similar because the drug is getting in at the same rate,
12 if you will, even though that term is kind of out of favor,
13 but to the same amount. So the only time I become concerned
14 is when that downstream phenomenon affects by ability to
15 look at what I am really interested in which is the release
16 of the drug substance from the drug product.

17 Then it becomes a concern because it is either a
18 real phenomenon that I should be concerned about or it is
19 something that just messes up my ability to look back at
20 what I want to look at. So, yes, there are lot of
21 pharmacokinetic phenomena that might happen, but you have to
22 ask yourself the question, if the input rate from two
23 products is virtually the same, the same phenomenon is
24 likely to occur.

25 DR. TAYLOR: Thank you very much, Dr. Connor.

1 Now we would like to have you comment, if you can.
2 Dr. Williams has provided you with a provocative question.
3 I certainly don't know the answer but, perhaps, some of the
4 committee members would like to try to comment on his
5 question.

6 Maybe they didn't understand what you were asking,
7 Roger.

8 DR. WILLIAMS: No; I have a feeling many of them
9 did understand what I was asking.

10 DR. TAYLOR: They usually have a lot to say. Do
11 you want to have one crystallization of it?

12 DR. WILLIAMS: No. I might say it might be
13 something they could all think about because I think we will
14 get the public comments in response to the draft guidance
15 and we can come back to the committee again at the right
16 moment and re-ask the question.

17 I think the committee was very correct in asking
18 us to look at our internal datasets, what is the value added
19 of a steady-state study, as well as conduct additional
20 simulations although I think some of the simulations we
21 showed you already go fairly far in terms of addressing the
22 question, in terms of what is more sensitive.

23 I think it is the single-dose study. And then I
24 would also remind the committee of Mei-Ling's proposal that,
25 for certain drugs--and this may get back to what Dr. Branch

1 was asking for--for certain drugs where C_{min} at steady state
2 is especially critical, we might look at that late exposure
3 metric in a single-dose study.

4 So there are all sorts of ways to mix and match
5 our approaches, but I think the core question is are there
6 any reasons to go to steady state for an extended-release
7 drug product.

8 DR. BRAZEAU: I think there is a public-safety
9 issue, particularly if it is a drug with a narrow
10 therapeutic window and you have a condition where you have
11 got a nonlinear kinetics. There could be a potential
12 problem, I would see. That might go back to there may be
13 certain drugs where it is going to be important to have this
14 done if know about the pharmacodynamics and we have a good
15 feel for what a concentration-response range is.

16 That might be the kind of drug and, if they
17 nonlinear kinetics--you are having a number of criteria that
18 would probably be important. Then I think it would be
19 critical to have a multiple-dose study.

20 DR. TAYLOR: We will try to think that through and
21 come back at our next meeting and maybe you could pose it to
22 us in the agenda so that we could refresh our memories.

23 We will move on now to issue No. 2 and that is
24 biowaivers. Dr. Vinod Shah will make that presentation.

25 **Biowaivers for Lower Strengths**

1 [Slide.]

2 DR. SHAH: A continuation of the second issue that
3 we would like to discuss again for the general guidance is
4 the biowaiver for lower strengths.

5 [Slide.]

6 21 CFR 320.22 indicates that a biowaiver may be
7 granted when the drug product is in the same dosage form but
8 in a different strength and is proportionally similar in its
9 active and inactive ingredients to another product for which
10 the same manufacturer has obtained the approval provided the
11 products meet an appropriate in vitro test.

12 The words here "proportionally similar," have been
13 interpreted by different people in different ways. That is
14 where some of the confusion has been coming up. As we
15 indicated in the morning, the main reason for this general
16 guidance is also to clarify some of the issues, expand and
17 provide the "how to" information.

18 So I would like to define "proportionally similar"
19 in the following terms.

20 [Slide.]

21 There are two ways how we are taking a look into
22 the proportionally similar wording. The first way is to
23 look where all active and inactive ingredients are exactly
24 in the same proportion; that is, all excipients are
25 qualitatively the same and quantitatively proportional

1 between the strengths.

2 What do we mean by that? Let's say if you take
3 the tablet, for example 25, 50 and 100 milligrams, and write
4 down the active ingredients and inactive ingredients, they
5 are all increasing or decreasing in the same proportion in
6 the same ratio as with the active drug.

7 So, in other words, it can be a total mix and it
8 can be compressed into three different strengths of product
9 so all the active, inactive ingredients will be
10 qualitatively and quantitatively in the proportion of the
11 active drug, itself.

12 The second way of looking at it is where the total
13 weight remains nearly the same for all the strengths and the
14 change in the strength is obtained by altering the amount of
15 the active ingredient and one or more of the inactive
16 ingredients.

17 In some cases, where the active ingredient is in a
18 very small amount like, maybe, 1 milligram or 5 milligrams
19 or even below these levels, it is very difficult for the
20 manufacturer to make the tablets differently. Here, what we
21 are indicating is that the total weight of the tablet would
22 remain the same, approximately the same, and the changes in
23 the amount of the active ingredient is compensated by the
24 change in the amount of the inactive ingredients.

25 So, in this case, the excipients are qualitatively

1 the same but quantitatively different between the strengths
2 because it has been adjusted for the strength of the active
3 ingredient. Related to both the forms of proportionality is
4 a certain range of the excipient changes may be allowed
5 without disturbing the allowances for the biowaiver.

6 This range should be based on the ranges specified
7 in the SUPAC IR because all these things are the biowaivers
8 here we are referring to is for the immediate-release or the
9 conventional-release dosage forms. As we indicated in the
10 morning, for all modified-release dosage forms, every
11 strength, you have to do the in vivo studies so there is no
12 waiver in that particular regard.

13 Also, I want to clarify, in terms of the
14 proportionally similar and the proportionalities, the other
15 term which we use is the dose proportionality normally
16 refers to the in vivo or the pharmacokinetic parameters dose
17 proportionality.

18 [Slide.]

19 So, with respect to the biowaivers, we are talking
20 about the following situations. One is the solutions, which
21 is clear from the dosage form, itself. The second one is
22 the immediate-release dosage forms for the lower strengths.
23 Generally, the biowaivers are appropriate for the lower
24 strengths and, in this case, the dissolution studies are
25 done and dissolution profile comparison, and it should meet

1 the f2 criteria that we have discussed before in this
2 advisory committee and also clearly identified it in our
3 diagnostic guidance.

4 For the extended-release dosage forms, or the
5 modified-release dosage forms for the lower strengths, when
6 the release mechanism is seen and for the post-approval
7 changes, it calls for a bioequivalency study. In those
8 cases following the guidance of the SUPAC MI, if there are
9 multiple strengths and the dose proportionality has been
10 established, then a biowaiver for the lower strengths could
11 be provided based on, again, the f2 criteria but it should
12 be following the SUPAC MI guidance.

13 Also, with respect to the beaded capsules,
14 normally the sponsor needs to do the study only at the
15 highest strength and it is assumed that the different
16 strengths are made up of the same quality of the pellets.
17 But the weight is adjusted by the fillers. And, in those
18 cases, the dissolution profile comparison using the f2
19 criteria should be done comparing the different dosage
20 strengths.

21 That concludes my presentation on the biowaivers.
22 Again, what we are trying to do here is clarify under what
23 circumstances the biowaiver could be granted.

24 I will be happy to answer questions from the
25 committee.

1 DR. TAYLOR: Thank you.

2 The presentation is open for discussion by the
3 committee.

4 DR. GOLDBERG: Vinod, I have a question on this
5 question of proportionality. If you have 25, 50 or 100
6 milligram, you could press one at X and one at 4X. It is
7 the same formulation and, of course, it is all dose
8 proportional. But if you compress all four of those, all
9 three of those dosage forms at, let's say, 700 milligrams,
10 there is a change.

11 The change, I think, in the excipients would be
12 greater than that amount allowed in the SUPAC. Would they
13 still be considered dose proportional?

14 DR. SHAH: It has to be exactly proportional or,
15 if you recall on my slide, we said nearly proportional. And
16 then you need to follow the dissolution comparison. If the
17 profile comparison still comes out to be the same, then it
18 would be considered proportional.

19 DR. GOLDBERG: Thank you.

20 DR. TAYLOR: Any further comments for Dr. Shah?

21 DR. BRAZEAU: With respect to your total weight,
22 it says, "total weight remains nearly the same." Can you
23 define what you would classify as "nearly the same?"

24 DR. SHAH: It is very difficult to exactly define
25 what is "nearly the same," but I would say within the ranges

1 allowed on the SUPAC IR guidance, like if you are changing
2 1 milligram of the active ingredient and you don't want to
3 change anything else, so it may be 1 milligram or
4 2 milligrams.

5 So the total weight of the tablet is changing only
6 by the small amount of the active ingredient. That is why I
7 used the word "nearly the same," rather than using the word
8 "exactly the same." So it may be 50 milligrams, maybe the
9 total weight in one case, and in the other case, it may be
10 51 milligrams or 52 milligrams.

11 DR. BYRN: Do we have any evidence or occasions
12 where biowaivers were granted and there were problems?

13 DR. SHAH: Not that I know of. As Dr. Gayle
14 Brazeau pointed out, how do I define "nearly the same." In
15 some cases, people have given the waiver where it is much
16 wider than that or, in some cases, people have said, "well,
17 this is not exactly proportional so we can't give you the
18 waiver." So you go and do the biostudies.

19 So just in order to overcome all these
20 differences, we are trying to put it into perspective.

21 DR. BYRN: But even in those cases right now where
22 they gave waivers that were wider than this, we never saw a
23 problem.

24 DR. SHAH: No.

25 DR. BYRN: The agency never saw a problem.

1 DR. SHAH: No. Exactly. That's true.

2 DR. WILLIAMS: I just wanted to ask--Vinod and I,
3 maybe we have already discussed this, but if you are willing
4 to waive lower strengths if it has the same rate-controlling
5 mechanism, would we be willing to do that for an abbreviated
6 application?

7 DR. SHAH: When you use the word "rate-controlling
8 mechanism," Roger, you are going into the world of modified-
9 released or controlled-release products.

10 DR. WILLIAMS: Extended release; yes.

11 DR. SHAH: Right now, we are saying no. We are
12 saying that every strength of an ANDA has to do a single-
13 dose bioequivalence study.

14 DR. WILLIAMS: I am not disagreeing with what we
15 are going to propose, I hope, but it does seem that there is
16 a little bit of a logical inconsistency there; is that true?

17 DR. SHAH: That's true. I mean, if want to still
18 further lower the regulatory burden, I would be happy to go
19 in that direction.

20 DR. WILLIAMS: I am not saying we should do that.
21 I am just pointing out an inconsistency--not to say the
22 agency always has to be consistent.

23 DR. LAMBORN: Just, again, a point of
24 clarification. As I understand it, this is not proposing a
25 change in what you are currently doing. This is just to try

1 to clarify what you are doing and be more consistent across
2 reviewers; is that--

3 DR. SHAH: That's true.

4 DR. TAYLOR: Thank you very much.

5 I am told that we have to take a break. I think
6 we are ahead of schedule slightly so we could take about a
7 fifteen-minute break and finish the other two presentations
8 and still be out on time.

9 [Break.]

10 DR. TAYLOR: The next presentations are for the
11 final afternoon session. The first presentation involves
12 issue 3 which is metabolite measurement. The presenter is
13 Funmi Ajayi.

14 **Metabolite Measurement**

15 DR. AJAYI: Good afternoon.

16 [Slide.]

17 Over the next few minutes, I will be presenting
18 the views of the Metabolites Bioequivalence Working Group on
19 the issues regarding measurement of metabolites during the
20 assessment of two products.

21 [Slide.]

22 I guess the first thing to bear in mind is what
23 the current regulation says about moieties to be measured
24 during bioavailability and bioequivalence assessment. This
25 can be found in 21 CFR part 320.26(c). It says that the

1 active drug ingredient or the therapeutic moiety or the
2 metabolites be measured for assessing bioavailability and
3 bioequivalence.

4 [Slide.]

5 The main questions that we grappled with are, one,
6 which moiety or moieties should be evaluated when looking at
7 bioequivalence. The second thing is how should we choose
8 that moiety. Should the choice be based on the abundance--
9 that is, the extent of systemic exposure--or the activity--
10 that is the contribution of each moiety to the in vivo
11 effect--or should there be a metric that has both abundance
12 and activity as components.

13 [Slide.]

14 As a prerequisite, we know that there is need to
15 have an adequate understanding of drug metabolism, a good
16 knowledge of the mechanism of the metabolism. We need to
17 know whether it is enzymatic or nonenzymatic and, if it is
18 enzymatic, is it phase I or Phase II. If there is any
19 enzyme system involved, what are the pathways, what are the
20 metabolites involved and what are their activities.

21 The other question is about the interconversion.
22 Do the metabolites go back to the parent or is the
23 interconversion complete or incomplete. For example, we
24 have estradiol. The other thing one can think of is the GI
25 degradation which is something that is very common.

1 Some drugs do undergo nonenzymatic hydrolysis in
2 the GI tract or metabolism or breakdown by the microflora in
3 the GI tract. How do we put all this information together
4 in trying to come up with the moieties that one needs to
5 asses when looking at bioequivalence studies.

6 [Slide.]

7 There are some important considerations. The
8 first one is about the activity. What do we mean by
9 activity in the questions that I posed earlier on? By
10 activity, I mean contribution to in vivo effect. And the
11 contribution is not only towards efficacy but also the
12 toxicity. Do we need to have an idea of the potency of each
13 of these moieties with regard to the efficacy and the
14 toxicity.

15 It is also important to know whether the toxicity
16 reaction is reversible or nonreversible.

17 What about the abundance issue, the extent of
18 systemic exposure. Do we need to have a particular
19 parameter for determining whether the abundance of a parent
20 versus the metabolite is significant? The abundance issue
21 has some analytical components to it and this has to do with
22 the specificity and the sensitivity of the analytical
23 method, especially for determining the metabolites.

24 The good thing is about the fact that recent
25 advances in analysis methodology have made it possible to

1 adequately determine low levels of moieties following
2 administration of a particular drug.

3 The first step that we think is important is to be
4 able to gather some information on the contribution of each
5 of these moieties to individual activity and also to try to
6 determine whether that contribution is significant or
7 important.

8 [Slide.]

9 As a second step, it is important to determine the
10 ability for each of these moieties to be reliably quantified
11 in biologic fluids, especially the blood or the plasma that
12 is used during the study.

13 [Slide.]

14 The question, then, becomes when do we have to
15 measure a metabolite for BE. In trying to come to some sort
16 of proposal on this issue, we came up with a decision tree
17 which we based on the views discussed in previous slides;
18 that is, the activity as well as the ability to be able to
19 determine each of these components in biologic fluids.

20 Also, we based our proposal on the current in-
21 house data that we have seen to date as well as some
22 information from the literature.

23 [Slide.]

24 Here comes the decision tree. The people at the
25 back may not be able to--but I am going to read it out. The

1 first question here is dealing with the ability to define
2 the activity of each of the components. So the question
3 here says are the active components well defined. If they
4 answer is yes, we are asking another question here about
5 where the primary activity resides following dosing. Does
6 it reside in the parent or the metabolite.

7 By "primary activity," we are referring to the
8 efficacy, the wanted effect. If the activity resides in the
9 parent, there is a question about the ability to be able to
10 reliably measure it. So the question here is is the parent
11 quantifiable. And if we can measure it in plasma or blood,
12 then the metabolites will be measured for bioequivalence
13 testing.

14 But if the parent can be quantified reliably, the
15 next question is is the metabolite highly potent. Here we
16 are referring to a few scenarios of cases where the
17 metabolites may have some toxicity effect that is
18 contributing. Here, if the answer is yes, we need to know
19 whether the metabolites can be measured or not.

20 If it cannot be measured, the parent would be
21 quantified or measured for the bioequivalence assessment.
22 However, if one can measure the metabolites, in those few
23 cases where that is a calling, the proposal now is to
24 measure the parent as well as the parent as well as the
25 metabolite.

1 We should realize that this is not a very common
2 scenario, but the situation may arise. And that is why we
3 have this here.

4 So let's go back to where the parent is active.
5 In summary, when the parent is active and is quantifiable,
6 then we measure the parent for bioequivalent assessment. If
7 the metabolite has some highly potent secondary effect to it
8 but is not quantifiable, the parent is measured.

9 However, if we can measure the parent compound,
10 although it has the activity, then we are left with the
11 metabolite. If you go back to the second side of the tree
12 where the activity resides in the metabolite--that is, we
13 have an active metabolite--we need to find out whether there
14 is extensive first-pass metabolite or GI degradation.

15 If the answer to that is no, we need to find out
16 whether the parent is quantifiable. If the parent is
17 quantifiable, then we measure the parent for BE assessment.
18 Although the metabolite has activity, here it is not
19 undergoing presystemic metabolism and so the proposal is to
20 measure the parent because data in-house and literature,
21 information, has shown that the parent is more sensitive to
22 formulation changes and that is the rationale for making
23 that suggestion here.

24 However, if the parent cannot be quantified, then
25 the metabolite will be measured for the assessment of

1 bioequivalence in such a scenario.

2 Let's look at the other scenario where there is
3 first-pass metabolism or GI degradation. We need to find
4 out whether the parent has second reactivity, unwanted
5 activity. An example that comes to mind here is that of
6 terfenadine.

7 If the answer is yes, if the parent has a
8 secondary activity and it is highly potent, we need to
9 measure the metabolite and evaluate the parent for the
10 amount of the parent in the systemic circulation.

11 So, to summarize, for a situation where the
12 metabolite is active, once we can measure the parent, the
13 parent will be used for the assessment of bioequivalence.
14 The only situation where the metabolites will be used for
15 the assessment of bioequivalence is when the parent is not
16 quantifiable, especially when there is no presystemic
17 metabolism or GI degradation.

18 However, when there is presystemic degradation or
19 metabolism or first-pass effect, then the metabolites will
20 be measured for bioequivalence assessment. The parents
21 would be included only in those few cases where the parent
22 has highly potent secondary activity.

23 Thank you.

24 DR. TAYLOR: Thank you very much.

25 This presentation is open for discussion by the

1 committee.

2 **Committee Discussion.**

3 DR. LAMBORN: I guess I just have a logic problem,
4 I think. The concept that if--let's say, for example, you
5 say if a metabolite is highly potent, if it is quantifiable,
6 then you want to measure both and make sure they meet the
7 criteria. But if it is not quantifiable, then you are
8 willing to accept just measuring the parent.

9 Somehow or other, you have given a benefit to the
10 situation where, if somebody does not develop an assay, then
11 they don't have a criteria that they have to meet. It seems
12 to me it is either important, and if you can't do that, then
13 you need to do something else to substitute or it is not
14 important and then it is not important whether or not you
15 can measure it.

16 DR. AJAYI: Actually, I have some bullet points or
17 asterisks on that if you look up there. What we have in
18 mind when we are looking at these is that are some
19 situations where you might be able to monitor the blood
20 levels, just get a few samples wherever you can. They may
21 not be able to do a full profile because of the limitation
22 with the assay, but we, more or less, with recent advances
23 in the methodology, we make it possible for sponsors to have
24 adequate analytical methods for any of these.

25 In most cases, we have interaction with the

1 sponsor before the study is actually carried out. And, at
2 that point, for such cases, we will be able to have an input
3 in the design of the study. So it is not going to be left
4 to the discretion of the sponsor not to actually make
5 efforts to monitor the blood levels for such highly potent
6 compounds.

7 DR. BYRN: How is the analytical method
8 determined, just to continue on with this discussion. For
9 example, is HPLC mass spec required or can people simply use
10 HPLC? Then, a related question, we are talking about BE,
11 bioequivalence. The drug master file on the original, on
12 the innovator, would have some methodology and does the
13 methodology have to be better?

14 Things have changed a lot. There are better
15 methods available. Is the drug master file investigated at
16 all with respect to methodology? I assume not but I am not
17 sure.

18 DR. AJAYI: In most cases, there would be
19 published information on the methodology which, I believe,
20 the generic firms tap into and try to--when they are
21 thinking of making the ANDA products. The other thing is
22 that the methods have been modified from time to time and a
23 summation before, because of the recent advances in the
24 analytical method, we are seeing more of the HPLC/SCMS
25 method.

1 guidance which, hopefully, will go out soon. Funmi, correct
2 me if I am wrong, I think we always encourage sponsors, at
3 the time they do their study, both pioneer and generic, to
4 use the most sensitive and specific assay.

5 DR. AJAYI: That's correct.

6 DR. WILLIAMS: So the burden is on them to stay up
7 to date.

8 DR. TAYLOR: Just to follow up and sort of put
9 this whole thing to bed, is it ever a situation where you
10 actually do allow an application to be presented and
11 approved where you do not have the sponsor quantify a parent
12 compound that is the active compound? According to this
13 decision tree, that is legal, if you look at the decision
14 tree.

15 That implies that there are situations where, if
16 the parent compound is not quantifiable, then you would
17 measure the metabolite and use that as the bioequivalence
18 standard for that drug.

19 DR. AJAYI: In such a situation, that is where you
20 have very low variable, and highly variable, levels of the
21 parent. If you can't quantify it, then we look at the
22 metabolite. I can give you a theoretical scenario which is
23 something that I have been saying before. If you have
24 something for diarrhea, for instance, it is for looking at
25 action in the GI tract.

1 Some of them do get absorbed, but you may not see
2 it as the parent. You may just see the metabolite. You
3 want to assure that the exposure, the extent of systemic
4 exposure following the dose of a particular product is
5 similar to what you see in the next one.

6 It is part of what Roger was saying this morning
7 about the product quality which is not only being looked at
8 in terms of efficacy alone but also you look at the safety
9 part of it.

10 DR. LAMBORN: I guess your example worries me more
11 than it makes me feel good because, if what you are saying
12 is the action is by the parent and is local and you are,
13 then, approving it based on the systemic level of a
14 metabolite, but you still, on that basis, feel comfortable
15 that you have equal efficacy of the parent in the GI tract.

16 I am just trying to make sure I am understanding
17 what you are saying.

18 DR. AJAYI: That is an example that is difficult
19 to really explain. In such situations, things for local
20 action--what you are actually looking at when you look at
21 the extent of systemic availability, part of it is you are
22 comparing how much exposure you get from the dose of one
23 particular product versus the other.

24 DR. LAMBORN: Right; that is a safety issue.

25 DR. AJAYI: That is a safety issue in such a

1 scenario.

2 DR. LAMBORN: But you also have to resolve the
3 efficacy issue.

4 DR. AJAYI: The efficacy issue has to do with what
5 goes on in the GI in terms of the release from the product
6 which is the BA part of it that Roger mentioned in the
7 morning in terms of the product quality. Some of that you
8 do obtain from the dissolution because that is the best you
9 can do in that scenario where you have something for local
10 action.

11 DR. LAMBORN: So you are saying that you would
12 accept in vitro evaluation of equivalence and then the
13 systemic metabolite for the purposes of safety, and that
14 would be considered to be sufficient.

15 DR. AJAYI: Because that is the only thing you can
16 get from such a product.

17 DR. LAMBORN: You can always say you don't have
18 enough and, therefore, you have to do an efficacy trial. We
19 are certainly going to be talking about other circumstances
20 where that is required.

21 DR. WILLIAMS: We can go down a lot of paths here
22 and I have a feeling you could get very complicated. Let me
23 see if I could frame it in a way--and I think Funmi did a
24 very nice job of talking about two key issues. One issue is
25 abundance and one issue is activity.

1 That is a very nice way to frame the debate. If I
2 put on my product-quality hat, I would say I don't really
3 care about activity. I just want a marker of release of
4 drug substance from the drug product. So maybe I could ask
5 the committee this fairly simple question.

6 Let's say I had prodrug that created its activity
7 via subsequent metabolite and, yet, the prodrug was abundant
8 and easily measured. Would you be willing to rely, second
9 question, on the measurement of the parent to assure
10 bioequivalence?

11 DR. TAYLOR: And the metabolite is the active
12 drug?

13 DR. WILLIAMS: This is a simple case. It
14 obviously gets much more complicated, but that is a simple-
15 case question.

16 DR. TAYLOR: In that case, I think you probably
17 would.

18 DR. WILLIAMS: I like that answer, Dr. Taylor,
19 because that speaks to me and I am trying to trend in the
20 direction of a product-quality kind of approach. But the
21 therapist, wearing his hat, would say, "Gee; I just
22 hate that answer."

23 DR. TAYLOR: So you measure both.

24 DR. WILLIAMS: Did I frame it correctly, Funmi? I
25 think your decision tree includes both approaches, both

1 activity and abundance. So your decision tree dealt with
2 both issues. If you answer the question the way you
3 answered it and everybody accepts that, your decision tree
4 could become a lot simpler.

5 DR. AJAYI: Yes.

6 DR. TAYLOR: Any other questions?

7 DR. BYRN: Let's say, in this scenario, that one
8 of the excipients affected the metabolism or an excipient in
9 a product X affected the metabolism of the prodrug and that
10 excipient wasn't in product Y--and we don't even know if
11 there is such an excipient so this is completely
12 hypothetical.

13 But then you would really want to test both the
14 parent and the metabolite because, otherwise, you wouldn't
15 have as much activity in the case where the excipient is
16 interfering.

17 DR. TAYLOR: I think, in that case, you would
18 really be looking at mechanism. The metabolite is not going
19 to appear from nowhere. It has got to come from the
20 prodrug, so there is a dynamics between the prodrug and the
21 metabolite. That is why the question Roger asked me was,
22 "Yes." Which hat am I wearing now?

23 DR. WILLIAMS: I can't think of it.

24 But I have a feeling, Steve, you are postulation a
25 subject-by-formulation interaction.

1 DR. BYRN: Yes. Just to go back--now, I am a
2 drug-product person so, normally, I would lean on the side
3 of it is okay to measure the parent. But let's say there
4 was something--you have a prodrug. It is perfectly
5 bioavailable. But there is an excipient in product A that
6 is in product B and that excipient affects its metabolism and
7 it is the metabolite that is active.

8 Then you have to measure the metabolite or you
9 don't catch it.

10 DR. AJAYI: That is one of the reasons why, if you
11 look at the decision tree, we suggest that if you have a
12 situation where the metabolite has activity and you have a
13 first-pass effect or GI degradation, then you look at the
14 metabolite. You measure the metabolite for bioequivalence
15 assessment.

16 The only situation where we are recommending the
17 parent to be measured, that is where the primary activity
18 resides in the metabolite is when there is no first-pass
19 involvement which means that, in that situation, the
20 metabolite is occurring after absorption has taken place.

21 So it is a secondary step away from the release of
22 the active ingredient from the formulation. In that
23 scenario, the parent will be more sensitive to formulation
24 changes.

25 DR. SHAH: I was going to make a comment on Dr.

1 Steve Byrn's comment. Under the scenario he described, like
2 you have an excipient which is going to affect the
3 metabolism of the prodrug and that means you need to measure
4 the prodrug and the metabolite, you are also assuming, in
5 that case, in this hypothetical case, that the excipient is
6 also absorbed, it goes into the blood stream, and only then
7 it is going to have the effect.

8 You are talking about too many hypothetical cases.
9 I would say that I would rule that out and I would say that
10 if you can measure the prodrug, then just measure the
11 prodrug and it should give you enough information for the
12 bioequivalency estimation.

13 DR. WALKES: Is there ever a situation where you
14 need to measure both the parent and the metabolite, or am I
15 confusing bioavailability and bioequivalence--like with
16 Seldane.

17 DR. WILLIAMS: May I comment? Is it okay, Funmi?

18 DR. AJAYI: That's fine.

19 DR. WILLIAMS: I think Dr. Walkes just brought up
20 a great example which I wanted to bring as the next example.
21 If you take the totally inactive prodrug and the metabolite,
22 that is one case. The next case, I think, is your case and
23 then it is terfenadine. Terfenadine, as we all know--I
24 think it is no longer with us for the reasons that I am
25 going to be talking about--but the primary efficacy activity

1 resides in the metabolite, fexofenadine.

2 The parent has the toxicity and yet it is low and
3 very difficult to measure and, also, highly variable. So it
4 creates another case for your decision tree. What would
5 your decision tree say there?

6 DR. AJAYI: It is actually on the decision tree.
7 That is the situation where the metabolite is active. There
8 is high extensive first-pass metabolism, but the parent has
9 a second reactivity. In that situation, the metabolite is
10 going to be measured for bioequivalence, but there you
11 monitor the parent just in case you have a situation where
12 you have an excipient that is altering the metabolism.

13 Because of the low levels, and because it is
14 highly variable, you may not be able to have the AUCs and
15 Cmaxs that you might want to look at, but, at least, you
16 will be able to monitor and compare whatever levels are
17 obtained following the administration of the two.

18 So the BE criteria would be placed on the
19 metabolite which is the more abundant moiety whereas you are
20 looking at the other for safety reasons.

21 DR. WILLIAMS: So the decision tree survives that
22 example.

23 DR. GOLDBERG: I just wanted to continue what Dr.
24 Shah started, and that is if you do have an interaction
25 between the parent and excipient, then the rate of change of

1 the parent will show up just as well. If either appearing
2 or disappearing is a function of excipient, it will be
3 noticeable.

4 DR. TAYLOR: Let me make a comment. After hearing
5 all this, I am not sure I am more enlightened or more
6 confused. One thing is for sure; the older I get, I realize
7 that one size does not necessarily fit all. I think you
8 need to go back and look at your decision and maybe you need
9 two decision trees, one for drugs that fit in X category and
10 another one for those that fit in Y category.

11 But, to put out a decision tree that creates
12 ambiguity, I think, does more of a disservice than it does
13 help the sponsor.

14 DR. LAMBORN: One more clarification. If I
15 understood it correctly, the far upper-right-hand box which
16 says, "Are the active components well defined; if no, see
17 specific drug guidance," simply means--this would be an
18 example of what you were just referring to. If the active
19 components are not well defined, then this decision tree
20 does not function and we go off to a specific way, how do
21 you handle those; is that correct?

22 DR. AJAYI: That is what I was going to say in
23 responding to that comment. We looked at that and, in fact,
24 the scenario that Dr. Shah brought up is true. You may have
25 situations where an excipient is causing some attrition in

1 the metabolism. You may or may not see it in the parent.
2 It depends on the abundance and it depends on where the
3 metabolism is occurring.

4 If you have a situation where you have a prodrug,
5 a true prodrug, and you have an abundance of about
6 80 percent of the metabolite, and you have an attrition in
7 the metabolic process, to a limited extent, you may not see
8 it because of the fact that we are given room--that window
9 of 20 percent may not be enough to catch what the difference
10 is.

11 That is why we put in something about the potency,
12 something about a safety valve, if you can use that word,
13 for drugs that are very potent, especially when you have
14 some safety issues. If both of them have activity, there is
15 no problem about that. But if you have a situation where
16 there is a secondary unwanted effect, then you want to be
17 able to catch that, especially if something is happening,
18 however low it is, you may be able to detect it. That is
19 where we are always asking for the best method out there for
20 use during the BE studies.

21 So that is the thinking process that goes into
22 that side of the decision tree.

23 DR. TAYLOR: I have thought about your comment and
24 I looked at what you were referring to, are the active
25 components well defined. Then the other, it says, "No; see

1 specific drug items." I can think of very few drugs where
2 the active components really were not well defined.
3 Conjugated estrogens is one such product, of course. I am
4 sure that is why you put that over there.

5 But are there other guidances that are available
6 for specific drug entities where the active components are
7 not well defined? I haven't thought about it long but I
8 would probably say no. So that doesn't help me a whole lot
9 by having that box over here.

10 DR. WILLIAMS: I may be confusing the decision
11 tree, but I think you were talking about the definition of
12 the metabolite activity, weren't you, Funmi?

13 DR. AJAYI: Activity, in general, yes, parent
14 activity as well as the metabolite activity.

15 DR. WILLIAMS: It may not be created in the
16 decision tree just right but I would agree with you, Dr.
17 Taylor, that usually the components in the active moiety are
18 well defined in most cases. Usually, it is a single
19 enantiomer or a racemate or an achiral drug.

20 So I think we really were trying to get the
21 message that it relates to the activity of the metabolite
22 and its abundance. I would argue there it is a little
23 trickier because, a lot of times, when a drug creates a lot
24 of metabolites--I'm sure all of you remember the
25 phenothiazine. It has a lot of metabolites some of which

1 are active and some of which are not.

2 It is very difficult, sometimes, in the drug-
3 development process to truly identify activity. The burden
4 sort of falls to the pioneer but sometimes, for some drugs,
5 it is difficult.

6 DR. TAYLOR: I agree.

7 DR. MAYERSOHN: I think probably most innovator
8 companies would be interested in characterizing quantitating
9 parent and metabolite, assuming they have got some
10 information about the metabolite. That is occurring earlier
11 and earlier, the so-called pre-preclinical programs that are
12 ongoing now.

13 So we learn more about the form of the metabolite.
14 We learn more about the activity of the metabolite. It is
15 probably in the best interest to characterize both. You get
16 area ratios, metabolite to parent. You learn about what is
17 going on in terms of formulation and metabolism.

18 I wanted to be sure I understood your conclusion
19 about the decision tree relative to the terfenadine issue.
20 With terfenadine, if you measured metabolite area, there
21 would be very little change in area if the metabolism was
22 inhibited, a major change in the parent area. Is that in
23 the decision tree? Did I understand that right?

24 DR. AJAYI: Yes. That is that side of the
25 decision tree. That is why it is suggested that the

1 bioequivalence decision would be based on the metabolite and
2 the parent. However, since you can't adequately measure or
3 quantify the parent because of the low and variable levels,
4 you may not be able to pull the regulatory criteria or the
5 confidence interval around whatever you measure. But, at
6 least, you will be able to know whether the level that is
7 obtained following a particular product is similar to what
8 you see in the next one.

9 We know the trigger level and the decision would
10 be made based on that in-house which would be a review
11 issue.

12 DR. MAYERSOHN: Because this is becoming more and
13 more of a problem. I think this happened with a Roche drug
14 a little while ago. It was taken off the market for a very
15 similar reason. I think part of that is going to be
16 resolved with the power in analytical chemistry.

17 In fact, analytical chemists are driving many of
18 us crazy because they have such sensitive, exquisitely
19 sensitive techniques, we don't know what to do with the
20 numbers we are coming up with. So I don't think that is
21 going to be a limiting problem.

22 Vinod, the concern I had about your comment
23 relative to Steve saying it was hypothetical--and this is
24 contentious--but I think the cyclosporine issue with the
25 improved bioavailability in a gel capsule may be the result

1 of 3A4 inhibition in gut. I think this is what Steve was
2 talking about. No? Well, that is why I say it is
3 contentious.

4 DR. BYRN: I wasn't trying to get into this issue,
5 incidently.

6 DR. SHAH: You are measuring the prodrug in the
7 blood and then the question of measuring the metabolite in
8 the blood and that change occurring because of an excipient
9 which means the excipient has to go into the blood stream
10 and then act on the prodrug to generate the different rates
11 of the metabolite.

12 DR. MAYERSOHN: I'm not sure that is true. There
13 are closely linked metabolic processes that may prevail
14 where it could all happen on the first passage through the
15 liver. So you were not thinking of the parent drug whose
16 metabolism was being altered, which is what I was proposing.

17 DR. TAYLOR: I think we have one last comment and
18 we are going to move on.

19 DR. LAMBORN: I had actually two thoughts. One is
20 when you talk about whether the metabolite, for instance, is
21 highly potent--Roger keeps referring back to the issue about
22 quantity which you mentioned, also. I am assuming, when you
23 talk about highly potent, you are talking about the relative
24 potency of the overall action and not just per milligram or
25 something.

1 DR. AJAYI: That's correct.

2 DR. LAMBORN: The other comment was that this
3 decision tree might be helped to address the issues about
4 what happens if the parent, for instance, is the one that is
5 important but you can only measure the metabolite is to have
6 those as boxes that don't just say you automatically go over
7 to measure the metabolite. Those are circumstances when
8 there would be a discussion with the regulatory agency to
9 determine whether, in those circumstances, it would be
10 appropriate to substitute the metabolite, so, in a sense,
11 build those boxes rather than looking as if it was
12 automatic.

13 DR. AJAYI: Okay. Thanks.

14 DR. TAYLOR: One last comment and that is the more
15 we learn about the different way stations in your decision
16 tree, the more we learn about the science of individual
17 compounds. That is sort of how we stumbled onto the
18 terfenadine problem. If you had applied terfenadine to this
19 not knowing what you know now, and probably did, then you
20 wouldn't have learned that.

21 But by trying to make sure that all the steps were
22 secure, you learned a lot about the science of terfenadine.
23 So there is a lot of merit to making sure that this
24 accurately reflects what you want to know. It gets back to
25 your question, what do you want to know. What we want to

1 know is more about how the drugs are metabolized and what
2 impact that metabolism has on the biological effect, either
3 toxicity or pharmacodynamics.

4 So there is work to be done, I guess.

5 DR. WILLIAMS: Dr. Taylor, I also wanted to
6 endorse what you said about one size fits all because I
7 would say, over the last several years in this committee, we
8 have talked, time and again, about moving away from that
9 approach. I think it permeates every discussion we have had
10 today and probably the discussion tomorrow.

11 I am delighted to do that because I think it
12 creates the opportunity for good science and appropriate
13 testing and the right test at the right time. But I also
14 will say I am very nervous about it because every decision
15 point requires a regulatory judgment that is open to debate
16 and dissention.

17 I think we have to be careful that we not let that
18 happen and that good science will prevail.

19 DR. TAYLOR: I think we can move on then. Again,
20 thank you very much for your presentation and for your
21 stimulating thoughts.

22 The last issue for today is the bioavailability
23 and bioequivalence aspects of chiral drugs. Dr. Chandra
24 Sahajwalla will make that presentation.

25 **Chiral Drugs**

1 DR. SAHAJWALLA: Good afternoon.

2 [Slide.]

3 The next slide is just a list of members of our
4 working group.

5 [Slide.]

6 In May, 1992, FDA issued a policy statement on
7 development of stereoisomers which did not address the issue
8 of how the bioequivalence should be assessed for
9 stereoisomers. So the question for our working group was
10 should bioequivalence of chiral drugs be based on
11 enantiomers and, if yes, what characteristics of the drug
12 would require that the bioequivalence be based on each
13 enantiomer?

14 [Slide.]

15 Some of the factors which may influence
16 bioavailability and, hence, the bioequivalence are:
17 dissolution or release from a formulation, absorption,
18 first-pass effect and effect of food.

19 [Slide.]

20 The next slide is a list of several publications
21 that have appeared in the literature discussing the merits
22 and demerits of assessing bioequivalence based on
23 enantiomers.

24 [Slide.]

25 The reasons given which are not in favor for

1 stereoselective assays is that a racemate contains the same
2 portion of each enantiomer and, in BE studies, availability
3 of drug is being compared in the same subject under
4 identical conditions. Also enantiomer-specific assays add
5 cost to the drug development.

6 [Slide.]

7 Further, many of the barriers that a racemate drug
8 has to travel are all passive processes and will affect both
9 the enantiomers equally. So, the assay of racemate in
10 bioequivalence studies is appropriate for most drugs.

11 [Slide.]

12 Reasons given by those in favor of assessing
13 bioequivalence based on stereoselective assay are:
14 stereoselective and slow absorption can show
15 bioinequivalence; presystemic metabolism; low active to
16 active concentration ratios; and what would be the
17 consequence of pooling a larger enantiomer plus and smaller
18 enantiomer and, also, that since enantiomer-specific assays
19 are now widely available, they should be used regularly.

20 [Slide.]

21 I will just focus on two of the publications with
22 commentaries which have been published recently. In 1996,
23 Aziz Karim published that maybe stereoisomers should be
24 categorized based on first-pass metabolism. First-pass
25 metabolism is negligible or non-stereoselective.

1 Second is that the less active enantiomer
2 predominantly undergoes first-pass metabolism. The third
3 category would be the more active and less toxic enantiomer
4 is predominant. He proposed that category I and II
5 enantioselective assays are not essential.

6 [Slide.]

7 Recently Midha et al. published this paper in
8 which he has given examples of these seven drugs which had
9 data based on racemate versus based on each enantiomer. He
10 concluded that, excepting for nadolol, other drugs showed
11 that using an enantioselective assay or a racemate did not
12 make any difference.

13 [Slide.]

14 Now, nadolol has two chiral centers, four optical
15 isomers and is largely excreted unchanged. And it has
16 bioavailability of about 35 percent. He showed that, based
17 on total drug or one of the optical isomers, bioequivalence
18 criteria were met. But, for the other three isomers, the
19 bioequivalence criteria were unmet.

20 So this showed there was a difference if you based
21 bioequivalence based on total versus each specific isomer.
22 However, looking at the multiple-dose study, it showed that
23 there was greater variability for isomers suggesting that
24 there was low statistical power and this high variability
25 could be associated with the analytical method. And so that

1 data was not conclusive.

2 [Slide.]

3 His final conclusions were that experimental data
4 currently available do not lend support to the use of
5 stereoselective methods in all BE studies. He is proposing
6 the question of the importance of stereoisomers in BE may be
7 eventually settled if drug-regulatory agencies start
8 requiring both stereoselective and non-stereoselective
9 methods.

10 [Slide.]

11 Our working group has come up with a decision tree
12 which says to look at the drug and if the pharmacodynamics
13 are enantiospecific. If they are not enantiospecific, then
14 measure the racemate. If they are enantiospecific, then the
15 question is is PK enantiospecific.

16 If PK are not enantiospecific, then it is okay to
17 measure racemate. If PK are enantiospecific, then the next
18 question is in which enantiomer does the majority of
19 activity reside. If the majority of activity resides in the
20 moiety which is predominantly available, then measure the
21 racemate. If not, then look at is PK linear or non-linear.

22 If PK are linear, then measure the racemate. If
23 PK are nonlinear, then measure enantiomers.

24 [Slide.]

25 These are the three questions our committee would

1 like to get guidance on; comments on the decision tree.
2 And, in the decision tree, when we mention predominant and
3 negligible activity, what should be the definition of that
4 and how do we decide on if the drug information becomes
5 available after they have gone off-patent.

6 Thank you.

7 DR. TAYLOR: Thank you.

8 **Committee Discussion**

9 DR. TAYLOR: Why don't we start with the
10 committee's responses to the first question which was to
11 critique the decision tree that you see on the overhead. We
12 will start with that one. I guess the question I have is if
13 you looked at drugs in your files that were racemates and
14 applied the decision tree to those drugs and what were the
15 findings in that regard.

16 DR. SAHAJWALLA: The problem is we don't have data
17 based on racemate and enantiospecific assay so we cannot
18 compare. I think that paper from Midha et al., which
19 recently came, has a summary of six or seven examples. Six
20 of them showed there was no difference but, based on the
21 decision tree, I think we would have predicted that there
22 was no use to carry out enantiospecific assay.

23 DR. TAYLOR: Because, when you look at the
24 decision tree, it always leads you back to the racemate--I
25 mean, almost all the time. I think you would have to define

1 the kinds of drugs that you would apply to decision tree to.

2 For those drugs that have a wide therapeutic index
3 or wide therapeutic window, it is probably not going to make
4 any difference what you measure. But, say, for a narrow
5 therapeutic-index drug, where the enantiomer that was not
6 predominant was the major pharmacodynamic moiety, then that
7 would lead you to measure the enantiomer.

8 I guess I am just trying to figure out how many
9 examples I can come up with that would lead me down to this
10 corner down here. I am not sure that there are a lot of
11 them. Does that make your decision tree good or bad? I
12 don't know.

13 DR. MAYERSOHN: I was struck by the same point.
14 In order to get to the bottom right-hand side, you have to
15 show an enantiospecific difference in dynamics followed by
16 an enantioselective difference in kinetics followed by a
17 negligible enantiomer form which is nonlinearly treated
18 kinetically.

19 I would think that would eliminate 98 percent of
20 all the isomers. Is that what you want? Is that what you
21 are trying to accomplish? If you go through this tree, as
22 Bob was saying, I suspect a very small percentage are going
23 to come down to the bottom right-hand side where you measure
24 enantiomers.

25 DR. SAHAJWALLA: No. We were going through our

1 scientific judgment. We came to the decision that only
2 under these circumstances you might see any differences. So
3 we were not trying to eliminate 98 percent of them.

4 DR. MAYERSOHN: No. But that may happen as a
5 consequence of your decisions.

6 DR. SAHAJWALLA: Right.

7 DR. MAYERSOHN: You are not separating toxicity
8 from efficacy here; is that correct?

9 DR. SAHAJWALLA: I am saying PD is defined as
10 either differences in efficacy or differences in toxicity.

11 DR. MAYERSOHN: But they may not follow the same
12 path. One enantiomer could be effective, active, and the
13 other could be nonactive but toxic.

14 DR. SAHAJWALLA: Right.

15 DR. MAYERSOHN: If the nonactive but toxic is a
16 negligible fraction, will it get down to the bottom right-
17 hand side?

18 DR. SAHAJWALLA: Yes; we will look at both things,
19 efficacy and toxicity, and follow the same decision tree.

20 DR. MAYERSOHN: This scheme is applied to two
21 questions. One is efficacy and the other is toxicity.

22 DR. SAHAJWALLA: Yes.

23 DR. MAYERSOHN: They are separate issues.

24 DR. SAHAJWALLA: Yes. I am saying in the first
25 box here that--

1 DR. MAYERSOHN: Yes; I know. But when I get down
2 to the next-to-the-last step and, let's say, we have a
3 negligible enantiomer, and you ask is the kinetics linear,
4 in order to pursue that enantiomer analytically, the answer
5 would have to be no. Is that appropriate? I think I would
6 still be interested in a toxic enantiomer negligibly formed
7 even though the kinetic is not linear, even if the very last
8 answer is yes.

9 DR. SAHAJWALLA: Okay. There is a footnote here.
10 When it is yes, then it is defined by enantiomeric ratios
11 remain constant with change in input rate.

12 DR. MAYERSOHN: That is pharmacokinetic linearity
13 assumes.

14 DR. SAHAJWALLA: Right.

15 DR. MAYERSOHN: I guess, in terms of
16 bioequivalence, it shouldn't matter. Okay.

17 DR. BRAZEAU: I guess I have another
18 clarification. The word "predominant." What does that
19 mean? With enantiomers, usually they may be a more equal
20 ratio. Can you help me with that?

21 DR. SAHAJWALLA: Actually, that was my question,
22 how do we define "predominant?" In the drug product, it is
23 equal. But when it is systemically available, you might
24 have differences. For example, verapamil. S-verapamil is
25 only 20 percent compared to R-verapamil. S is more active.

1 So, in that respect, predominant is which has less activity.

2 So, actually, that would fall under here,
3 possibly.

4 DR. TAYLOR: Is that something that ought to be in
5 the decision tree, though? If both enantiomers are active,
6 then why would you look at just the one that was predominant
7 in quantity?

8 DR. BRAZEAU: I think it would be very rare when
9 you have one enantiomer that is going to be active and one
10 that is maybe inactive. You will probably have different
11 potencies and I am not sure that this decision tree can make
12 that distinction.

13 DR. TAYLOR: Actually, there are a few. I think
14 warfarin is one, for example. Isn't that right?

15 DR. WILLIAMS: I would have said, in most
16 instances, one enantiomer has the dominant activity and the
17 other one, if you buy Arian's argument, is isomeric ballast,
18 or whatever he calls it. But there are a few examples
19 where, in terms of activity, the less dominant enantiomer
20 does create some toxicity or some problem.

21 DR. BRAZEAU: Is PK affected by activity? Does it
22 become nonlinear if the activity is greater? I don't know.
23 Is that part of it?

24 DR. TAYLOR: Repeat that for me again.

25 DR. BRAZEAU: Is PK affected by activity? Does it

1 become nonlinear if it is more active?

2 DR. TAYLOR: PK?

3 DR. BRAZEAU: Yes.

4 DR. WILLIAMS: I would say the answer is no.

5 Dr. Taylor, I am sure the committee sees the
6 correspondence between the discussion here and the prior
7 discussion about metabolite. It relates to abundance and
8 activity. So I think some of our thinking back there can be
9 helpful. But I think Chandra was right in saying that, I
10 think if you follow the decision tree, for the most part,
11 you would measure the racemate.

12 So, Mike, I agree with you that this would tend to
13 lead towards, most of the time, measuring the racemate to
14 look at bioequivalence. Obviously, to look at
15 bioavailability to study a new drug, you would ask for a
16 different set of information.

17 I might use warfarin as an example, Dr. Taylor,
18 because that is a narrow-therapeutic-index drug, surely. I
19 think it does have, in the RNS--one of them has a much
20 faster half-life. I am going to ask people to help me here
21 if I am wrong. I think the activity resides in one of the
22 species.

23 DR. TAYLOR: Yes.

24 DR. WILLIAMS: I can't remember whether it is
25 faster or not.

1 DR. TAYLOR: I can't remember.

2 DR. WILLIAMS: But I think it exhibits linear
3 kinetics so the final conclusion, after you go through that
4 tree, would be to measure the racemate.

5 DR. TAYLOR: Yes; it would be.

6 DR. MAYERSOHN: I think Desmar's question--there
7 is an illustration. If I am not mistaken, it is
8 propranolol. One of the isomers affects liver blood flow
9 which, in turn, can affect the clearance of the active
10 material; isn't that right? Where is my clinical
11 pharmacology colleague.

12 Is that right, Bob?

13 DR. BRANCH: That's correct. If you are giving
14 the racemate, you have got active drug there and it actually
15 affects the kinetics of both. You only get the separate
16 action when you give the enantiomers separately.

17 DR. MAYERSOHN: But that is a legitimate question.

18 DR. TAYLOR: Yes; but that is an unusual case.

19 DR. MAYERSOHN: Because that is the one we found.

20 DR. TAYLOR: That is the one we know about.

21 DR. LAMBORN: I am wondering, just listening to
22 this, whether there is a way to simplify this tree. If you
23 look at the only circumstance in which you are going to wish
24 to measure an enantiomer, it is when the PK is nonlinear.
25 Is that correct?

1 DR. SAHAJWALLA: No. When PD is enantiospecific
2 and PK is nonlinear.

3 DR. LAMBORN: But my point is, at minimum, you
4 have to have the PK nonlinear.

5 DR. SAHAJWALLA: Right.

6 DR. LAMBORN: So if we could start with is the PK
7 nonlinear, yes/no. If it is linear, we stick with that. If
8 it is nonlinear, is there a substantial activity in the
9 enantiomer that is the minority component. That would be
10 the circumstance that would take us to measure the
11 enantiomers.

12 DR. SAHAJWALLA: Actually, if PK is nonlinear but
13 PD is not enantiospecific, then just we can measure
14 racemate.

15 DR. LAMBORN: Okay. But I just had a feeling that
16 the logic for how you got there was the science but now, if
17 you really wanted to get to the logic for the actual making
18 of the decisions, I think this can probably be collapsed
19 some.

20 The reason I am bringing it up is because I think
21 it may get away from some of the problem of predominant
22 versus negligible because if the one that is less
23 predominant has some substantive activity, and if the PK is
24 enantiospecific, then that is the circumstance. So it is
25 not really a matter of whether it is predominant or whether

1 it is negligible, which leaves a whole range in between, if
2 you have the couple of components, then, if there any
3 substantive activity, then you need the enantiomer analysis.

4 I don't know if I am being clear at all, but I am
5 after avoiding the problem of predominant versus negligible
6 to simply say if there is an activity that is substantive,
7 regardless of whether it is predominant, if the other
8 conditions hold, that that should be the decision component.

9 DR. TAYLOR: Again, we will have to define how
10 much is that. If the difference is more than 20 percent?

11 DR. LAMBORN: I have to have some of the others
12 help but I just think predominant and negligible is too
13 extreme.

14 DR. SAHAJWALLA:.. We had tried some words like
15 "major" and "minor," "evident" and "nonevident." But we
16 were not able to come to any consensus.

17 DR. TAYLOR: I guess the conclusion, based on what
18 I am hearing, is that we don't like those words. They
19 cannot be uniformly interpreted. In that case, it opens up
20 a level of ambiguity for those people who have to interpret
21 it back at their home place. That disturbs me.

22 I can't help you out of the dilemma except to say
23 that you need to go back and really think about that again
24 and use some of the similar discussions and extend them
25 further than what we have done today. There is a way out of

1 it but I am not sure which way to go yet.

2 DR. WILLIAMS: I agree completely and I think
3 Kathleen was making a good point. Sometimes, when we think
4 about it, or at least when I think about it, simplistically,
5 you could say if it is linear, you can measure the racemate.
6 Sometime, we have said that publicly if you don't have
7 first-pass metabolism or enantioselective first-pass
8 metabolism, and it is linear, then just measure the
9 racemate.

10 DR. LAMBORN: Right; get rid of a large bulk of it
11 without having to deal with the predominant versus the
12 negligible.

13 DR. WILLIAMS: Yes. And I think we can bring the
14 nomenclature in tune, too, between activity--and here we are
15 using predominant and nonpredominant. So I hope when we
16 have the guidance and it finally comes out, there will be a
17 lot of tuning up of the nomenclature.

18 DR. TAYLOR: The last question is how to decide on
19 drugs for which enantiospecific information becomes
20 available after the drug has gone off-patent.

21 DR. SAHAJWALLA: Basically, for generic drugs, if
22 the sponsor had not provided--we didn't have the available
23 information which is needed for this decision tree at the
24 time of the NDA, although our '92 guidance now suggests that
25 all this information should be available.

1 But if some drug which was approved, say, five
2 years ago and it is going off-patent, then do we require
3 them to follow that decision tree even though the original
4 sponsor had not--

5 DR. TAYLOR: So what you are asking is should you
6 put additional regulatory burden--

7 DR. SAHAJWALLA: On generics.

8 DR. TAYLOR: On the generic product because we
9 didn't know enough science about the drug five years ago.

10 DR. SAHAJWALLA: Yes.

11 DR. TAYLOR: I don't know. That seems a bit
12 unfair to me but, on the other hand, if it is a safety
13 issue, it needs to be approached. Any feeling from the
14 committee on that?

15 DR. MAYERSOHN: What are you thinking of, Prozac
16 or something like that, as an example, because that is a
17 situation where one of the enantiomers is more active.
18 Would that be an example?

19 DR. SAHAJWALLA: I haven't thought of that.

20 DR. MAYERSOHN: Am I depressing you with this
21 question?

22 DR. SAHAJWALLA: I work in neuropharm, so it is
23 okay.

24 DR. MAYERSOHN: Is that the type of situation you
25 are thinking of?

1 DR. TAYLOR: Let's say it is.

2 DR. BYRN: Or it could even be broader. It could
3 be should science be applied? We can scientific do it now,
4 but it wasn't scientific possible then. Should the best
5 science be applied broadly in all cases?

6 DR. MAYERSOHN: Regardless of cost, which I guess
7 is an issue.

8 DR. BYRN: There is cost; yes. There is safety
9 and there is cost.

10 DR. TAYLOR: It seems to me if our knowledge of
11 the drug and its properties are more advanced than they were
12 when the drug was originally approved, it would be foolish
13 for us to ignore that new information as we develop new
14 policy.

15 DR. BRAZEAU: I agree.

16 DR. TAYLOR: I don't see a way out of it. I think
17 the answer is yes. In fact, if the pioneer product comes
18 back for a SUPAC or some other--you may require that, then,
19 as well.

20 DR. WILLIAMS: I would hope we would always use
21 the up-to-date science. I think one of the purposes of
22 these guidances is to give both pioneer and generic sponsors
23 an idea of what we care about in terms of the latest
24 understanding and ask for that when they make a submission.

25 DR. TAYLOR: Actually, generally, after the drug

1 has been on the market for that length of time, that kind of
2 information is in the general scientific literature anyway
3 so it is not proprietary information by the time we get back
4 to the generic formulation of it, in general.

5 Any other comments?

6 DR. MAYERSOHN: Just a question. You are
7 following this literature. What is the current state of
8 analytical capability in the way of quantitating
9 enantiomers?

10 DR. SAHAJWALLA: It is pretty advanced. There are
11 a couple of companies just primarily doing chiral assays.

12 DR. MAYERSOHN: On-column separations?

13 DR. SAHAJWALLA: On-column separations; yes.

14 DR. MAYERSOHN: Any time I have done them, I have
15 had to go through a derivitization period which is very
16 lengthy.

17 DR. SAHAJWALLA: Some chiral columns are available
18 and on-column separations are also being done.

19 DR. MAYERSOHN: So it is practical.

20 DR. SAHAJWALLA: Yes; it is practical.

21 DR. STEWART: In fact, I can pretty much tell you
22 you can separate almost any enantiomers now. There are all
23 kind of specialized columns but you can even use something
24 like C-18 columns with cyclodextrins in mobile phases and
25 that. You can separate almost anything.

1 DR. TAYLOR: Thank you very much.

2 **Administrative Topics**

3 DR. TAYLOR: We have come to almost the end of the
4 agenda. There is a discussion of administrative topics. I
5 would like to ask Dr. Williams to give some summary comments
6 of today's meeting and then that would be followed--Dr.
7 Mayersohn, did you want to--Dr. Mayersohn has asked for a
8 few minutes to present some pictures from the Internet--is
9 it pictures from the Internet?

10 DR. MAYERSOHN: No. Are you talking about our
11 lunchtime discussion?

12 DR. TAYLOR: He wants to present some data briefly
13 and then we will have some administrative topics that
14 Kimberly Topper will give us.

15 Roger, would you go ahead?

16 DR. WILLIAMS: Just very briefly, I would, as
17 always, like to thank the committee. I see this guidance
18 that we are talking about as being a very powerful one, as I
19 say, for moving beyond, if you will, what it says in the
20 1977 regulations, to be more explicit, more clarifying, more
21 "how to," if you will, for all sponsors, pioneer and
22 generic, in satisfying our interests in bioequivalence.

23 With certain exceptions, I think there always is
24 the intent to get the right test for the right question and
25 reduce regulatory burden where it is consistent with our

1 public-health objectives. We are under a mandate not to do
2 unnecessary human experimentation but we are also under a
3 mandate to insure that stability in the performance and
4 quality of products after they are approved.

5 So I think this is a very useful discussion. As I
6 say, this is kind of a preview discussion for the committee
7 because we do intend to get public comments, do further
8 internal work. And I hope we can come back within a
9 reasonable time frame and have maybe a concluding discussion
10 with some final decisions from the committee on what we are
11 actually proposing.

12 DR. TAYLOR: Thank you.

13 DR. MAYERSOHN: Roger, just one general comment.
14 When did the idea of working groups first come up? About
15 how long ago?

16 DR. WILLIAMS: I would say the center began
17 forming these coordinating committees, I would say five to
18 seven years ago and the concept of a coordinating committee
19 and bodies, technical committees and working groups.

20 DR. MAYERSOHN: Because I can't recall a meeting I
21 attended which is as fruitful as this. I think the efforts
22 of these working groups are coming to fruition and this is
23 exactly, I think, what was planned when the Division of
24 Pharmaceutical Sciences was proposed.

25 DR. WILLIAMS: I am glad you are saying that,

1 Mike. If I may, I was going to use some of my subsequent
2 time as an opportunity to thank everybody in the room who
3 has presented here and who has represented the work of their
4 working group. This is all coming out of everybody's hide,
5 as I say. They have many intense review commitments.

6 We have no FTE allocations for this kind of effort
7 but people do it willingly and I think you can see there is
8 a tremendous amount of thought that goes into it. I think
9 you are right; the payoff is coming soon.

10 DR. MAYERSOHN: I think the people who presented
11 should also recognize it is very easy for us to sit back,
12 stretch out, listen and then criticize. It is a very easy
13 thing to do. We recognize all the work that has gone into
14 this discussion so they shouldn't walk away feeling as if
15 they have been hit over the head. That is not the point.

16 DR. TAYLOR: Now we are going to go to a few
17 overheads.

18 DR. MAYERSOHN: Mr. Chairman, I am going to make
19 this very brief. There is only one point I want to bring
20 up. I see the fear in the committee members' eyes, but this
21 is not going to be a lecture.

22 DR. BYRN: Once a professor gets started, no
23 telling when they will stop.

24 DR. MAYERSOHN: I will stop. This addresses the
25 issue of experimental design which is touched upon in some

1 of the material that we have gotten.

2 [Slide.]

3 It deals with the concern about
4 intrasubject/interoccasion variability. The typical design
5 right now is a two-way crossover which can't handle the
6 subject-by-formulation problem. The ideal approach is the
7 bottom approach--oh; I am showing here time, by the way, the
8 bars on the X axis.

9 The ideal approach is the so-called simultaneous
10 dual-isotope approach where, on one occasion, it is a
11 single-period design. Two forms of the drug are given. It
12 could be a solution of an isotope, for example, radio or
13 stable isotope, and a production lot of the product. I am
14 going to get back to this in a second.

15 The other approach is semi-simultaneous. The only
16 reason I am standing here is because there has been no
17 mention of the semi-simultaneous technique and I wanted to
18 bring it to your attention.

19 [Slide.]

20 The simultaneous, single-occasion, one-period dual
21 isotope design, as I say, is the ideal approach because you
22 give two materials at the same time. They are distinguished
23 only by the fact that one is an isotope of the other. There
24 is no intrasubject variation because there is only a single
25 clearance on this one occasion. It is an extraordinarily

1 powerful, statistically powerful, technique.

2 The problem is it cannot be applied to a
3 production lot because you are not going to make deuterated
4 or radioactive forms on a production basis. And the other
5 problem is the analytical need for either a stable or
6 radioisotope, and that is no longer much of an issue. But
7 you do need two assays.

8 [Slide.]

9 The technique that has received some attention in
10 the literature is called semi-simultaneous. I call it a
11 near single-occasion, approximately one-period, single
12 isotope design. It is nearly ideal because the two products
13 are given almost at the same time but they are separated by
14 a little bit of time.

15 The clearance is essentially the same during this
16 experiment. There is minimal, if no, intrasubject
17 variability. It is very powerful. You can use the
18 production lot of these products. Only one assay is
19 required because there is no isotope.

20 One of the problems is that you have to increase
21 the dose and, therefore, you have to assume linearity and
22 also there may be issues of toxicity because you are getting
23 double doses.

24 [Slide.]

25 This is what the thing looks like. Roger are you

1 familiar with this? I hadn't heard it brought up. This is
2 a semi-lot plot. You give product No. 1, solid line, but
3 you stop sampling after you are in the terminal phase. You
4 are going to make an assumption. You probably have data
5 previously to know when that happens.

6 You continue sampling. That dotted line is what
7 would happen if you didn't do anything else. The
8 concentrations just decline, I am assuming, exponentially.
9 But, before that happens, you give product No. 2. One is a
10 test. One is a reference.

11 The dashed line represents the concentrations you
12 would achieve from that second product. The solid line is
13 what would be actually what you are measuring because it is
14 only a single isotope. There is no distinction. So you
15 take the total area under the curve, subtract from it the
16 area from the first product which is an extrapolated area,
17 and that gives you the area for the second product.

18 Potentially, by lengthening the window just a
19 little bit, it is virtually a single occasion comparable to
20 a dual-isotope technique. This, I think, is near ideal if
21 you can overcome some of the practical issues that I
22 mentioned in terms of linearity assumption, no toxicity with
23 double dosing, additional blood samples that have to be
24 taken.

25 But this, I think, gets around all the concerns

1 about intrasubject variability and interoccasion
2 variability. So I wanted to bring this to your attention.

3 Thank you.

4 DR. TAYLOR: We have a minute or two for comments
5 from the committee. Dr. Williams?

6 DR. WILLIAMS: I appreciate, Mike, bringing this
7 to our attention. The history of this approach, as I
8 recall, came out of somebody's Ph.D. thesis in Sweden.

9 DR. MAYERSOHN: It was Sweden.

10 DR. WILLIAMS: It is a very interesting approach
11 and I think it does merit further consideration. I think I
12 have seen people talk about it in terms of long half-life
13 drugs and as a way of solving that long washout period. So
14 that you might give your first test or reference, wait a
15 certain period of time until you were reasonably sure GI
16 transit for that formulation was over, and then give the
17 second one and do the kind of analysis that Mike was talking
18 about.

19 I think it is a very intriguing way to look at
20 bioequivalence for long half-life drugs. We would certainly
21 be glad to come back before the committee and discuss it in
22 more detail as a regulatory application.

23 DR. MAYERSOHN: In theory, Roger, it will apply to
24 any half-life. It doesn't really matter what it is. I have
25 a feeling, and I am not sure about this, that some of the

1 pharmaceutical companies are actually using this technique.
2 I would be very curious to hear from anybody in the audience
3 who could confirm that.

4 DR. TAYLOR: Perhaps it is a proprietary secret.
5 But I think it is worthy for the committee to discuss
6 perhaps, briefly, at a future meeting. Thank you, Dr.
7 Mayersohn.

8 Any administrative concerns relative to today's
9 meeting or to tomorrow's meeting? Tomorrow's meeting, as
10 you know, will be a combined meeting of this committee with
11 the Dermatologic and Ophthalmic Drugs Advisory Committee. I
12 am told that it will be crowded and you are advised to
13 arrive early. The meeting will begin at 8 o'clock.

14 DR. WILLIAMS: I will speak very briefly. I will
15 say that, at FDA, we have a word we use a lot and we use it
16 very carefully which is "generally." In contrast to that
17 word, we use the word "always" very carefully. So one of
18 the ways we get off the hook is to say "generally."

19 But I will say, now, that I am always delighted to
20 be able to thank the members of the advisory committee who
21 are leaving us. Unfortunately, I'm sad to say, I think we
22 have six members who are leaving us so this committee's
23 structure will change very dramatically.

24 But I do want to speak to all of you and thank you
25 very heartily and very deeply for the contribution you make

1 here, time and again, over the years, and your service to
2 the public health.

3 I can tell you I have had an opportunity to look
4 at many regulatory systems and societal systems and I might
5 say that I think the FDA advisory committee structure is
6 more or less unique in the world. As you can see, it is a
7 terrific opportunity that serves many purposes. There is
8 always a text and a subtext that you see operative here
9 today.

10 Then I will also say I am always very sad to bid
11 adieu to members of the committee. I say that from the
12 heart because we get to know each other and we become
13 friends. But I always know that it is never good bye.

14 I will start by saying to Gayle, Dr. Brazeau--and
15 I won't read these letters. I will let you read the
16 letters, but we actually have two, now. You get one from
17 the Center Director, Dr. Woodcock, and also one from our
18 Acting Commissioner, Dr. Friedman, thanking you for your
19 service.

20 So, Gayle, if you would like to come up here and
21 be a recipient of these plaques. They are kind of heavy.
22 I'm amazed. So, Gayle, thank you very much and
23 congratulations.

24 [Applause.]

25 Mike, I am also very sad, just as I am sad about

1 Gayle, to say goodbye to you, but I do want to thank you and
2 you, too, also get two heavy plaques from the Center
3 Director and our Acting Commission. Thank you very much.

4 [Applause.]

5 Finally, and, certainly, last but not least, I
6 would like to thank Desmar. Desmar, if you would come, I
7 have your two plaques. I would like to say a special word
8 about Dr. Walkes. She has been a consumer advocate but she
9 has been a very strong consumer representative to this
10 committee in her role as a practicing physician.

11 I can tell you that I think of Desmar as being on
12 the front lines dealing with a lot of the issues that we
13 struggle with in this committee in terms of substitution,
14 product quality, do drugs work, if they don't, why not. So,
15 thanks very much, Desmar and congratulations.

16 [Applause.]

17 I would also like to say we are losing some other
18 contributors who are very strong. Dr. Vestal is leaving the
19 committee. Dr. Zimmerman is leaving the committee. And Dr.
20 Gonzalez is leaving the committee. All of them made very
21 strong contributions and we will mail their plaques to them.

22 So thanks to them as well, and thanks to you all.

23 DR. BRAZEAU: I think I am speaking on behalf of
24 those of us who are leaving this committee, but we also want
25 to thank the agency and Roger and take the opportunity to do

1 that because I think we have grown and gained experience,
2 better experience, and I think we are all appreciative of
3 having the opportunity to serve in this capacity.

4 [Applause.]

5 DR. TAYLOR: With that, then, the meeting stands
6 adjourned. We will see you at 8 o'clock in the morning.

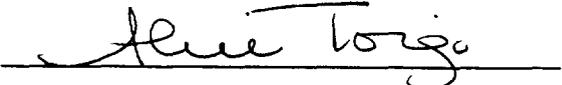
7 [Whereupon, at 5 o'clock p.m., the meeting was
8 adjourned.]

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C E R T I F I C A T E

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in cursive script, reading "Alice Toigo", is written above a horizontal line.

ALICE TOIGO