DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

Wednesday, April 14, 2004

8:30 a.m.

Advisors and Consultants Staff Conference Room
5630 Fishers Lane
Rockville, Maryland

                        PARTICIPANTS

    Arthur H. Kibbe, Ph.D., Chair
    Hilda F. Scharen, M.S., Executive Secretary

    MEMBERS:

    Gerald P. Migliaccio, Industry Representative
    Marvin C. Meyer, Ph.D.
    Patrick P. DeLuca, Ph.D.
    Charles Cooney, Ph.D.
    Melvin V. Koch, Ph.D.
    Cynthia R.D. Selassie, Ph.D.
    Nozer Singpurwalla, Ph.D.
    Jurgen Venitz, M.D., Ph.D.
    Marc Swadener, Ed.D., Consumer Representative

    SPECIAL GOVERNMENT EMPLOYEES:

    Paul H. Fackler, Ph.D.
    Gordon Amidon, Ph.D., M.A.
    Judy Boehlert, Ph.D.
    Leslie Benet
    Charles DiLiberti
    Laszlo Endrenyi

    FDA:

    Gary Buehler, R.Ph.
    Ajaz Hussain, Ph.D.
    Helen Winkle
    Lawrence Yu, Ph.D.

C O N T E N T S

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

 2                       Call to Order

 3            DR. KIBBE:  By the clock on the wall, I

 4    think we are at 8:30.  It looks like our

 5    electronics are working so we will be in good

 6    shape.  We need to start off with the reading of

 7    the conflict of interest statement.

 8               Conflict of Interest Statement

 9            MS. SCHAREN:  Good morning.  I am Hilda

10    Scharen.  I am the executive secretary for the

11    Advisory Committee for Pharmaceutical Science and I

12    am going to be going through the conflict of

13    interest statement for the committee.

14            The following announcement addresses the

15    issue of conflict of interest with respect to this

16    meeting and is made a part of the record to

17    preclude even the appearance of such at this

18    meeting.

19            Based on the agenda, it has been

20    determined that the topics of today's meetings are

21    issues of broad applicability and there are no

22    products being approved at this meeting.  Unlike

23    issues before a committee in which a particular

24    product is discussed, issues of broader

25    applicability involve many industrial sponsors and
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 1   academic institutions. All special government

 2   employees have been screened for their financial

 3   interests as they may apply to the general topics

 4   at hand.

 5   To determine if any conflict of interest

 6   existed, the agency has reviewed the agenda and all

 7   relevant financial interests reported by the

 8   meeting participants. The Food and Drug

 9   Administration has granted general matters waivers

10   to the special government employees participating

11   in this meeting who require a waiver under Title

12   XVIII, United States Code Section 208.

13   A copy of the waiver statements may be

14   obtained by submitting a written request to the

15   agency's Freedom of Information Office, Room 12A-15

16   of the Parklawn Building.

17   Because general topics impact so many

18   entities, it is not prudent to recite all potential

19   conflicts of interest as they may apply to each

20   member and consultant and guest speaker. FDA

21   acknowledges that there may be potential conflicts

22   of interest but, because of the general nature of

23   the discussion before the committee, these

24   potential conflicts are mitigated.

25   With respect to FDA's invited industry

 1   representative, we would like to disclose that

 2   Gerald Migliaccio is participating in this meeting

 3   as an industry representative, acting on behalf of

 4   regulated industry. Mr. Migliaccio is employed by

 5   Pfizer. Dr. Paul Fackler is participating in this

 6   meeting as an acting industry representative. Dr.

 7   Fackler is employed by Teva Pharmaceuticals U.S.A.

 8   In the event that the discussions involve

 9   any other products or firms, not already on the

10   agenda, for which FDA participants have a financial

11   interest, the participants' involvement and their

12   exclusion will be noted for the record. With

13   respect to all other participants, we ask in the

14   interest of fairness that they address any current

15   or previous financial involvement with any firm

16   whose product they may wish to comment upon. Thank

17   you.

18   DR. KIBBE: Thank you, Hilda. Just so

19   that our audience knows who all is here, I would

20   like to ask everybody to introduce themselves and

21   give their affiliation. We will start with Dr. Yu.

22   Lawrence?

23   DR. YU: Lawrence Yu, Director for

24   Science, Office of Generic Drugs, Office of

25   Pharmaceutical Science, CDER, FDA.

 1   DR. BUEHLER: Gary Buehler, Director,

 2 Office of Generic Drugs, Office of Pharmaceutical

 3 Science, CDER.

 4   DR. HUSSAIN: Ajaz Hussain, Deputy

 5 Director, Office of Pharmaceutical Science, CDER.

 6   MS. WINKLE: Helen Winkle, Director,

 7 Office of Pharmaceutical Science, CDER.

 8   DR. AMIDON: Gordon Amidon, University of

 9 Michigan.

10   DR. VENITZ: Jurgen Venitz, Virginia

11 Commonwealth University.

12   DR. SELASSIE: Cynthia Selassie, Pomona

13 College.

14   DR. BOEHLERT: Judy Boehlert, and I have

15 my own pharmaceutical consulting business.

16   DR. SWADENER: Marc Swadener, consumer

17 representative, retired from University of

18 Colorado, Boulder.

19   DR. KIBBE: I am Art Kibbe and I am

20 Professor of Pharmaceutical Sciences at Wilkes

21 University.

22   DR. MEYER: Marvin Meyer, formerly

23 University of Tennessee professor, now living in

24 Boca Raton, Florida.

25   DR. SINGPURWALLA: Nozer Singpurwalla,

 1   George Washington University.

 2   DR. KOCH: Mel Koch, the Director for the

 3   Center for Process Analytical Chemistry at the

 4   University of Washington.

 5   DR. COONEY: Charles Cooney, Professor of

 6   Chemical and Biochemical Engineering at MIT.

 7   DR. DELUCA: Pat DeLuca, University of

 8   Kentucky.

 9   MR. MIGLIACCIO: Gerry Migliaccio, Pfizer.

10   DR. FACKLER: Paul Fackler, industry

11   representative, Teva Pharmaceuticals.

12   DR. KIBBE: Thank you. We are going to

13   start this morning and Dr. Yu will set us up for

14   our discussion. Lawrence?

15   Bioequivalence of Highly Variable Drugs

16   DR. YU: Good morning. My slides I guess

17   are in a different file so I will give my

18   introduction without the slides.

19   Dr. Kibbe, Chair of the FDA Advisory

20   Committee for Pharmaceutical Science, members of

21   the FDA Advisory Committee for Pharmaceutical

22   Science, distinguished speakers, distinguished

23   guests and distinguished audience, I am Lawrence

24   Yu. I am Director for Science, Office of Generic

25   Drugs, Office of Pharmaceutical Science, CDER, FDA.

 1   This morning it gives me great pleasure

 2 and privilege to introduce to you the first topic

 3 of bioequivalence, bioequivalence of highly

 4 variable drugs. The objectives of this discussion

 5 are to explore and define bioequivalence issues of

 6 highly variable drugs, to discuss and to debate

 7 potential approaches in resolving them,

 8 specifically the pros and cons of the solutions and

 9 the benefits and limitations of these potential

10 approaches.

11   The bioequivalence issues of highly

12 variable drugs have been discussed in many

13 conferences and meetings nationally and

14 internationally. The issue is obvious because of

15 the high variability of the drugs or drug products

16 that require a large number of subjects or

17 volunteers in order to pass the confidence interval

18 of 80-125 percent. Despite many, many discussions,

19 despite many, many publications in scientific

20 literature, to date there is no consensus and no

21 solutions have ever been reached. In fact, there

22 is no regulatory definition with respect to the

23 high variability drugs or drug products. So, there

24 are various approaches in resolving this in the

25 scientific literature, for example, expansion of

 1   the bioequivalence limits; for example, using

 2   scaling approaches.

 3   We have invited a panel of distinguished

 4   speakers this morning to discuss this issue related

 5   to the bioequivalence of highly variable drugs from

 6   various perspectives, from practical difficulties

 7   of bioequivalence of highly variable issues, from

 8   mechanistic understanding of what causes the high

 9   variability of drug or drug products, from

10   understanding of different approaches to resolve

11   understanding of clinical implications why high

12   variability drugs are safer, from case studies and,

13   finally, from regulatory options.

14   At the end of these presentations you will

15   be asked to discuss or address the following

16   questions. First, what is actually the definition

17   for highly variable drugs or drug products?

18   Second, with respect to expansion of

19   bioequivalence limits, what additional information

20   should we gather in order to answer this question?

21   We also ask you to comment on scaling approaches.

22   With this introduction, I want to turn the

23   podium over to our first speaker, Charlie

24   DiLiberti. Charlie?

25   Why Bioequivalence of Highly Variable Drugs

1   is an Issue

2   MR. DILIBERTI: Thank you, Dr. Yu. Before

3   I start I need to disclose the potential conflict

4   of interest in that I am employed by Barr and I am

5   also a shareholder and option holder in the firm.

6   Also, before I get into the actual

7   discussion I would like to say that in the context

8   of preparing this presentation I had numerous

9   discussions with many of my colleagues in the

10   industry and, based on the feedback that i got from

11   them, it seems to me that the views that I am about

12   to portray in my presentation are quite widely held

13   in the industry.

14   [Slide]

15   With that, let's start off with the

16   definition of highly variable drugs. Oftentimes,

17   highly variable drugs are defined in the context of

18   within-subject variability in terms of a

19   bioequivalence study. I would like to take it one

20   step further and look at variability within the

21   patient and what does this high level of

22   variability mean to an individual patient taking

23   the drugs.

24   Commonly, the often used definition of

25   highly variable drugs is those drugs whose

 1   intra-subject or, as I characterize it here as

 2   intra-patient, coefficient of variation, or CV, is

 3   approximately 30 percent or more. I will use that

 4   as my guideline for the rest of this presentation.

 5   [Slide]

 6   What are the current criteria? Just very

 7   briefly, for bioequivalence they involve a

 8   comparison between test and reference product,

 9   involving the natural log transformation of the

10   data. The current criteria are that the 90 percent

11   confidence intervals around the geometric mean

12   test/reference ratios have to fall entirely within

13   the range of 80-125 percent.

14   These criteria really apply to all drugs

15   here, in the U.S., regardless of the inherent

16   variability of the drugs. These criteria do have

17   other implications. For example, they can be used

18   by innovator and, for that matter, generic firms to

19   justify a substantial formulation change so it is

20   not just in the context of approving a generic.

21   [Slide]

22   This really speaks to the crux of the

23   issue with highly variable drugs in that it

24   portrays the number of subjects that you would have

25   to plan on using in a two-way crossover

 1   bioequivalence study given a particular

 2   intra-subject CV. You can see that for very low CV

 3   drugs the number of subjects required is fairly

 4   small and quite manageable from a practical

 5   standpoint but, as the CV increases, you can see

 6   that the number of subjects required can increase

 7   to quite large numbers, possibly in the hundreds.

 8   [Slide]

 9   Why do we possibly need alternative

10   criteria for highly variable drugs? Well, first of

11   all, we have an ethical mandate to minimize human

12   experimentation. Second of all, the prohibitive

13   size of some bioequivalence studies for some highly

14   variable drugs impacts on the availability of a

15   generic version of that drug, which may mean that

16   in the absence of a generic many Americans can't

17   afford the reference product so they may go either

18   untreated or they may be subdividing their doses

19   contrary to the prescription.

20   Also, changing criteria will reduce the

21   number of participants in the BE studies and I

22   think it can't be done without compromising the

23   safety and efficacy of the product. Also, there is

24   experience elsewhere in the world with criteria

25   other than 80-125 percent.

1   [Slide]

2   This slide shows some of the

3   bioequivalence criteria in other countries and

4   regions in the world. These are not specific to

5   highly variable drugs and in many cases they don't

6   apply necessarily to all drugs. That is why I have

7   "most drugs" or "some drugs" listed here. But,

8   certainly, there is experience with certain drugs

9   in these different regions with confidence

10 intervals that are either wider than 80-125 or, in

11 the case of Canada for many drugs there is no

12 confidence interval criterion, just a point

13 estimate criterion.

14   [Slide]

15   What types of drugs are highly variable?

16 Well, the types of drugs really cut across all

17 therapeutic classes and include both new and older

18 products. The potential savings to American

19 consumers could possibly be in the billions of

20 dollars if generics are approved. In saying this,

21 I want to be clear that the bioequivalence issues

22 for many of these drugs are not the only barriers

23 to getting a generic. In some cases there might be

24 patent issues or formulation issues as well, but

25 still the bioequivalence issues do represent some

1   sort of a barrier.

2   What are some examples? This is a very

3   brief list and the list can go on and on but just

4   to give you some kind of representative examples of

5   drugs that cut across many therapeutic areas, some

6   of which are on-patent, some off-patent, just to

7   give a flavor.

8   [Slide]

9   Another issue is that as of last year we

10   now have to meet confidence interval criteria for

11   fed bioequivalence studies. So now the variability

12   under the fed state is of concern. There is

13   generally very little information available on the

14   variability of drugs in the fed state, and we have

15   found that some drugs do show more variability

16   under fed conditions than under fasting conditions,

17   leading to the potential for bioequivalence

18   failures because they may be under-powered. What I

19   am trying to get across here is that because of the

20   lack of information on many drugs under fed

21   conditions, there may in fact be many more highly

22   variable drugs than we are led to believe.

23   [Slide]

24   Why aren't the current criteria

25   appropriate for some highly variable drugs? Well,

 1   I will start off by saying that the current

 2   criteria are, I believe, appropriate for drugs with

 3   low to moderate variability because the

 4   dose-to-dose variability that a patient would

 5   experience is comparable and consistent with the

 6   width of the criteria.

 7   However, in the case of highly variable

 8   drugs this is not true where the dose-to-dose

 9   variability experienced by a patient may often be

10   much larger than the width of the criteria. I will

11   illustrate this point later on with some graphs.

12   Highly variable drugs are oftentimes wide

13   therapeutic index drugs. In other words, they have

14   shallow response curves and wide safety margins. I

15   want to qualify this statement by saying when I say

16   highly variable drugs, highly variable in a patient

17   with respect to the parameter that is variable. If

18   a patient experiences high variability, that means

19   that the drug is safe and effective despite this

20   wide variability in the patient. Therefore, I

21   believe that modifying bioequivalence criteria on

22   highly variable drugs to reduce the number of

23   participants in bioequivalence studies could be

24   accomplished while still maintaining safety and

25   efficacy assurance.

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 1              [Slide]

 2              Different highly variable drugs may

 3  require different approaches.  One size may not fit

 4  all.  As we can see from the earlier power graphs

 5  that I had plotted, obviously the number of

 6  subjects required for a drug with, say, 30 percent

 7  coefficient of variation is very different from the

 8  number of subjects required for a drug with, say,

 9  70 percent intra-subject CV.  And, there are other

10  considerations that we have to take into account.

11              [Slide]

12              Probably one of the more important

13  considerations is whether the drug accumulates in a

14  patient at steady state.  Let's first take the case

15  of a drug that does not experience significant

16  accumulation to steady state in a patient.  These

17  are typically short half-life drugs, in other

18  words, short half-life with respect to the dosing

19  interval.  Here are some examples.  We could

20  possibly consider some sort of modification to the

21  criteria for both AUC and Cmax because an actual

22  patient would experience significant dose-to-dose

23  variability for both Cmax and AUC because neither

24  is smoothed out at steady state.  Therefore, the

25  drug could be considered to exhibit a wide
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 1 dose-to-dose variation in blood levels irrespective

 2 of chronic dosing.

 3   The same sort of logic could potentially

 4 apply to a highly variable drug that is not dosed

 5 chronically. One particular application of the

 6 scenario of a relatively short half-life drug that

 7 does not undergo accumulation might be the case of

 8 a parent drug with a short half-life and high

 9 variability where there is also a metabolite that

10 needs to be measured which has a much longer

11 half-life and low variability. I could easily

12 envision the case where the confidence interval

13 criteria are somehow modified to accommodate the

14 higher variability of the parent drug but, in the

15 same compound, the current 80-125 criteria could be

16 applied to the metabolite.

17   [Slide]

18   Now let's look at the case of accumulation

19 to steady state. Typically, this is a case where a

20 drug is used chronically and with a half-life long

21 relative to the dosing interval so there is some

22 accumulation going on. Here are a few examples.

23   In this case, because the accumulation

24 process will tend to reduce the fluctuation in AUC

25 and Cmax, both at steady state, actually in

1   essence, the drug to a patient may not really be

2   highly variable because the variability may be

3   small at steady state. However, the Cmax and AUC I

4   think need to be looked at in a different light.

5   At steady state the test/reference ratio for two

6   drugs, assuming linear accumulation, will be about

7   the same as the test/reference ratio that we see in

8   a single dose study because the accumulation

9   process preserves that test/reference ratio.

10   However, for Cmax, generally speaking, the

11   test/reference ratio that we see at single dose

12   conditions will be the most extreme and the

13   test/reference ratio observed upon accumulation to

14   steady state will go closer and closer to unity,

15   one. So, that is why I think we potentially need

16   to consider these two cases differently in the case

17   of a drug that accumulates.

18   [Slide]

19   The other possibility with drugs subject

20   to accumulation is to actually conduct the steady

21   state study but this has all sorts of practical

22   limitations for some drugs, including toxicity.

23   [Slide]

24   What I have tried to do in this graph is

25   to get some sense of the magnitude of day-to-day

 1   fluctuations in a pharmacokinetic parameter--I have

 2   plotted this as if it were Cmax but it could

 3   equally apply to AUC--in the case of a drug that

 4   does not undergo accumulation.

 5   What is plotted here, in orange, is

 6   simulated data representing the sequential

 7   day-to-day Cmax's that might be seen in a given

 8   patient taking a single drug over the course of 30

 9   days where the drug has a true mean of 100 percent.

10   In fact, the sample mean here for this set of 30

11   data points is 100 and is the geometric mean, and

12   the CV of this data set is 10 percent. So, you can

13   see that the drug is fairly well controlled within

14   a fairly narrow range. Just as a yardstick for

15   variability, I have plotted the bioequivalence

16   limits, the 80 percent limit and the 125 percent

17   limit. I want to make it clear these limits do not

18   apply to individual day-to-day values, but I am

19   just plotting them here to give some sense of

20   scaling.

21   What I have plotted here, in the green, is

22   a different formulation, formulation B of the same

23   drug that has a mean here of 125. So, it is a 25

24   percent higher mean than this. CV is still 10

25   percent. So, this could be seen to represent the

 1   magnitude of change that one would expect upon

 2   switching a patient from one formulation to a

 3   second formulation with a higher mean. You can see

 4   that there is some degree of overlap between the

 5   second formulation and the first but, just

 6   eyeballing this, it is not too hard to see that

 7   there is visually some discernible shift in the

 8   overall levels.

 9   [Slide]

10   Let's see what the case looks like for a

11   drug with 30 percent intra-subject CV. You can see

12   here that there are many more excursions on a

13   single formulation outside the range of 80-125

14   percent. Overall, there is much more overlap

15   between formulation B and formulation A despite the

16   fact that these two formulations differ by 25

17   percent.

18   [Slide]

19   Let's increase the variability one notch

20   further to 50 percent CV, and we can see even more

21   day-to-day excursions in Cmax for a patient on a

22   given formulation, many of them outside 80-125.

23   You can see now that the overlap between

24   formulation B and formulation A, again a 25 percent

25   difference here, is almost not discernible at all

1   to the eye.

2   [Slide]

3   Finally, let's turn it up one notch

4   further to 70 percent intra-subject CV. With a

5   drug that is this variable you end up, while on a

6   single formulation with no switch involved, with a

7   range of Cmax values that could be as far as a

8   5-10-fold range day-to-day. So, there are wide

9   swings in the Cmax's achieved for a given subject.

10   In light of this, suppose that this is a

11   reference drug that is already approved by the

12   agency and known to be safe and effective, that

13   safety and efficacy is true in spite of the wide

14   variability from day-to-day so, therefore, the drug

15   cannot have a narrow therapeutic index and must

16   necessarily have a relatively wide therapeutic

17   index if it is safe and effective despite such wide

18   variation.

19   Also, you can see that the switch-over

20   product, formulation B, again a 25 percent higher

21   mean, is virtually indistinguishable now from the

22   range of blood levels that you see with formulation

23   A.

24   I think that the criteria, which are still

25   plotted here, 80-125 percent, need to be

 1   commensurate with the degree of overlap that we are

 2   trying to achieve between formulations. Even

 3   though these are the criteria, I would like to

 4   point out that in order to pass the criteria the

 5   actual observed mean in a bioequivalence study

 6   generally has to be in a very narrow range, maybe 5

 7   or 10 percent deviant from 100. Outside of that,

 8   your chances of passing a bioequivalence study on a

 9   very variable drug are very, very poor.

10   [Slide]

11   There are certain special considerations

12   that we need to take into account in the discussion

13   of highly variable drugs, one of which is where

14   parallel studies are conducted for long half-life

15   drugs.

16   Oftentimes you can't do a crossover study

17   because the wash-out period would be too long.

18   Powering parallel studies depends on between

19   subject variability rather than within subject

20   variability. Between subject variability is often

21   large, necessitating large bioequivalence studies

22   just as with highly variable drugs. However, the

23   high between subject variability does not

24   necessarily imply high within subject variability.

25   Instead, it could be due to inter-individual

 1   differences in absorption, metabolism, etc. So,

 2   these drugs, from a clinical perspective, may not

 3   really be highly variable but we are still faced

 4   with the powering problems in terms of conducting

 5   bio studies. In these cases, generally speaking,

 6   multiple dose studies are not feasible, and we

 7   might consider some sort of alternative criteria

 8   for such studies.

 9   [Slide]

10   A second issue that arises and is directly

11   related to the issue of highly variable drugs is

12   the issue of pooling data from multiple dosing

13   groups. Because of the large number of subjects

14   often required for highly variable drugs,

15   oftentimes you have to split up dosing into

16   multiple dosing groups.

17   Currently, the FDA requires a statistical

18   test for the poolability of the data from these

19   multiple dosing groups and the test is a measure of

20   the significance of the group by treatment

21   interaction terms in the analysis of variance. If

22   this interaction term is statistically significant,

23   then you are not permitted to pool the data from

24   the multiple dosing groups. The consequence of

25   this is that each group is then evaluated on its

 1   own merit and, because each group is generally

 2   considerably smaller than the total pool of

 3   subjects, each group will be grossly under-powered

 4   to achieve bioequivalence and, therefore, if you do

 5   have a statistically significant interaction term,

 6   overall you are likely to have failed the criteria.

 7   This procedure results in discarding and

 8   having to repeat about 5 percent of studies based

 9   on random chance alone, even if there is no genuine

10   underlying effect. The concern here I think is

11   that even if there were some sort of underlying

12   explanation for the statistical significance of the

13   interaction term, for example differences in

14   demographics among the dosing groups, I believe

15   that there is no reason not to use the data from

16   all the dosing groups because had they been dosed

17   together in a single group it would be perfectly

18   usable and we wouldn't be having this discussion.

19   [Slide]

20   Conclusions--while the current

21   bioequivalence acceptance criteria I believe are

22   appropriate for drugs with ordinary variability, I

23   believe that they may not be appropriate for some

24   highly variable drugs.

25   Current bioequivalence acceptance criteria

 1   make it difficult or impossible to develop generics

 2   in some cases, which has the public health issue of

 3   effectively denying treatment to many patients

 4   because of affordability issues.

 5   I believe that practical, scientifically

 6   sound alternative bioequivalence acceptance

 7   criteria could be implemented for highly variable

 8   drugs to reduce the bioequivalence study size while

 9   still maintaining assurance of safety and efficacy.

10   Different approaches may be needed for

11   different types of drugs depending on accumulation

12   following multiple dosing, and also depending on

13   the variability of the drug. And, other related

14   situations, i.e., the issue of parallel studies and

15   multiple dosing groups should also be considered in

16   conjunction with any changes to acceptance criteria

17   for highly variable drugs. Thank you.

18   DR. KIBBE: Does anybody on the panel have

19   questions for our presenter to clarify information?

20   Nozer?

21   DR. SINGPURWALLA: Certainly, I do. I

22   have four questions and five comments. Do I have

23   time?

24   DR. KIBBE: You have until everybody

25   leaves to go to the airport!

 1   DR. SINGPURWALLA: The first question is a

 2   question of clarification. What is Cmax? when

 3   somebody puts C and a max I think of the maximum.

 4   MR. DILIBERTI: That represents the

 5   maximum because concentration achieved within a

 6   given patient or subject over the course--

 7   DR. SINGPURWALLA: So, it is maximum blood

 8   concentration?

 9   MR. DILIBERTI: Yes, it is maximum blood

10   concentration.

11   DR. SINGPURWALLA: Thank you. What is

12   AUC?

13   MR. DILIBERTI: Area under the curve,

14   which is generally taken to be a measure of the

15   extent of absorption.

16   DR. SINGPURWALLA: The third question is

17   why did you take natural logs?

18   MR. DILIBERTI: It is conventional in the

19   analysis of bioequivalence data to do a log

20   transformation. This is already established as

21   standard--

22   DR. SINGPURWALLA: Log transformation of

23   the whole data or just the maximum?

24   MR. DILIBERTI: You would log transform

25   each of the individual Cmax's and then follow that

 1   by appropriate analysis of variance. The same log

 2   transformation also applies to the individual AUCs

 3   prior to analysis of variance.

 4   DR. SINGPURWALLA: Well, I can see doing a

 5   log transformation of all the data to get

 6   approximate normality if the distribution is log

 7   normal.

 8   MR. DILIBERTI: Yes, that is true.

 9   DR. SINGPURWALLA: Just taking the log of

10   the maximum--I don't know. By geometric mean, you

11   mean product divided by--what do you exactly mean?

12   MR. DILIBERTI: The geometric mean is what

13   results from the log transformation. You do the

14   log transformation and conduct analysis of

15   variance. From the analysis of variance you get a

16   least-squares mean on a log transformed variable.

17   When you back-transform that by exponentiating it

18   you end up with, in essence, a geometric mean.

19   DR. SINGPURWALLA: Okay. Now we will go

20   to comments. As somebody who is new to all this

21   and doesn't know, the thought that first comes to

22   my mind is that this HVD, highly variable drug,

23   should really be looked at as a bivariate problem.

24   You have two variables. One variable is the extent

25   of absorption and the other variable is the rate of

 1   absorption. So, I would look at it as a surface

 2   because the following is possible, suppose you have

 3   a drug which has a low variability with respect to

 4   absorption but high variability with respect to

 5   extent of absorption, how do you classify it? So,

 6   what we need is a better measure of classifying a

 7   highly variable drug which is a bivariate measure.

 8   That is the first comment.

 9   You proposed, I think, abolishing the

10   confidence limit notion.

11   MR. DILIBERTI: No, I didn't. I am not

12   here to propose solutions to the problem; I am just

13   here to really identify what the concerns and

14   problems are.

15   DR. SINGPURWALLA: Okay, but do you have

16   any sense of what is an alternative?

17   MR. DILIBERTI: Various alternatives have

18   been proposed, including reference scaling or some

19   fixed point scaling that is different from 80-125--

20   DR. SINGPURWALLA: But you are not putting

21   those forward?

22   MR. DILIBERTI: I am not really here to

23   discuss that.

24   DR. SINGPURWALLA: So, your basic focus is

25   criticizing what is there but without an

 1   alternative in mind?

 2   MR. DILIBERTI: Right, I think many of the

 3   later speakers will address the issue of potential

 4   solutions.

 5   DR. SINGPURWALLA: Now, in these charts

 6   that you showed, how did you choose the particular

 7   patient whose charts you were showing?

 8   MR. DILIBERTI: It is simulated data. It

 9   is log normally distributed random independent

10   variables. It is not patient data. I am sorry, I

11   thought that that was clear. It is entirely a

12   computer simulation just to give some sense of the

13   relative magnitude of the variability.

14   DR. SINGPURWALLA: Well, I didn't get that

15   message. I thought that was a real patient--

16   MR. DILIBERTI: No, no, no.

17   DR. SINGPURWALLA: --those data you were

18   showing.

19   MR. DILIBERTI: No.

20   DR. SINGPURWALLA: But you don't need to

21   show it because if it is simulated we can

22   appreciate it. The last point is when you talked

23   about pooling the data between two groups, how is a

24   group defined? What constitutes a group?

25   MR. DILIBERTI: By the day on which dosing

 1   occurs. For example, it may be impractical to dose

 2   100 patients or subjects in a clinic all on the

 3   same day. So, you may have to dose half of them

 4   today and maybe the other half several weeks from

 5   today.

 6   DR. SINGPURWALLA: So the groups are

 7   random depending on who shows up.

 8   MR. DILIBERTI: Essentially, yes.

 9   DR. SINGPURWALLA: Suppose one were to

10   think about forming these groups based on some

11   other, you know biological or--defining a group in

12   a certain way, conceivably you could justify

13   pooling. This is completely random.

14   MR. DILIBERTI: Right, and I believe that

15   the way that the groups are conventionally arranged

16   in a typical bioequivalence study pooling may be

17   justified even if you do have a statistically

18   significant interaction term.

19   DR. SINGPURWALLA: See, what I am afraid

20   of is that if you did this on some other day and

21   you had the same policy of pooling at random you

22   may see a completely different result in the sense

23   that the point you are making may not be made.

24   Well, thank you.

25   MR. DILIBERTI: Thank you.

1   DR. KIBBE: Anybody else? Go ahead.

2   DR. SELASSIE: You mentioned that

3   potential savings to patients are in the billions

4   of dollars if generics are approved. Can you tell

5   me or do you have an idea of what percentage would

6   actually be the lack of savings due to the fact

7   that there are no generics for each of these as

8   opposed to other patent issues?

9   MR. DILIBERTI: That is very difficult to

10 assess because, for example, in looking at patents

11 you need to look even beyond the "Orange Book."

12 Some of these formulations have patents that are

13 not listed in the "Orange Book." So, to compile

14 data like that would be a Herculean task. However,

15 I do know from personal experience that the

16 difficulties in meeting bioequivalence criteria do,

17 in fact, pose a very real barrier to the

18 development of some generics.

19   DR. MEYER: If I could give an example, if

20 your wife is on premarine you know you insurance

21 co-pays $20.00, because there is no generic

22 currently available because of bioequivalence

23 issues, instead of $5.00.

24   MR. DILIBERTI: Right.

25   DR. MEYER: Since my light is on I will

 1   just add that I do agree with you about pooling

 2   data together. A clinical trial, after all, has a

 3   patient come in to a doctor's office; they take a

 4   measurement. A week later another patient comes in

 5   and now you have two groups, and you don't analyze

 6   those separately. So, unless there is really some

 7   reason to think that two groups of 50 can't be put

 8   together to make one group of 100, I think it is

 9   silly not to put them together.

10   DR. KIBBE: Paul?

11   DR. FACKLER: If I could just make a

12   couple of comments, one addressing the issue of AUC

13   and Cmax, there are very few drugs where I think

14   Cmax is not highly variable but AUC is. I would

15   say that from our experience it is the other way

16   around.

17   DR. SINGPURWALLA: I am sorry, I missed

18   that. You are saying that the two are correlated.

19   DR. FACKLER: I am saying that there are

20   very few examples of drugs that are highly variable

21   on AUC but not highly variable at Cmax. Generally

22   it is the other way around, AUC is not as variable

23   as Cmax.

24   DR. SINGPURWALLA: So, it makes my point

25   that you may have a bivariate situation.

1   DR. FACKLER: Yes, absolutely.

2   DR. SINGPURWALLA: Thanks.

3   DR. FACKLER: One of the things I wanted

4   to ask Charlie was on the simulated data you

5   represented 80 percent and 125 percent. I am

6   wondering did you happen to calculate the

7   confidence intervals for the simulated data sets to

8   show where the 90 percent confidence intervals

9   would have resulted? Because I am certain they are

10   far beyond 80-125.

11   MR. DILIBERTI: That is right. No, I did

12   not go through that calculation.

13   DR. FACKLER: The last point I wanted to

14   make was that on the graph of the number of

15   subjects needed to get to 80 percent power versus

16   the variability, it is important to recognize that

17   80 percent power means that one out of five studies

18   under those conditions will fail to show

19   bioequivalence, or only four out of five will. So,

20   even if a product is tested against itself with,

21   for instance, 30 percent variability, using the

22   number of subjects in that particular graph one out

23   of five studies will fail to show that the product

24   against itself is bioequivalent.

25   DR. KIBBE: Shall we move along? I think,

 1   Gordon, you are up.

 2   Highly Variable Drugs: Sources of Variability

 3   DR. AMIDON: I am going to talk about

 4   sources of variability and emphasize mechanisms of

 5   absorption and focus on bioequivalence from an

 6   absorption point of view. It is the approach I

 7   have been taking for the past 10 to 15 years.

 8   [Slide]

 9   If you think about bioequivalence where we

10   are comparing drug products, then the question of

11   bioequivalence is really a dissolution question.

12   Right, the same drug? So, we should be looking at

13   mechanism and dissolution and processes that are

14   controlling absorption and develop our tests around

15   that mechanism, what is controlling the process.

16   Of course, plasma levels are the gold

17   standard. Our business is to ensure that plasma

18   levels match the innovator product used in the

19   clinical testing. That is the criterion, no

20   question about that; no argument about that. The

21   question is what test.

22   [Slide]

23   So, I want to show some of the factors.

24   We tend to focus on bioequivalence from a plasma

25   level point of view over here. We focus on the

 1   plasma which is the gold standard. But if

 2   absorption is controlled by the dissolution

 3   process, dissolution controls the presentation of

 4   drug along the gastrointestinal tract and,

 5   therefore, controls the rate and extent of

 6   absorption. If the rate and extent of absorption

 7   is the same, then the plasma levels will be the

 8   same. So, in the question of bioequivalence then

 9   the real scientific issue is how do we set a

10   dissolution standard? My position may be a little

11   extreme because no one seems to want to think about

12   that very much but that is the reality of the

13   science.

14   [Slide]

15   So, I think if you have two drug products

16   that present the same concentration profile along

17   the gastrointestinal tract, they will have the same

18   rate and extent of absorption and systemic

19   availability. You may want to think about that,

20   the same rate and extent of absorption implies the

21   same systemic availability. So, we need to focus

22   on product.

23   [Slide]

24   Some of the processes in the

25   gastrointestinal tract that can lead to the

 1   variability--and I will just illustrate some of the

 2   processes here--would be the gastric emptying,

 3   intestinal transit, luminal concentration both of

 4   pH and surfactants, phospholipids, presence or

 5   absence of food. When you think about it, there

 6   are a lot of sources of variability just in the

 7   gastrointestinal tract.

 8   [Slide]

 9   Systemic availability--what should our

10   testing ensure? It is the gold standard, no

11   question about it. But the question then is what

12   is the best test? What is the best test to ensure

13   plasma levels? And, when plasma levels are

14   difficult to measure or, in the case of highly

15   variable drugs where it requires a lot of subjects,

16   then I think it really requires us to think what is

17   the source of that variability and then what type

18   of test might we set.

19   I would argue that if two highly variable

20   drug products dissolve the same way in the

21   gastrointestinal tract they will be bioequivalent.

22   It might require 100 subjects to show that. I

23   think that is unnecessary. I think you just do it

24   with a dissolution test and the answer will be far

25   simpler.

38

1   [Slide]

2   So, what are some of the physicochemical

3   factors? Clearly, particle size and distribution;

4   wetting and solid-liquid contact; and, of course,

5   in some cases chemical instability such as prodrugs

6   and esterases and peptidases in the

7   gastrointestinal tract can lead to highly variable

8   absorption and, hence, systemic availability.

9   [Slide]

10   I just put one graph in here showing the

11   dependence here of dissolution time, ranging up to

12   30 hours, and gastrointestinal transit time as a

13   function of particle size. I can't manipulate this

14   in this presentation but the dissolution time

15   increases dramatically as the drug solubility

16   decreases. Particle size becomes a critical factor

17   for low solubility drugs. Of course, everyone

18   realizes that but it is not particle size that we

19   put into the formulation, it is the particle size

20   that comes out of the formulation in the

21   gastrointestinal tract. So, those process

22   variables are important.

23   [Slide]

24   Some of the factors in the

25   gastrointestinal tract then are gastric emptying,

 1   intestinal transit, position dependent permeability

 2   along the gastrointestinal tract--duodenum,

 3   jejunum, ileum and colon and, of course, intestinal

 4   mucosal cell metabolism, and in particular CYP3A4

 5   which is highly expressed and differentially

 6   expressed along the gastrointestinal tract, and

 7   potentially PGP expression along the

 8   gastrointestinal tract.

 9   [Slide]

10   To give you an example of variability in

11   gastric emptying rates, we can just look at the

12   light blue because that is administered with 200

13   ml, the approximate glass of water that we use. We

14   used 200 ml here because we did this before we got

15   involved in drug regulatory standards and realized

16   that a glass of water was the U.S. standard; not

17   the standard in Japan. We are trying to figure

18   that out, what is a glass of water in Japan. So,

19   with 200 ml you can see that the variability in

20   gastric emptying. Depending on when you dose in

21   the fasting state, it ranges from 5 minutes to

22   about 22 minutes. There is about a 4-fold

23   variation in gastric emptying rate depending on

24   when you administer to a particular subject. This

25   is because of the different contractual activities

 1   in the fasted state, shown here as phase 1, 2, 3

 2   and 4.

 3   [Slide]

 4   Clearly, intestinal transit--again, this

 5   is a movie but I can't show it with this

 6   presentation--transit through the gastrointestinal

 7   tract where the drug is released in the duodenum.

 8   It has a very short transit time, maybe 10, 15

 9   minutes through the duodenum, jejunum, ileum and

10   colon. The dissolution rate, particularly of a low

11   permeability drug where the permeability appears to

12   be the rate-determining step to absorption, the

13   permeability profile along the gastrointestinal

14   tract is very important.

15   [Slide]

16   There are about 10 L of fluid processed in

17   the gastrointestinal tract per day, actually

18   depending on which book you read, 8 to 10. Of the

19   10 L that are processed, only about 2 L are

20   actually ingested as external. The other 8 L are

21   ourselves. We are continually secreting and

22   reabsorbing not only fluids but cells and proteins

23   and other ions that are secreted into the intestine

24   so there is a tremendous amount of variability and,

25   of course, food has a large impact on that as well.

 1   So, that is a major factor that can be involved in

 2   the variability and dissolution and absorption in

 3   the gastrointestinal tract.

 4   [Slide]

 5   I show here just ranitidine, a low

 6   permeability drug. This is animal data. I don't

 7   have human data and, in fact, it is very hard to

 8   get human data although there is some data

 9   available. The duodenum, jejunum, ileum--there is

10   a significant difference in permeability. So, you

11   can envision a slowly dissolving ranitidine

12   product--I don't know if there are any, but

13   releasing in the ileum would have very poor

14   absorption. So, dissolution for a low permeability

15   drug is probably more important because, in

16   general, the permeability in the upper part of the

17   gastrointestinal tract is more important or higher,

18   I should say.

19   You know, we used to use language like

20   "rapidly but incompletely absorbed." You would see

21   that in the literature after analysis of

22   pharmacokinetic data and I would say how can that

23   be? It doesn't make sense to me. If it is rapid

24   it should be well absorbed. Right? Clearly, there

25   has to be position-dependent permeability and the

 1   absorption rate must decrease dramatically at some

 2   point very quickly after the drug is administered.

 3   Presumably, that is the result of drug getting into

 4   the ileum or distal in the small intestine where

 5   there is lower absorption.

 6   [Slide]

 7   PGP--this is some immunoquantitation

 8   results on CYP3A4 showing the variation in the

 9   duodenum, ileum and colon, much less in the colon

10   so that there is less metabolism, particularly if

11   there is a controlled release formulation releasing

12   drug in the colon and, of course, much more in the

13   liver. I don't know, maybe Leslie is going to say

14   more about the metabolism source of variability,

15   maybe not. You are shaking your head, no.

16   [Slide]

17   I am going to propose that we classify the

18   drugs, highly variable drugs using BCS. Here is

19   what I think we would see. We need to actually

20   look at particular drugs. In fact, I would like to

21   see a list of drugs perhaps based on the

22   variability of reference products, whatever we

23   could find today, develop a list of highly variable

24   drugs or that we think might be highly variable,

25   and then look at their properties and decide what

 1   are the likely sources of variability.

 2   Anyway, I know there are certain so-called

 3   highly variable drugs that are Class I drugs. They

 4   have to be low dose, low solubility drugs but they

 5   are soluble enough to dissolve in a glass of water.

 6   That is our criteria at the present time. So, if

 7   those drug products dissolve rapidly--if they do; I

 8   don't know if they do, we should look at that and

 9   it is over; there is no issue. It is all biologic

10   variability; nothing to do with the product

11   variability. Again, that is a hypothesis.

12   Probably the majority of the drugs that

13   are highly variable are in Class II where there is

14   low solubility, potentially Class IV for some

15   higher molecular weight compounds. There, the

16   solubility-dissolution metabolism interaction can

17   be difficult to separate and that is where we would

18   need to look more carefully at the drug products to

19   determine whether it is the solubility and

20   dissolution variability or whether it is a

21   metabolism variability that is leading to the high

22   variability in plasma levels.

23   [Slide]

24   So, I think that the BCS classification

25   can help focus on the source of the high

 1   variability. Then, in the case of rapid

 2   dissolution of Class I and Class III drugs a

 3   dissolution standard may be enough. There may not

 4   be too many highly variable drugs because I think

 5   the majority would be the low solubility Class II

 6   or Class IV drugs and there I think metabolism

 7   and/or dissolution can be the source of

 8   variability. In the case of metabolism, the

 9   metabolism variation would be due to the

10   variability and dissolution and presentation along

11   the gastrointestinal tract. So, again, it comes

12   back to a dissolution issues.

13   In fact, I would propose that we look more

14   carefully at the highly variable drugs, the sources

15   of variability, again asking the critical question

16   what is the best test? What is the best test? I

17   will go back to the original implementation of BCS

18   in the case of high solubility, high permeability,

19   rapidly dissolving drugs. Plasma levels are

20   telling us nothing about the product differences.

21   It is only telling us about gastric emptying

22   differences at the time of administration of

23   patients or subjects. So, again, focusing on

24   dissolution and classification I think can help us

25   unravel and simplify some--maybe not all. Maybe

 1   not all of the highly variable drugs can be

 2   simplified this way but I think some of them can be

 3   simplified this way. For those drugs that are

 4   complicated, we just say they are complicated.

 5   Take a drug like premarine. You have already

 6   mentioned that, Marvin. I think that premarine is

 7   a complicated drug. That is life; that is the way

 8   it is. It is too complicated for us to unravel

 9   today because of the way we regulate drugs and

10   approve drugs. So. I am happy to answer any

11   questions by the committee.

12   DR. KIBBE: Questions, folks? Jurgen?

13   DR. VENITZ: I agree with you, I am very

14   much in favor of identifying sources of variability

15   and what you are presenting are obvious sources of

16   variability, and it always bothers me when we talk

17   about highly variable drugs and they are defined

18   phenologically. All we are doing is a clinical

19   study. We are measuring Cmax and AUC and we find

20   that they vary a lot, and that is the end of it,

21   and now let's change criteria to see whether they

22   can fit bioequivalence. So, I agree with you on

23   that.

24   What I won't agree with you, at least not

25   fully, is that it is all a dissolution issue. I

 1   think you are ignoring, in my mind at least, the

 2   effects that excipients may have that could be very

 3   different between formulations so that may not have

 4   an impact on dissolution but may have an impact on

 5   pH, may have an impact on permeability and may have

 6   an impact on GI metabolism. Now, I don't know

 7   whether that is a significant problem or not but I

 8   think it is more than dissolution that you are

 9   looking at. It doesn't preclude what you are

10   recommending, which is basically do dissolution

11   tests and find out if that is an issue and then see

12   how that matches your in vivo data. That is just a

13   comment.

14   DR. AMIDON: If we extend the dissolution

15   to dissolution of the excipient, that is, the

16   dissolution of the excipient and the drug, then I

17   think we would be okay; I think my statement would

18   be okay.

19   DR. VENITZ: But if you have products that

20   have different excipients, that is my point.

21   DR. AMIDON: Yes, okay.

22   DR. VENITZ: As you said, life is

23   complicated. Sometimes it works; sometimes it

24   doesn't.

25   DR. AMIDON: Right. So, that is the

 1   function of what is the source of the variability.

 2   DR. VENITZ: Yes.

 3   DR. KIBBE: Ajaz?

 4   DR. HUSSAIN: I worked with Gordon for

 5   many years on developing the BCS guideline, and so

 6   forth, and we actually did examine that very

 7   question of excipients and their impact not only on

 8   the dissolution process but on permeability and

 9   metabolism and it is a serious issue and I think we

10   learn more about transport every day. Therefore,

11   clearly, I think when Gordon mentioned dissolution,

12   we have discussed that so many times and we always

13   include that as a source of variability and that

14   has to be considered.

15   But, Gordon, I wanted to push you in a

16   different direction. One of the hesitations as we

17   developed the BCS guidance was the reliability of

18   the in vitro dissolution test. We were not

19   confident that the current test really was good

20   enough to extend it to the slower releasing

21   products. So, that was the reason we crafted

22   rapidly dissolving and said dissolution is not rate

23   limiting and, therefore, we can rely on the current

24   dissolution test to do that.

25   I think as we move forward here, I think

 1   what we have done with the PAT initiative is to

 2   sort of say, all right, let's really ask the

 3   question what are the criteria variables, what are

 4   the root causes of this. So, go back to the basics

 5   as to particle size, and so forth, and if you

 6   really understand those relationships then you have

 7   a better link between your formulation and your

 8   excipients; you have your process directed to the

 9   clinical relevance. So, that is the opportunity

10   that technology is offering us to do that without

11   having to do an artificial in vitro test where

12   questions keep continuing and increasing with

13   respect to the relevance of that in vitro test.

14   DR. AMIDON: I certainly obviously agree,

15   Ajaz. We have talked about these issues for many

16   years. I did use the word in vivo dissolution.

17   There is a big step from in vitro to in vivo. I

18   don't think it is magic; it is just complicated and

19   I think we can figure that out. I think we can

20   determine for any particular drug what might be a

21   good representative dissolution test, and I might

22   call that a bioequivalence dissolution test rather

23   than a QC, quality control, dissolution test. But

24   you are absolutely right. The issue is really in

25   vivo dissolution and how do we capture that in some

 1   in vitro methodology. I don't think we have

 2   thought about that very hard at all. I am not sure

 3   why. We use the term dissolution very generically

 4   when it should be much more specific.

 5   DR. KIBBE: Les wants to comment and then

 6   Nozer. Can you make a comment, Les, because you

 7   are not part of the committee?

 8   DR. BENET: They said as a visitor I can.

 9   I wanted to comment on BCS and what Jurgen brought

10   up in terms of the excipients. When we initiated

11   BCS I was very strong concerning the potential for

12   excipients on Class I drugs and we have written the

13   rules to make sure that these excipients don't have

14   an effect. In fact, I now recognize that with

15   Class I drugs that is not a problem, that the

16   excipients won't be a problem in terms of affecting

17   at least the transporters. But they will be a

18   problem with Class III drugs.

19   So, so far I have been very opposed to

20   moving the Class III drugs because I can make a

21   Class III formulation that will pass dissolution,

22   any dissolution, and fail. The reason is that

23   Class III drugs need uptake transporters to get

24   absorbed and, therefore, I can block an uptake

25   transporter in the gut with a substance that has no

 1   dissolution criteria. So, I still think we are a

 2   little early in translating this dissolution

 3   criteria beyond Class I, but I think we were

 4   correct in Class I and the extra safeguards we put

 5   in actually really turn out not to be necessary.

 6   DR. SINGPURWALLA: I like this concept of

 7   looking at the causes of variability. I see this

 8   as a first step towards going to a Bayesian

 9   alternative for the existing methodology that was

10   criticized by the first speaker. But I do have a

11   question perhaps both for you and also for the

12   first speaker. Has anybody looked at the

13   reliability of the testing instrument itself?

14   Because if the testing instrument itself shows a

15   large variability--if the instrument itself shows a

16   large variability then you don't know whether the

17   variability is coming from the instrument or from

18   the particular drug or the combination of the

19   instrument, the drug and the patient.

20   DR. KIBBE: Anybody? Who wants to handle

21   that?

22   DR. VENITZ: I think by instrument what

23   you mean is the human being used in those studies.

24   Are you talking about dissolution or are you

25   talking about in vivo?

 1   DR. SINGPURWALLA: Both.

 2   DR. VENITZ: Well, then let's talk about

 3   in vivo and I will leave it up to you to talk about

 4   dissolution. What you are looking at is the Cmax's

 5   and the areas under the curves. They do not only

 6   depend upon absorption and dissolution; they depend

 7   on everything that happens after the drug gets in

 8   the body, which is something we are not interested

 9   in. If that contributes significantly to the

10   variability, then you are looking at primarily

11   variability and disposition which determines why we

12   have a highly variable drug, not because there is

13   variability in absorption. So, your instrument

14   would be a very noisy instrument I think, to use

15   your lingo.

16   DR. SINGPURWALLA: Right. You have an

17   instrument by which you measure these things, like

18   a thermometer. If your thermometer is bad--

19   DR. VENITZ: I am saying that for some

20   drugs it could well be that you have a very noisy

21   instrument and the noise is not related to what you

22   are trying to measure.

23   DR. SINGPURWALLA: Exactly.

24   DR. KIBBE: Let me just take the

25   prerogative of the chair for half a second and then

 1   I will let you speak. It is very difficult for us

 2   to understand the real noise level of the

 3   instrument. The instrument is the bioequivalency

 4   test itself and the agency gets submissions with

 5   bioequivalency tests that are passed. The question

 6   is how many were done that failed before the one

 7   that passed, and what was done to make that work?

 8   I think if you go back and we got a bunch

 9   of data together, which we can't but it would be

10   interesting to look at, we would find that the

11   instrument is very crude and the reason we live

12   with it is that it is close to the clinical

13   therapeutic outcomes that we really want to measure

14   in terms of steps away from that outcome. What

15   Gordon is recommending is that we even eliminate

16   the human from our decision-making process, which

17   brings us further away from the ultimate goal which

18   is to know that it therapeutically equivalent, and

19   we have to be sure that our predictor is going to

20   hold true. Those are the problems I think that we

21   all have been struggling with for 25 years.

22   DR. HUSSAIN: Now I have three comments.

23   With respect to the instrument variability, I think

24   it is a very important question. In the case of

25   bioequivalence testing we try to minimize that and

 1   try to make it more precise and more accurate by

 2   doing a crossover study. We test the two products

 3   in the same patient in a crossover fashion. So,

 4   that is our attempt to minimize that. The other

 5   attempt that we had to minimize is to get a group

 6   of more similar individuals but we wanted to move

 7   away from that in the general population because

 8   the crossover is a way to minimize that. I also

 9   pointed out with respect to variability the

10   dissolution test. I think as we think about that,

11   we need to address that.

12   But the point I think, going back to the

13   key question, is what are the important questions

14   here? Dr. Kibbe's comment was, in a sense,

15   bioequivalence. For therapeutic equivalence our

16   approach is very simple. First you need to be

17   pharmaceutically equivalent and then, if there is a

18   need, you do a bio study. For example, for

19   pharmaceutical equivalence for solutions you don't

20   need a bio study. So pharmaceutical equivalence,

21   bioequivalence and then therapeutic

22   equivalence--those come together to define that. I

23   could sort of generalize what Gordon has said, in a

24   sense if we understand our formulations, if we

25   understand our processes, if we understand the

 1   mechanisms, pharmaceutical equivalence essentially

 2   is defining therapeutic equivalence.

 3   DR. AMIDON: To come back to your question

 4   about the dissolution apparatus, there is a range

 5   of dissolution apparatus in the USP that are used

 6   internationally, and you can study many of the

 7   variables that change in vivo by pH and surfactants

 8   in those apparatus. The apparatus themselves have

 9   been proven perhaps historically to be very

10   reliable, although you could argue maybe today that

11   we could design a better apparatus but that is very

12   complicated because these things are used in many

13   companies internationally with defined procedures

14   that are approved by the regulatory agencies and

15   making change in an apparatus is a very complex

16   process.

17   But, yes, we can study the various

18   variables in vivo and I think that a dissolution

19   test that included changes in pH and surfactant to

20   reflect what is happening in vivo is something we

21   should do. We don't do that; we just do fixed pH

22   and follow the dissolution as a function of time.

23   So, I don't think we use our apparatus very

24   insightfully actually.

25   DR. KIBBE: I would argue that the way we

 1   use dissolution is reliable but insensitive, and we

 2   need to do a lot more to be able to make that

 3   conversion. Anybody else?

 4   DR. MEYER: Gordon, I listened to the PAT

 5   stuff all day yesterday and what I got out of it is

 6   that it is applicable to this so the idea of why do

 7   we have variability--right now we are proposing to

 8   potentially change our release specifications

 9   because our product is too variable and that is not

10   acceptable in the manufacturing arena. You go back

11   and figure out why it is too variable. I wonder

12   how much data is really available on if I gave

13   myself a rapidly absorbed drug once for the next

14   three weeks, what would my profiles look like? I

15   don't know that there is a lot of data that shows

16   reproducibility in a subject, unless it was the old

17   multiple dose studies where the drug was

18   essentially eliminated in 24 hours.

19   So, I think we need some more information.

20   I don't know, maybe the agency does this, but when

21   the innovator firms do special populations and they

22   find the elderly are different than the young, do

23   they have to then go further and explain is that

24   gastrointestinal pH, is it transit, is it

25   metabolism, what is the reason for it. Because I

 1   think then we can get some background information

 2   on source of variability.

 3   Just to bounce off an idea which is

 4   undoubtedly ludicrous, do we need in a sense to

 5   prescreen some subjects so we have a calibrated man

 6   or, if you will, a USP man or woman that is then

 7   allowed into the study so if they have less

 8   variability they get into our study? Could we do

 9   that? One thing that really troubles me is the

10   current policy, and I understand why it is and I

11   think I support it, of having different mechanisms

12   of release tested against each other in a

13   bioequivalence study, an oral study versus a

14   particular dosage form. Intestinal transit can

15   have a profound difference on those two so if you

16   have a uniform man, that uniform man may show them

17   to be equal but if you throw in a vegetarian, that

18   vegetarian might show the oral tablet is excreted

19   in four hours and the other person may take much

20   longer. So, just some support really for the idea

21   of knowing where the problems are; can we reduce

22   variability somehow; are subjects legitimately--is

23   that a viable approach?

24   DR. AMIDON: I don't know, I am not sure I

25   would want to take on preselecting subjects because

 1   what criteria are you going to use? Normal in what

 2   sense?

 3   DR. MEYER: I am thinking more in terms

 4   of, say, rapid metabolism or poor metabolism. We

 5   do that now somewhat routinely.

 6   DR. AMIDON: Right.

 7   DR. MEYER: So, we might give a

 8   panel--CROs now, they use the same subjects over

 9   and over again anyway. Let's characterize them

10   first before they are allowed into subsequent

11   studies.

12   DR. KIBBE: Paul, go ahead.

13   DR. FACKLER: If I can just comment on

14   that, we used to do bioequivalence studies in males

15   only and restricted their ages from 18 to 45, I

16   believe. The agency has recently requested that BE

17   studies be done in a larger group of people, more

18   representative of the American population so we now

19   include females and we include the elderly, and it

20   just makes the variability problem that much worse.

21   I mean, I agree completely that ideally if we would

22   get 15 people all exactly the same way, all exactly

23   with the same physical habits, generally with the

24   same diet, it would make BE studies easier to pass

25   because we have reduced the variability in the

1   subjects. But the agency has been going, at least

2   recently, in the opposite direction, making these

3   products in particular less likely to pass against

4   themselves again.

5   DR. KIBBE: It is my impression, and I am

6   sure the FDA people will correct me, that they are

7   trying to get two answers using one study, and that

8   is, are the two formulations behaving the same,

9   should be their behavior independent of the

10   subjects studied, and are there variabilities

11   between product-subject interactions that might be

12   significant in special populations. I think it is

13   really hard to do that in one study, and that is

14   one of the problems you are running into. What I

15   think Gordon is suggesting is if we understood the

16   variables we might not have to use that blunt a

17   tool to estimate what will happen in the average

18   patient.

19   I would love to see us be able to do that.

20   There was a wonderful report done--Les will

21   remember because he is almost as old as I am--by

22   the agency that looked at dissolution and tried to

23   correlate it with bioequivalency data that they had

24   almost twenty years ago and there was absolutely no

25   way that dissolution predicted any of the results

 1   that they got on those studies. So, it is more

 2   complicated than it first appears.

 3   DR. AMIDON: I got involved in this

 4   process about that time, and my position is you

 5   just did the wrong test. Okay? That is the

 6   problem. So, it is a matter of refining the

 7   dissolution test to make it more relevant to the

 8   variables that we need to control to ensure

 9   bioequivalence. We haven't done enough of that.

10   DR. KIBBE: Ajaz, you have a comment?

11   DR. HUSSAIN: The key aspect I think is

12   that we need to keep the focus on asking the right

13   questions and if a bioequivalence study is only

14   for, you know, males 18 to 45, is that the right

15   question from the public health aspect because the

16   product is going to be used in all populations?

17   So, you really have to go and look at the

18   fundamentals of what is a bioequivalence study. If

19   it is just confidence interval criteria, then that

20   is one aspect.

21   DR. SINGPURWALLA: Why not have a separate

22   set of drugs for different categories of people?

23   Like, you know, you have cholesterol drugs 20 mg,

24   10 mg and you specify your milligrams based on the

25   population.

 1   DR. HUSSAIN: That is a major aspect of

 2   dose finding and then labeling that goes into the

 3   new drug development process itself.   The

 4   bioequivalence essentially has been a quality

 5   assurance approach to making sure that a

 6   pharmaceutically equal product has an in vivo rate

 7   and extent of absorption similar to the innovator.

 8   That is one of the main reasons for doing the bio

 9   study, to make sure that your assumptions and your

10   in vitro methods are more reliable or at least

11   conform from that perspective.

12   DR. KIBBE: Thank you.   Unless someone

13   else has a comment we will let you off the hook for

14   a few minutes, and go to Dr. Benet who will

15   enlighten us.

16   Clinical Implications of Highly Variable Drugs

17   DR. BENET: I am older!

18   [Laughter]

19   Thank you.   It is a pleasure to be here.

20   I think the last two times I have appeared before

21   this committee I stayed in my office but it is nice

22   to be here in person, and I thank you for the

23   opportunity.

24

25   We have been discussing at an

 1   international level, I was reminded as I heard

 2   this, for 15 years--we held our first sort of

 3   consensus conference in 1989 to try to develop

 4   standards for bioequivalence and we are still at

 5   it.

 6   [Slide]

 7   This was said by the first speaker but

 8   this is a slide that is now maybe 12 years old, or

 9   at least parts of it. The current U.S. Procrustean

10   bioequivalence guidelines: the manufacturer of the

11   test product must show using two one-sided tests

12   that a 90 percent confidence interval for the ratio

13   of the mean response--usually the area under the

14   curve and Cmax--of its product to that of the

15   reference product is within the limits of 0.8 and

16   1.25 using log transformed data. It is

17   Procrustean, and those of you who don't remember

18   your mythology, the Procrustes himself was a robber

19   that took people when they came through his gate

20   and put them on his bed, the Procrustean bed. If

21   they were too long he cut off their feet. If they

22   were too short he stretched them out until they fit

23   the bed. And, that is exactly what we have,

24   Procrustean guidelines that say all drugs must fit

25   the same criteria no matter what the issues are.

1   Now, BCS, biopharmaceutical classification

2   system, is non-Procrustean. It is an advance and

3   the obvious answer, Arthur, to why a study failed

4   in looking at dissolution is that we didn't

5   understand the flawed classifications. So, the

6   only time dissolution is going to have any

7   relevance to bioequivalence or bioavailability is

8   for Class I and Class III drugs. Since we looked

9   at all drugs about 20 years ago, we were obviously

10   going to fail. So, we are making some advances.

11   But I strongly believe and have suggested over a

12   number of years that there need to be other

13   non-Procrustean advances and that is what I will

14   talk about today.

15   [Slide]

16   What are we trying to solve? What are the

17   bioequivalence issues and what concerns patients

18   and clinicians so that they have confidence in the

19   generic drugs that are approved by the regulatory

20   agencies so that they feel there are no questions

21   related to their therapeutic efficacy?

22   It doesn't help to tell them--and that is

23   a true fact, it doesn't help to tell them that

24   there has never been a drug that passed the U.S.

25   FDA bioequivalence issues that ever caused any

 1   therapeutic problems in a prospective study. That

 2   doesn't help them because they always say, well, it

 3   is the next drug and they have a lot of emphasis

 4   out there from people who would like them to

 5   question the bioequivalence criteria. So, this is

 6   always in my mind, that one of the major issues

 7   that we face is not necessarily scientific but it

 8   is creating an environment where the American

 9   public has confidence in the regulations that we

10   use and the drugs that we say can go on the market.

11   But what we have done and what our

12   concerns are now with therapeutic index drugs, NTI,

13   we need to have practitioners have assurance that

14   transferring a patient from one drug product to

15   another yields comparable safety and efficacy, and

16   a few years ago we termed that switchability and we

17   developed or tried to develop a number of

18   statistical criteria to approach that. The issues

19   we are facing today are for a wide therapeutic

20   index, highly variable drugs which do not have to

21   study an excessive number of patients to prove that

22   two equivalent products meet the preset one size

23   fits all statistical criteria. So, these are the

24   issues I want to address and ask the committee to

25   take cognizance of.

```
 1            [Slide]

 2            Now, it was not obvious a few years ago

 3   but it is very obvious today that if you have a

 4   narrow therapeutic index drug it is very easy to

 5   pass the bioequivalence criteria, and that is

 6   because narrow therapeutic index drugs, by

 7   definition, must have small intra-subject

 8   variability.  If this were not true for narrow

 9   therapeutic index drugs, patients would routinely

10   experience cycles of toxicity and lack of efficacy,

11   and therapeutic monitoring would be useless.  So,

12   in fact, it is not an issue.  Narrow therapeutic

13   drugs we take care of and we do very well from a

14   scientific issue.  We might not have the

15   confidence, and I will come back and address that.

16            [Slide]

17            Let's look at some narrow therapeutic

18   index drugs.  They have high inter-subject

19   variability and they have low intra-subject

20   variability.  That is why we don't have to worry;

21   when we get the patient to the right place, they

22   stay there.  The question was are they all Class I,

23   Class II.  Theophylline is a Class I drug.  So,

24   there are drugs on this list that are Class I drugs

25   although most of them are Class II drugs.
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 1   Getting back to the reliability of the

 2   instrument, I would just like to make a comment.

 3   Look at the warfarin sodium intra-subject

 4   variability. The clinical measure that the

 5   clinician uses to judge the status of the patient

 6   in terms of his blood thinning capability, the INH

 7   measurement, is significantly more variable. So,

 8   in fact, what the clinician does in testing if the

 9   drug is working is more variable than the patient

10   is going to experience from dose to dose in terms

11   of the criteria for this particular drug. So,

12   these are interesting questions.

13   [Slide]

14   Now, we tried to address this

15   switchability issue over a long period of time with

16   the concept called individual bioequivalence, and I

17   chaired the expert panel for about three years and

18   tried to address this issue. The ideas about

19   individual bioequivalence were that we were going

20   to get these promises, we would address the correct

21   question, switchability in a patient. We would

22   consider the potential for subject by formulation

23   interaction. There would be incentive for less

24   variable test products. Scaling would be based on

25   variability of the reference product both for

 1   highly variable drugs and for certain

 2   agency-defined narrow therapeutic range drugs.

 3   And, we would encourage the use of subjects more

 4   representative of the general population.

 5   In fact, none of that worked and we gave

 6   up on it. So, did it address the correct question?

 7   Well, the question was, was there even a question

 8   and was there any necessity for this at all, and

 9   there is no evidence that the present regulations

10   are inadequate and that we need to be more rigorous

11   in our definition related to switchability.

12   [Slide]

13   Consider that the subject by formulation

14   interaction turned out to be an unintelligible

15   parameter from both the agency and the exterior

16   scientific community.

17   Incentive for less variable test products,

18   yes, but that could be solved by average

19   bioequivalence scaling and that is what at least I

20   am here to talk about today.

21   Scaling based on variability of the

22   reference product both for highly variable drugs

23   and for certain agency-defined narrow therapeutic

24   index drugs, again average bioequivalence with

25   scaling could solve this issue.

 1   Encourage the use of subjects more

 2   representative of the general population, that was

 3   a good hope but it completely failed in terms of

 4   how people designed their study. So, it didn't

 5   work.

 6   [Slide]

 7   I recognized in Lawrence's introduction

 8   that the FDA doesn't have a definition for highly

 9   variable drugs. This is the consensus definition

10   that came out of a number of international

11   workshops, highly variable drugs should be those

12   when the intra-subject variability is equal or

13   greater than 30 percent. The idea is that for wide

14   therapeutic index highly variable drugs we should

15   not have to study an excessive number of patients

16   to prove that two equivalent products meet this

17   preset one size fits all statistical criteria.

18   This is because, by definition, again

19   highly variable approved drugs must have a wide

20   therapeutic index, otherwise there would have been

21   significant safety issues and lack of efficacy

22   during Phase III testing. In fact, highly variable

23   drugs fall out; don't get to the market. They fall

24   out in Phase II because the company can't prove

25   that they work and they can't prove that they are

 1   safe. So, we don't have highly variable narrow

 2   therapeutic index drugs. We only have drugs that,

 3   with this tremendous variability that we

 4   potentially saw in the first speaker's slide, don't

 5   have any problems. And, those individual patients

 6   having very high levels one time, low levels the

 7   next time, high areas under the curve one time, low

 8   areas under the curve the next time get through.

 9   In fact, for those highly variable drugs we don't

10   need to worry about the genetic differences in

11   their enzymes. It has already been shown that,

12   yes, there are tremendous differences. Somebody is

13   going to have very high levels because they lack

14   the enzyme; somebody is going to have very low

15   levels but still they are safe and effective

16   because they are wide therapeutic index drugs.

17   [Slide]

18   But it makes it very difficult, as was

19   also pointed out by the first speaker, to get them

20   to be bioequivalent and here is my champion or what

21   I think is the champion from the data that I have

22   seen, and this is progesterone which I believe is

23   the poster drug for highly variable variability. A

24   repeat measures study of the innovator's product

25   was carried out in 12 healthy post-menopausal

 1   females and it yielded intra-subject variability in

 2   an AUC of 61 percent for the coefficient of

 3   variation and intra-subject coefficient of

 4   variation for Cmax of 98 percent.

 5   If you did the calculations, it came out

 6   that you needed 300 women just to meet the

 7   statistical criteria and, in fact, this was not a

 8   study that a generic company, or at least the

 9   company interested in this, could afford to carry

10   out because, for sure, we know that the way we

11   design the studies there is a chance, even if you

12   had the right numbers, that one out of ten or one

13   out of five studies would fail just on statistical

14   chance and you have carried out a study with 300

15   people in it to prove that this highly variable

16   drug is bioequivalent. This is the issue that we

17   are asking you to talk about today, and can we

18   solve this problem so that we don't have highly

19   variable, very safe, wide therapeutic index drugs

20   for which we can't prove bioequivalence because of

21   the inherent variability of the innovator product.

22   [Slide]

23   I appeared before this committee three and

24   a half years ago to give the recommendations of the

25   FDA expert panel on individual bioequivalence, and

 1   these are some of the recommendations. One that I

 2   didn't put on here is that all generic drug studies

 3   must be submitted to the agency, and I am very

 4   pleased that that has happened and congratulations

 5   to the agency.

 6   Our recommendations at that time were that

 7   sponsors may see bioequivalence approval using

 8   either average bioequivalence or individual

 9   bioequivalence, and we recommended that the subject

10   by formulation parameter be deleted since no one

11   knew what to do with it and we couldn't justify it

12   statistically.

13   We asked that scaling for average

14   bioequivalence be considered, that the agency and

15   the statistical group go into this and it be

16   something to be followed up and presented to this

17   advisory committee at some time in the future.

18   We recommended at that time that if an IBE

19   study, individual bioequivalence study, was carried

20   out and the test product fails you could not then

21   reanalyze with average bioequivalence because in

22   those days we said you had to pick one or the

23   other.

24   Here is something that we recommended that

25   I want to bring up again today because this has to

 1   do with confidence. We recommended the point

 2   estimate criteria be added, and we added this not

 3   on any scientific basis that we are going to rule

 4   out products, we said that these criteria are

 5   always met today and what we have is a conception

 6   or a view outside that it would be possible to have

 7   products that differ by 25 percent, and that we

 8   would be well served if we would say let's put a

 9   point estimate criterion in addition to our

10   criteria--AUCs of at least plus/minus 15 for point

11   estimate criteria and Cmax plus/minus 20 percent no

12   matter what you do, and if you have narrow

13   therapeutic index drugs make it even smaller, make

14   the point estimate plus/minus 10 percent for AUC

15   and plus/minus 15 percent for Cmax.

16   [Slide]

17   So, what I am suggesting here today and

18   what I am recommending to the committee to do is

19   ask the agency to develop methodology, and we are

20   going to hear some, to allow approval based on

21   weighting of average bioequivalence analytical for

22   highly variable drugs so that we can bring some

23   drugs to the market that can't be studied because

24   of the progesterone example. Also, that the point

25   estimate criteria be added to the criteria because,

 1   in fact, all products will pass these criteria at

 2   the present time and we won't be harmed, or we will

 3   increase the confidence of those that say, you

 4   know, you could have two products that differ by 50

 5   percent because look at what the FDA criteria say.

 6   Now, the FDA criteria, as they used to be

 7   written two years ago, were easily misinterpreted

 8   but that also changed two years ago and now the

 9   criteria are written in a way that no clinician can

10   understand them in the first place so they won't be

11   misinterpreted.

12   [Laughter]

13   They still say exactly the same thing but

14   they can't be misinterpreted to say you could have

15   two products that differ by 50 percent. So, these

16   are my recommendations. Thank you for listening to

17   me.

18   DR. KIBBE: Questions for Dr. Benet?

19   DR. SINGPURWALLA: I have a comment not

20   just to you but to everyone else. This example of

21   highly variable drugs shows, to me, how the drug

22   industry is buried under the tombstone of

23   frequentist methods. Such methods ignore clinical

24   and biopharmaceutical knowledge, and it is bogged

25   down by its own weight.

 1   DR. BENET: I disagree.

 2   DR. SINGPURWALLA: Why?

 3   DR. BENET: I think you are coming to this

 4   fresh and that is good, but what we are interested

 5   in is safety and efficacy, and in all cases

 6   measures of safety and efficacy are more variable

 7   than any pharmacokinetic measure. What we are

 8   really interested in, what the agency is interested

 9   in is safety and efficacy.

10   DR. SINGPURWALLA: Who said that Bayesian

11   methods do not incorporate high variability? It is

12   these confidence intervals and these confidence

13   limits, and the comment you make is a failure to

14   understand Bayesian methods.

15   DR. BENET: I understand Bayesian methods.

16   DR. SINGPURWALLA: No, you don't; you

17   wouldn't say this.

18   DR. BENET: Well, I welcome the

19   committee's spending the time discussing this with

20   you and if you adjourn I get to go home.

21   [Laughter]

22   DR. MEYER: I think I agree with

23   everything you have said and it embarrasses me no

24   end to say that!

25   [Laughter]

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 1   Is there still going to be a perceived

 2   problem when you have, let's say, a Cmax point

 3   estimate of plus/minus 15 percent? Isn't that

 4   going to solicit illustrations of, well, look, my

 5   Cmax was 115 units and their Cmax was 85 and the

 6   high and low can be switched in the marketplace?

 7   DR. BENET: I think we are never going to

 8   get around that. There are always going to be

 9   people who will take the present situation and use

10   it to their marketing advantage. So, I don't think

11   we can get around that. You know, we have the same

12   issues today. I am not sure that everyone on the

13   committee is aware that in terms of BCS Class I,

14   where you don't have to do a clinical study--I

15   don't know of a generic company that has used that

16   for exactly the reason you are bringing up, Marvin.

17   They would be afraid that someone will go out there

18   and say this product has never been tested in

19   humans; it was approved on the basis of a

20   dissolution. You have confidence in this product

21   so that people that use BCS Class I at the present

22   time are the innovators who use it when they have a

23   SUPAC change or something like that. So, I think

24   we are always going to face that, and I think what

25   we need to do is just try to do the best job that

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 1    we can in making it happen.

 2            DR. KIBBE:  Let me just ask about an

 3    application of one of your recommendations to your

 4    own example.  If you use methodology that is

 5    developed as a weighted average, how would that

 6    play out with progesterone?  In other words, what

 7    kind of numbers would we start to work with?

 8            DR. BENET:  I mean, I do agree with

 9    weighting to the variability of the innovator

10    product.  In other words, that would be the term in

11    the denominator that you would weight.  But there

12    are different statistical issues that have to be

13    addressed that I can't do so we need the expert

14    statisticians to tell us how to approach that.  But

15    that is what I want.  I would want a weighting on

16    the variability of the innovator product in terms

17    of the coefficient of variation for Cmax as one

18    criterion and for AUC as another criterion.

19            DR. KIBBE:  I have always found

20    intellectually attractive the concept of three ways

21    where we could look at variability and then compare

22    it to the generic.  Is that going to help us get to

23    the numbers that we need to make these kinds of

24    decisions?

25            DR. BENET:  Well, there is going to have
```

 1   to be some measure of intra-subject variability.

 2   We need to know that, and I have requested the

 3   agency for many years to make this a requirement

 4   for new drugs, that a measure of intra-subject

 5   variability in humans or even in patients be

 6   included in the approval process and be included in

 7   the package insert. So, we do have to have that

 8   measure some place.

 9   I am very encouraged, even though the

10   agency does not require that, that we are starting

11   to see with many new products, when you look at

12   their package insert, measures of intra-subject

13   variability included because it is important

14   criteria and value that clinicians want to know.

15   What is the inherent pharmacokinetic variability so

16   that then I can say is the pharmacodynamic

17   variability more than this inherent pharmacokinetic

18   variability. If they don't know the inherent

19   pharmacokinetic variability, then they have a tough

20   time making any decision about whether the change

21   in efficacy is related to pharmacokinetics or to

22   real variability. So, somebody has to do this,

23   Arthur, and I think that has to come out of what

24   you recommend.

25   DR. MEYER: Les, you put a little bit less

 1   weight on Cmax than you do on AUC; there is a less

 2   stringent requirement. Is that because Cmax is

 3   more variable because we don't measure it very

 4   precisely, or is it because Cmax is less important

 5   than AUC? And, I would quarrel that we don't have

 6   enough data for the latter conclusion.

 7   DR. BENET: Well, in some cases we do but,

 8   as was initially discussed, it is confounded. As

 9   we all know, Cmax is a very confounded measure and

10   the agency and many academics have spent years and

11   years in trying to develop a new measure. None of

12   them turned out to be any better. So, it is very

13   confounded and, as was stated, is always more

14   highly variable than AUC. I know of no case.

15   DR. MEYER: But it is the only measure we

16   have that has any component of rate in it.

17   DR. BENET: That is correct, but it is

18   more variable.

19   DR. VENITZ: Les, I agree with your

20   additional recommendation to put constraints on the

21   point estimates. You mentioned one of the reasons

22   being that the public needs to be reassured that,

23   indeed, no matter whether it is unintelligible

24   regulation or not, we do have generics that are

25   bioequivalent.

1   What I am personally not certain about is

2   whether I agree with the reference scaling--and,

3   again, we are going to have some more presentations

4   on that--because you are now, in my mind,

5   aggregating variance and mean differences, and I am

6   not sure whether one can offset the other. In

7   other words, if you have a large mean difference,

8   can that be offset by differences in variance?

9   When we had the discussion last time with IBE,

10   surprisingly there were drugs out there in the

11   database that the FDA provided us with that passed

12   IBE but wouldn't have passed ABE, which I think was

13   counter-intuitive for most of us, at least on the

14   committee, in terms that we expected IBE to be much

15   more conservative than ABE and it didn't turn out

16   that way. So, I still personally withhold judgment

17   on the reference scaling but I am very much in

18   favor of putting in additional constraints.

19   DR. BENET: Let me just answer that. I

20   think having the additional constraints solves part

21   of the problem.

22   DR. VENITZ: Yes, that was the reason why

23   I think the committee at that time went along with

24   that because we were worried about the IBE not

25   being conservative enough. Right now you are

1   basically breaking drugs down into two categories,

2   NTIs and non-NTIs, in terms of the criteria that

3   you are going to use or that you are proposing to

4   be used for BE assessment.

5   DR. BENET: Yes.

6   DR. VENITZ: Can you think of additional

7   criteria along the lines that we heard Gordon talk

8   about, that if we understand where the variability

9   comes from we might use different criteria? In

10   other words, is NTI the only thing that we have in

11   some decision tree that decides which way we are

12   going to go?

13   DR. BENET: As I said, the NTI statement

14   there has nothing to do with science because it is

15   easy to prove bioequivalence of NTI drugs. It just

16   has to do with confidence. So, that is why I made

17   it lower, because it is easy to pass.

18   I definitely believe that as we progress

19   we are going to have different criteria, and I

20   think BCS has a real potential for it. I have a

21   big list, my BCS list, and I looked to see what

22   drugs were there and that is why I made sure that

23   theophylline was a Class I drug. I think as we

24   progress--and I presented to the agency last

25   November my newest concepts in terms of using BCS

 1   or some sort of variant of BCS to actually predict

 2   drug disposition, and I think we are going to

 3   progress a lot in the next few years.

 4   DR. KIBBE: Nozer?

 5   DR. SINGPURWALLA: Well, just a general

 6   comment. I was pleased to hear you acknowledge

 7   that newcomers can identify things like

 8   confounding, but I also think that newcomers can

 9   look at an old problem and come up with new methods

10   of addressing that. Therefore, I urge you to pay

11   more attention to alternate methods and not get

12   committed to an old, archaic notion of confidence

13   intervals. These have been criticized in the

14   literature. And, what we see here is repeated use

15   of confidence limits, and the difficulty that

16   confidence limits poses both to the FDA and also to

17   the drug industry in getting their drugs approved.

18   So, I am going to urge you to start paying more

19   attention to alternatives and don't dismiss it.

20   DR. BENET: I don't dismiss it, and my

21   colleague, Dr. Scheiner, has spent a lot of time

22   informing the committee and the agency of these

23   approaches and the Bayesian approach, and I think

24   we are all well aware of it and do recognize it.

25   It is important to have fresh eyes and fresh views

1   of these kinds of issues, but it is also important

2   to recognize that the agency's criteria are safety

3   and efficacy, and when we have criteria that have

4   never failed it is tough to say that we move beyond

5   that criteria to untested criteria in terms of this

6   particular issue. So, that is why the agency must

7   be very careful in the changes that they make.

8   DR. KIBBE: Thank you, Les. We have one

9   more speaker before the break. Dr. Endrenyi,

10   welcome.

11   Bioequivalence Methods for Highly Variable Drugs

12   DR. ENDRENYI: Thank you.

13   [Slide]

14   This presentation was put together with

15   Laszlo Tothfalusi and I would like to acknowledge

16   that.

17   [Slide]

18   I would like to raise a number of

19   questions which I believe that this committee will

20   have to make recommendations about eventually that,

21   certainly, the agency ought to consider. I would

22   like to go through the first part fairly quickly

23   because much of that has already been considered.

24   So, we have the usual criterion of comparing two

25   formulations and the confidence limits for the

 1   ratio of geometric means should be between 0.8 and

 2   1.25. This has already been stated.

 3   [Slide]

 4   It has also been stated that for highly

 5   variable drugs this presents a problem because with

 6   large variations it is very easy to hit that 0.8 to

 7   1.25 and, therefore, many subjects may be needed in

 8   order to satisfy that.

 9   [Slide]

10   For the purpose of this presentation but

11   not necessarily as the final word at all, the

12   coefficient of variation has been considered

13   exceeding 30 percent for highly variable drugs.

14   [Slide]

15   This slide would simply ask is there an

16   issue and this has already been asked and the

17   answer was probably yes. In this case, two

18   formulations of isoptin are considered in the same

19   subject repeatedly, and two different occasions

20   different relationships between the two

21   formulations were obtained. So, it looks as though

22   the drug is not really bioequivalent with itself

23   and that is a concern, but this has already been

24   demonstrated by Dr. DiLiberti.

25   [Slide]

 1   This is perhaps more recent. This was

 2   obtained from Diane Potvin, from MDS, who

 3   demonstrated that, indeed, things look reasonable

 4   as long as the intra-individual CV is up to about

 5   70 percent but beyond that it is very difficult to

 6   satisfy the criteria. There are many, many studies

 7   submitted that failed.

 8   [Slide]

 9   Then she went on, very kindly, to look at

10   details of these highly variable drugs. From this,

11   one could conclude that there is a relationship

12   between the coefficient of variation and failure

13   rate, higher failure rate with higher coefficient

14   of variation. Mind you, these are all submitted

15   studies so this analysis is still biased because

16   the company submitted them in the hope that they

17   would pass, so these are not all studies at all.

18   The second conclusion is that, indeed,

19   AUCs fail less frequently than Cmax's but they

20   still fail with a high frequency. So, the

21   variation of AUCs should not be dismissed.

22   [Slide]

23   Study condition--perhaps I would omit this

24   almost entirely because it is considering single

25   dosing versus steady state. In the U.S. this is a

 1   non-issue because U.S. goes by single

 2   administration even though it has been demonstrated

 3   and we know that frequently in steady state we get

 4   lower variation--not frequently but not always.

 5   [Slide]

 6   This is a study showing that and in the

 7   U.S. I think this is largely at the moment

 8   irrelevant.

 9   [Slide]

10   Study designs, which one to choose? A 2 X

11   2 traditional or replicate design? It need not be

12   a 4-period replicate design; it could be 3.

13   [Slide]

14   Now, the advantage of replicate designs

15   includes that one gets clear estimates of

16   within-subject variations. Particularly the

17   concern would be to get a clear estimate of

18   within-subject variation for the reference product.

19   I would note that this design is favored by K.K.

20   Midha who has worked long years and is certainly

21   one of the foremost experts on the bioequivalence

22   of highly variable drugs and drug products. So,

23   his voice ought to be respected.

24   Secondly, on the other hand, my concern is

25   that one can have a pooled criterion which could

 1   have better properties, pooled criterion related to

 2   the test and reference products together.

 3   There are issues that these replicate

 4   design studies can be evaluated by various

 5   procedures, and a question is whether these

 6   procedures would give the same results and,

 7   therefore, would agencies be able to check how

 8   those results would be calculated and were

 9   calculated.

10   Another question arises, namely, is a test

11   comparing the variations of test and reference

12   products useful; is it needed? Or, perhaps is an

13   estimate of these variations simply sufficient or

14   is that needed?

15   [Slide]

16   Turning to the 2 X 2 crossovers, they are

17   simple; simple to execute, simple to evaluate. An

18   advantage is that there are many studies on file

19   and they could be evaluated retrospectively.

20   Another comment is that the ratio of

21   within-subject variabilities could be estimated.

22   There are procedures that would permit this even

23   from 2 X 2 crossover studies. For example, the

24   procedure suggested here by Guilbaud and Gould is

25   to have for each subject the sum of the test and

1   reference response, AUC or Cmax in this case, and

2   then the difference of the two; plot them against

3   each other, have a linear regression and evaluate

4   the slope, and then apply the slope in that fashion

5   which gives the ratio of the estimated variances.

6   So, it would be possible to evaluate this ratio

7   from 2 X 2 crossovers. However, features of this

8   procedure have not been studied and they ought to

9   be evaluated.

10   [Slide]

11   Now, various possible methods of

12   evaluation, the usual procedure is unscaled average

13   bioequivalence with a criterion of 0.8 to 1.25 for

14   the ratio of geometric means, the GMR. It is also

15   possible to apply unscaled average bioequivalence

16   with expanded bioequivalence limits. One way of

17   doing it is to present these bioequivalence limits.

18   It has been shown that some jurisdictions do this.

19   For example, the ratio of GMR could be between 0.75

20   and 1.33 or 0.7 to 1.43. This is one possibility

21   which is practiced in some areas, or to expand the

22   bioequivalence limits flexibly depending on the

23   estimated variation. I shall talk more about these

24   procedures.

25   Another approach is the scaled average

 1   bioequivalence and, again, I shall refer to this

 2   and shall talk about this, and I also should

 3   mention scaled individual bioequivalence for

 4   comparisons only.

 5   [Slide]

 6   To talk about unscaled average

 7   bioequivalence--these scissors are supposed to be

 8   less than or equal signs so instead of scissors, it

 9   is less than or equal--the unscaled average, as we

10   have seen--this is a bit more formalized but, as

11   you see here, the ratio of geometric means should

12   be between, say, 0.8 or 1.25 or 0.75 and 1.33.

13   This is the same statement as saying that the

14   logarithmic bioequivalence limits should be plus

15   and minus and in between is the difference of the

16   logarithmic means, and that is a useful way to look

17   at it. Now, the procedure is simple but as the 0.8

18   and 1.25 limits were arbitrary so would be any

19   other criteria.

20   But another concern is that whatever way

21   it would be decided, if this is the way to go, then

22   0.75 to 1.33 is a partial solution because it may

23   help drugs with, say, 30, 40 percent intra-subject,

24   intra-individual variation but not those which have

25   higher variations and 50, 60 percent would still be

1   the cut off.

2   [Slide]

3   Another approach would be to expand the

4   limits in proportion to the estimated variation.

5   This has been suggested by Boddy and coworkers.

6   So, here there is a proportionality factor, and the

7   other factor is the estimated standard deviation,

8   intra-subject variation. This procedure has the

9   advantage that the usual testing procedure can be

10   applied with some proviso. The statistical power

11   is independent of the variation and the statistical

12   power is higher, much higher than the unscaled

13   average bioequivalence with the usual criterion so

14   we need fewer subjects.

15   On the other hand, the criterion is that

16   bioequivalence limits, as shown there, are really

17   random variables because they include the estimated

18   standard deviation, estimated intra-subject

19   variation. So, the limit itself is a variable.

20   Therefore, the two one-sided test procedure is not

21   quite correct, however, it is becoming

22   approximately correct with large samples.

23   [Slide]

24   Scaled average bioequivalence is very

25   similar to the previous one except that the S from

 1   the bioequivalence limits, here, came over to the

 2   measure that we apply. So, it is formally very

 3   similar and we have developed and have recommended

 4   procedures for setting the bioequivalence limits.

 5   Again, the advantages are that the

 6   statistical power is independent of the variation

 7   and with the same sample size is much higher than

 8   the unscaled average bioequivalence. I am going to

 9   demonstrate this. There is a sensible

10   interpretation. The first interpretation is very

11   similar to that applied with individual

12   bioequivalence, namely, the expected change to

13   switching is being compared with the expected

14   difference between replicate administrations and

15   one can make sense of that.

16   A second interpretation is that the

17   standardized effect size is being applied which is

18   a clinical interpretation. There are procedures to

19   evaluate confidence limits. If it is a 2 X 2

20   crossover, then non-central t-test can be applied,

21   or there is a procedure recommended by Hyslop and

22   her coworkers which is somewhat more involved but

23   still reasonable I think.

24   [Slide]

25   This is a demonstration comparing the

1   procedures and effectiveness of various approaches.

2   They include the scaled individual bioequivalence,

3   scaled average bioequivalence and unscaled average

4   bioequivalence. You see the probability of

5   acceptance. These are results of simulations. It

6   amounts to the probability of acceptance at various

7   distances between the two means. The first thing

8   you can see is that for individual bioequivalence

9   the range is very wide. Ranges are much narrower

10   with scaled average bioequivalence. So, this wide

11   range raised the concern of Dr. Benet. The second

12   observation is that scaled average bioequivalence

13   is, indeed, much more powerful than unscaled

14   average bioequivalence. So, we again need fewer

15   people.

16   [Slide]

17   What is the limiting variation for highly

18   variable drugs? This is obviously a subject of

19   regulatory decision, as are the others. The

20   procedure could be that we apply unscaled average

21   bioequivalence if the variation is less than the

22   cut-off measure and use some kind of a different

23   procedure appropriate for highly variable drugs if

24   the variation is higher.

25   Perhaps I should go down here. This is

 1   the same kind of mixed model that was suggested for

 2   individual bioequivalence but, just as Dr. Benet

 3   suggested, it is not reasonable that a sponsor

 4   should play both ways. The sponsor should declare

 5   the intention of using one procedure or the other

 6   in the protocol.

 7   I wouldn't necessarily dismiss these other

 8   possibilities. For example, K. Midha recommends 25

 9   percent. The outcome of those probabilities that

10   you have seen on the previous slide depend on how

11   you set these limiting variations. Obviously, 30

12   percent is stricter than 25 percent. In all cases

13   you and the agency will ask what is the practically

14   reasonable criterion that one can live with, the

15   agency can live with and the industry can live

16   with, and the public can live with. So, don't

17   necessarily set everything on the 30 percent; do

18   consider what the effect of, say, 25 percent would

19   be.

20   [Slide]

21   Now, this method of the secondary

22   criterion has arisen in connection with the

23   features of individual bioequivalence. So, we talk

24   about two approaches, that of individual

25   bioequivalence and today we are talking about

1   highly variable drugs. There are two very

2   different concerns.

3   First of all, we have already seen that

4   for highly variable drugs the potential variation

5   is smaller than with individual bioequivalence. In

6   the case of individual bioequivalence the

7   deviations arose because the regulatory criterion

8   was changed. A much more liberal regulatory

9   criterion was introduced whereas in the case of

10   highly variable drugs it is a natural change of the

11   variability between the two means. You know this

12   very well. With the usual kind of drug the

13   variation between the means just fluctuates

14   slightly. Most of the differences are probably

15   between the two means and are within the range of

16   10 percent. But with highly variable drugs those

17   means also fluctuate much more. So, to impose a

18   constraint of 10-15 percent on this natural

19   variation means that the natural fluctuation is

20   altered so the sources of the concern are very

21   different. Whereas in the case of individual

22   bioequivalence you have to deal with the criterion,

23   here you have to deal with the natural variation.

24   [Slide]

25   So, I would like to raise some caution.

 1   In addition, the imposition of the secondary

 2   criterion has serious consequences. I present this

 3   from my life earlier when I dealt with individual

 4   bioequivalence because we had the results then; I

 5   don't have many results for average bioequivalence.

 6   But, again, here you have the results for

 7   individual bioequivalence. This is the probability

 8   curve for the constrained criterion alone and this

 9   is then the application of the combined criterion.

10   The combined criterion is expected and

11   does always run below the two separate criteria.

12   But when the GMR criterion is highly constricting,

13   as in this case, then the combined criterion is

14   really a GMR criterion essentially and has nothing

15   to do, or very little to do with the bioequivalence

16   criterion. So, if you were to consider the

17   secondary criterion, then this slide suggests to do

18   it with great caution and after serious

19   consideration.

20   [Slide]

21   Here are the questions again which I have

22   raised for the committee's consideration and for

23   the agency's consideration. They certainly suggest

24   that many of these issues require further

25   consideration and further investigation.

1   Originally I wanted to end with this loose and

2   compliant mode, however, I looked at the questions

3   being raised and, since after this I may have to

4   shut up, I would like to call attention to question

5   2(b) in which the application of scaling is

6   combined with the application of this secondary

7   criterion. I would like to call your attention to

8   the fact that these are two separate questions.

9   Both of them ought to be studied further but, to my

10   mind, the restriction criterion is much more

11   controversial and requires thorough exploration for

12   its need as well as for its application. So, I

13   would recommend a separation of those questions.

14   Also, I have a question about reference

15   scaling. I would certainly like to be an advocate

16   for scaling, but whether the scaling ought to be

17   reference scaling I would like again to be a

18   subject for study. Thank you.

19   DR. KIBBE: Thank you. Questions?

20   Jurgen?

21   DR. VENITZ: I have a question about your

22   first simulation slide where you compare the IBE to

23   the ABE and scaled ABE. My question basically is

24   that you are assuming for the purposes of

25   simulation that the COVs for both test and

 1   reference are the same, 40 percent. Is that

 2   correct?

 3   DR. ENDRENYI: Yes.

 4   DR. VENITZ: What would happen if you had

 5   differences in COVs between test and reference? In

 6   other words, let's assume that the test product has

 7   much less intra-individual variability than the

 8   reference, how would that affect your curves?

 9   DR. ENDRENYI: It does affect the curves,

10   but mainly the curve of the individual

11   bioequivalence. It affects little the average

12   bioequivalence curve.

13   DR. VENITZ: What about the scaled average

14   BE?

15   DR. ENDRENYI: The same. But that is an

16   artifact in a way because here we consider the

17   scaling by reference product so we didn't

18   have--these were 4-period studies. Your question

19   is relevant if you consider the 2-period studies.

20   DR. VENITZ: Right, right.

21   DR. ENDRENYI: Which we haven't done, but

22   that is an interesting question. It would be worth

23   investigating.

24   DR. VENITZ: So, the answer that you are

25   using then is the reference variation.

96

 1   DR. ENDRENYI: That is right.

 2   DR. VENITZ: So, you are assuming that you

 3   know but you wouldn't necessary do a 2 X 2--

 4   DR. ENDRENYI: No, the estimated

 5   reference.

 6   DR. VENITZ: So, you could get that from a

 7   2 X 2 design?

 8   DR. ENDRENYI: Well, it is a different

 9   interpretation. Yes, we could but it has to be

10   validated whether it works or not. We haven't done

11   that.

12   DR. KIBBE: Anybody else? Ajaz, do I see

13   you leaning forward? No? Go ahead.

14   DR. SINGPURWALLA: I just have a technical

15   comment. Somewhere in your slides you had a

16   restricted maximum likelihood. Right?

17   DR. ENDRENYI: Yes, as a possible

18   procedure.

19   DR. SINGPURWALLA: As a possible

20   procedure?

21   DR. ENDRENYI: Yes.

22   DR. SINGPURWALLA: Well, this is a

23   technical comment, the maximum likelihood is

24   advocated because of its asymptotic properties in

25   the sense that it converges to the center. You

 1   know, you get the central limit theorem. When you

 2   restrict your maximum there is no assurance that

 3   you converge, the central limit theorem.

 4   Therefore, the value of that process cannot be

 5   really evaluated. I don't know what impact all

 6   that has on the proposals you have made but I just

 7   want to caution you.

 8   DR. ENDRENYI: You are absolutely right,

 9   but the point I think was that in the case of

10   replicate design probably the procedure of

11   evaluation would have to be defined very clearly

12   and very strictly, otherwise one can go in all

13   different directions and that will be another task

14   if the agency goes that way.

15   DR. KIBBE: Go ahead.

16   DR. BENET: Just a quick follow-up on

17   Laszlo's comment, I think it would be worthwhile if

18   the agency went back and looked at the content

19   uniformity criteria and published two sets of data.

20   I think it would be worthwhile to go back and look

21   at the bioequivalence data and look and see how

22   often it falls within certain criteria. You have a

23   big database and it would be nice to see what those

24   numbers were, and I think that would be useful for

25   the committee on the secondary criteria.

 1   DR. YU: Actually, you will see that in

 2   the last talk. Sam is going to talk about data.

 3   DR. KIBBE: It is always good to have data

 4   when we are having a discussion. No one else?

 5   Marv?

 6   DR. MEYER: This is probably a

 7   statistically ignorant question but under the

 8   scaled condition, however you want to scale it, is

 9   it possible to have a product with a scale

10   confidence limit that was, say, 60-90? If so, then

11   let's say the ratio would be somewhere around 75

12   percent and that wouldn't be acceptable. So,

13   without the point estimate constraint you have a

14   potential for allowing 60-90 approved and 120-140

15   to be approved.

16   DR. ENDRENYI: No--

17   DR. MEYER: Two different studies?

18   DR. ENDRENYI: In two different

19   studies--within each study it should be one and I

20   wouldn't envision between study variation and I

21   don't--I doubt it very much.

22   DR. MEYER: Even if the test product only

23   released 70 percent of its dose and the innovator

24   released 100 percent of its dose the true ratio

25   would be 0.7 and you wouldn't know that; you would

 1   be looking for 1.0. It is not possible?

 2   DR. ENDRENYI: No, I think if it is

 3   inter-study variation, then with the low variation

 4   drugs each of them would be between 0.8 and 1.25

 5   but the two in comparison with each other could be

 6   quite different. That is equally possible but it

 7   is not likely. If it is the same reference

 8   product, then it is not possible.

 9   DR. KIBBE: I see no other questions.

10   Thank you very much. We will take our break now.

11   We will be back at 10:52.

12   [Brief recess]

13   DR. KIBBE: We have open public hearing at

14   one o'clock but there are no presentations to be

15   made at that time so what we will be able to do is

16   modify our schedule to try to get everything done

17   and get back on schedule. I know there is a lot of

18   interest in what we are talking about so we might

19   allow our speakers a little extra time and some

20   questions and answers to go a little further. I

21   see our next speaker is at the podium, ready to go,

22   Barbara Davit.

23   Bioequivalence of Highly Variable

24   Drugs Case Studies

25   DR. DAVIT: I am pleased to be able to

 1   respond to one of the questions that Les raised, in

 2   that we do have a survey of some of the data that

 3   has been submitted to the Division of

 4   Bioequivalence.

 5   [Slide]

 6   When Dale and I were talking about putting

 7   this presentation together for the advisory

 8   committee, one of the things we thought we would

 9   consider is looking at what has been submitted to

10   the Division of Bioequivalence and to answer the

11   question of whether highly variability is a

12   significant issue in these bioequivalence studies

13   in ANDA submissions.

14   By looking at these data and focusing on

15   some case studies, we thought also we could maybe

16   answer the questions in a limited number of cases

17   of what is contributing to the variability or what

18   are some of the sources of this variability.

19   [Slide]

20   So, what we were trying to do is see if

21   there is a significant problem with highly variable

22   drugs, and I would like to mention, first of all,

23   that this obviously represents a biased sample

24   because we receive predominantly studies that have

25   passed the 90 percent confidence interval criteria.

 1   So we obviously don't see the big picture like

 2   people from industry would be seeing. We don't see

 3   what percentage that is of the total number of

 4   drugs in a company's pipeline for example.

 5   But of the submissions we saw, which are

 6   passing studies, what percentage were for highly

 7   variable drugs? Did these studies involve

 8   enrolling a large number of subjects because that

 9   has been one of the issues that has been raised

10   today, the large number of subjects that might be

11   necessary to show bioequivalence for these generic

12   products of highly variable drugs? Also, how

13   narrow and wide are these 90 percent confidence

14   intervals? That goes along with how many subjects

15   are necessary for a passing study.

16   [Slide]

17   We collected data from all the

18   bioequivalence studies that were submitted to the

19   Division of Bioequivalence in 2003. We used the

20   root mean square error as an estimate of

21   intra-subject variability. I realize this is just

22   a rough estimate and it is not a pure estimate of

23   the intra-subject variability but, unfortunately,

24   most of the studies that we had to look at were

25   two-way crossover studies so the best estimate that

 1   we could get of the intra-subject variability was

 2   the root mean square error.

 3   We defined a highly variable drug as one

 4   with a root mean square error which is greater than

 5   0.3, representing 30 percent intra-subject

 6   variability. The data that I am going to present

 7   is only solid oral dosage forms, and I would like

 8   to point out that all the studies that I am going

 9   to be presenting passed our 90 percent confidence

10   interval criteria, but that is because for the most

11   part we don't receive submissions of studies where

12   the product did not pass bioequivalence criteria.

13   [Slide]

14   First of all from 2003, this was a total

15   of 212 in vivo bioequivalence studies. Of these

16   212, looking at only those studies in which the

17   root mean square error of AUC or Cmax was greater

18   than 0.3, in 15.5 percent of these studies, AUC or

19   Cmax, was greater than 0.3. In other words, in

20   about 15 percent of our studies the drug would

21   qualify as having highly variable characteristics.

22   Most of this was due to Cmax and this has been

23   discussed today. So, in about 13 percent of the

24   total only Cmax was highly variable. There were no

25   studies in which only AUC was highly variable. But

 1   there were 5 studies in which both AUC and Cmax

 2   were highly variable, and this was 2.5 percent of

 3   the total.

 4   [Slide]

 5   This goes along with the previous slide

 6   and it just shows the number of studies in which we

 7   saw a root mean square error of a particular value

 8   for Cmax. There is an error in this particular

 9   slide in your handout but this is the correct

10   slide. Really, obviously, for most of the Cmax

11   values the root mean square error is below 0.3. I

12   have a line here representing 0.3. I think I said

13   earlier that 15 percent of all the studies, 15.5

14   percent of all the studies that came in had a root

15   mean square error for Cmax of greater than 0.3.

16   [Slide]

17   This is for AUC. Of course, the AUC is a

18   lot less variable than Cmax. Really, for the most

19   part the root mean square errors were hovering

20   around 0.1 to 0.15, so quite a bit less variability

21   in AUC than Cmax.

22   [Slide]

23   One of the questions that we wanted to ask

24   was what is contributing to this variability.

25   Since for a lot of products we look at

 1   bioequivalence studies in fasted subjects as well

 2   as fed subjects, we wanted to see what impact was

 3   having on variability. I mentioned 33 studies.

 4   This represented a total of 24 of the ANDAs that

 5   were submitted and reviewed in 2003. Of these,

 6   both AUC or Cmax were highly variable in both the

 7   fed and fasted studies. In 8 of these the

 8   pharmacokinetic parameters were highly variable in

 9   only the fed study, and for 7 the PK parameters

10   were highly variable in only the fasted study. But

11   this is a little bit skewed too because we have

12   submissions, for whatever reason, which contain

13   only a fed study and submissions that contain only

14   a fasted study--not a lot but it does happen.

15   [Slide]

16   This shows some of our data. I think

17   these are all the Cmax values from the 212 studies

18   I was talking about in which Cmax was variable in

19   only the fed study and not the fasting study. So,

20   this would suggest, of course, that we are seeing

21   variability because of food effects. I am not

22   giving the names of the drugs but I have

23   illustrated them by class.

24   There is a variety of reasons I think for

25   the variability. Some of these are prodrugs. We

 1   have a number of angiotensin converting enzyme

 2   inhibitors and most of these are prodrugs.

 3   Generally the parent is present at low

 4   concentrations so this could contribute to the

 5   variability. A number of these drugs also are

 6   highly metabolized and this would contribute to the

 7   variability. But, in this case, obviously there

 8   was a food effect. The variability was observed in

 9   the fed state, not in the fasting state. In these

10   studies too the number of subjects ranged from

11   about 27 to 51 I guess, so all over the place in

12   terms of numbers of subjects.

13   [Slide]

14   It is pretty unusual to only see a highly

15   variable Cmax in the fasting study and not the fed

16   study, and this occurred in only two cases last

17   year. These were both angiotensin converting

18   enzyme inhibitors, both prodrugs. For one of them

19   the bioequivalence was based on measuring the

20   parent. For the other one the company could not

21   measure the parent despite I guess a number of

22   attempts. This is actually true for pretty much

23   everyone who has worked with this particular drug.

24   So, the bioequivalence here is only based on the

25   metabolite. But that is quite rare. In the vast

 1   majority of submissions that we have the

 2   bioequivalence is based on the parent.

 3   [Slide]

 4   This table shows the Cmax data where Cmax

 5   was highly variably in both fed and fasted studies.

 6   So, for this drug product obviously there will be

 7   highly variable regardless of whether it is the fed

 8   study or the fasted BE study. This was six drug

 9   products, various drug classes, various reasons for

10   variability; some prodrugs, some highly metabolized

11   drugs; some drugs that undergo extensive first-pass

12   metabolism. The number of subjects varied from I

13   guess 18 to 57.

14   [Slide]

15   Finally, this table is for two-way

16   crossover studies and shows the data for which both

17   AUC and Cmax were highly variable, and this was for

18   four drug products. For the one that I have shown

19   in yellow, for this particular product both AUC and

20   Cmax met the highly variable criteria in both the

21   fed and the fasting state. For the other drugs

22   there was high variability in the fed but not

23   necessarily the fasted, or Cmax and not necessarily

24   AUC. So, this was four drugs that fell in this

25   class. The number of subjects that the companies

 1   used varied from 26 to 62.

 2   [Slide]

 3   In trying to explore some of the sources

 4   for this variability, we wanted to compare the

 5   intra-subject variability for the test versus the

 6   reference product. We don't see very many

 7   replicate design studies anymore. In this

 8   particular class of drugs we only had two

 9   submissions last year so these are the data from

10   the two submissions.

11   These data are a good sign because what

12   they show is that the variability, based on the

13   root mean square error, was comparable for the test

14   and the reference product for both of these drug

15   products. That is obviously what we are looking

16   for because we want to see people achieve a generic

17   product that is the same as the reference product.

18   So, in this case I would say the variability was

19   comparable, test versus reference.

20   One study used 33 subjects. The other,

21   this would obviously fall into a category where it

22   necessitated a lot of subjects because this was not

23   only 77 subjects, it was also a replicate design so

24   it meant that each of these 77 subjects received

25   the drug product four times, on four occasions.

 1   So, this was quite an extensive study.

 2   [Slide]

 3   Another question we wanted to ask was are

 4   there ever cases in which the pharmacokinetic

 5   variability is a function of the drug product as

 6   opposed to the drug substance. We found two

 7   instances last year, two different drug products

 8   and I will call them drug C and drug D. This was

 9   the same RLD for both studies for drug C and the

10   same RLD for both studies with drug D. Drug C was

11   an extended release tablet. Drug D was an

12   immediate release tablet.

13   We will look at drug C first. In one

14   study, conducted by one applicant, using I guess 33

15   subjects in the fasted and 35 subjects in the fed,

16   this product would not qualify as a highly variable

17   drug. Notice root mean square errors of 0.18,

18   0.11, 0.21, 0.24. However, for the same reference

19   product, in other words it is the same product,

20   different formulation, another company, 0.31, 0.38,

21   0.25, 0.34.

22   This could be due to a number of reasons.

23   I looked at the data and, obviously, the extended

24   release dosage forms are more complex than the

25   immediate release dosage forms and the two

 1   formulations were quite different. So, there could

 2   have been, you know, differences in variability due

 3   to the formulation. Also, the bioequivalence

 4   studies were done at different sites. I looked at

 5   the assays. They were both LCMS assays. I didn't

 6   get the specifics of the extraction methods but I

 7   noticed that the two studies had different limits

 8   of quantitation and there were different doses in

 9   the two studies. I am not sure how much of a

10   factor this was. This was an extended release

11   product for which I believe there were three

12   different strengths. One company submitted a study

13   on the highest strength and I think used two times

14   15 mg, which was 30. The other company did studies

15   on 5 mg and used 4 times 5 mg, which was 20. So,

16   different doses in the two studies. So, there are

17   all these factors that could be contributing to the

18   variability. At least, those are the factors I

19   could think of.

20   Drug D--this was an interesting issue.

21   Once again, in the hands of one sponsor, one

22   applicant, we saw root mean square errors of 0.16,

23   0.25, 0.13 and 0.2; the other applicant, 0.38,

24   0.55, 0.22 and 0.24. This was an immediate release

25   product and I noticed that the formulations of

 1   these two were qualitatively identical;

 2   quantitatively there were some differences.

 3   These were done at two different sites and

 4   in this particular application the bioanaytical

 5   methods were done at a CRO that we have had some

 6   issues with in the past. They seemed to be having

 7   problems with some of their data. So, it could

 8   have been a contributing factor here.

 9   I would like to stress that of all the

10   applications that we saw last year, these were the

11   only four in which we saw that there was a

12   difference which was possibly due to drug

13   formulation or possibly due to where the studies

14   were done that was contributing to the high

15   variability.

16   [Slide]

17   Then we thought we would look at how many

18   study subjects are usually enrolled in these

19   studies. Once again, I emphasize that this is

20   really a biased sample because we only see the

21   studies that have passed. We don't know how many

22   tries this represents. We don't know how many

23   studies were done where the company just couldn't

24   get the study to pass the confidence interval

25   criteria so these are just the passed studies.

 1   I was expecting to see a much bigger

 2   increase in the number of subjects as we went above

 3   0.3 and we really didn't. This could probably be

 4   in part because, as you know, the root mean square

 5   error is not really a true estimate of variability;

 6   it is just a rough estimate. But in general, I

 7   guess of all the studies that came in last year,

 8   that came in and were reviewed, there were only 14

 9   that enrolled more than 50 subjects, and for those

10   that met our high variability criteria there were

11   only 5 that enrolled more than 50 subjects. I

12   think there are about 14 with root mean square

13   errors greater than 0.3 that enrolled more than 40

14   subjects. But in some cases we are seeing high

15   numbers of subjects but this particular graph shows

16   that it is possible for companies to do a study

17   with under 40 subjects with a drug that is

18   considered highly variable and still pass

19   confidence interval criteria.

20   [Slide]

21   Then I wanted to see what would happen if

22   we plotted the width of the confidence interval

23   versus the number of subjects, and this was done

24   for Cmax. These are the 33 bioequivalent studies

25   in which the root mean square error of the Cmax was

 1   greater than 0.3. Really not a big surprise. As

 2   the number of subjects increased the width of the

 3   confidence interval became narrower, suggesting, as

 4   has been mentioned this morning, that with a higher

 5   number of subjects it is much easier to meet the

 6   confidence interval criteria because the confidence

 7   interval of the product becomes narrower.

 8   [Slide]

 9   These are the data for AUC. We have data

10   from a combination of fed and fasted studies. I

11   would like to point out the two at the top. These

12   are fed bioequivalence studies and they don't meet

13   our present confidence interval criteria, but these

14   studies were submitted before the new food guidance

15   was put into effect, which was in January. If a

16   study was submitted before January of 2003, we were

17   evaluating the study based on our old criteria for

18   fed bioequivalence studies, meaning that only the

19   point estimate had to fall within the limits of 0.8

20   to 1.25. That is why, if you look at the

21   confidence intervals, if these studies had been

22   done later these would not have met our criteria

23   but they met our criteria at the time.

24   Once again, you can see a trend where, as

25   the number of subjects increases, the confidence

 1   interval narrows. I suspect that these two

 2   products, with more study subjects, probably would

 3   have been able to squeeze into the 0.8 to 1.25

 4   confidence interval.

 5   [Slide]

 6   In conclusion, I would just like to sum up

 7   that these are observations from the data that we

 8   looked at from 2003, and 15.5 percent of all the

 9   bioequivalence studies that were submitted and

10   reviewed last year were for drugs that met the

11   highly variable criteria. Cmax was more variable

12   than AUC. In general, higher pharmacokinetic

13   variability occurred in the fed bioequivalence

14   studies. The two replicate design studies that we

15   were able to look at showed comparable

16   pharmacokinetic variability for the generic and the

17   RLD product.

18   [Slide]

19   In two cases for two drug products the

20   variability was associated with the formulation or

21   other factors in conducting the bioequivalence

22   studies. In general, the width of the 90 percent

23   confidence interval narrowed as the number of

24   subjects increased. Of the 212 passing

25   bioequivalence studies, only 14 enrolled more than

 1   50 subjects. Of the 33 passing bioequivalence

 2   studies of highly variable drugs, only 5 enrolled

 3   more than 50 subjects.

 4   [Slide]

 5   I would like to acknowledge the members of

 6   our working group at the FDA. This is a group of

 7   individuals who have been discussing the highly

 8   variable drug issues and what types of

 9   presentations to put together for the advisory

10   committee meeting today. I would like to give a

11   special thanks to Devvrat Patel, one of our

12   reviewers in the Division of Bioequivalence, who

13   collected all the data that I showed you today. I

14   would also like to thank all of our reviewers for

15   their hard work in putting the reviews together

16   from which Dev was able to collect these data.

17   Thank you for your attention.

18   DR. KIBBE: Questions, folks? Go ahead,

19   Jurgen.

20   DR. VENITZ: Just one clarification. This

21   was an interesting presentation, Barbara but just

22   one clarification, the root mean square error that

23   you calculated, is that the pooled intra-individual

24   variability across test and reference?

25   DR. DAVIT: Yes, it is.

115

 1   DR. VENITZ: Then if you go back to your

 2   slide number 14, this is where you look at the

 3   effect the drug product may have and you compare

 4   the extended release and the immediate release. In

 5   case number one, I guess manufacturer number one,

 6   it looks like it is a low variability drug and for

 7   manufacturer number two is a high variability drug.

 8   DR. DAVIT: Right.

 9   DR. VENITZ: Could that indicate that the

10   test product for manufacturer two actually has a

11   higher variability and the reference drug still has

12   the same, whatever variability, it has?

13   DR. DAVIT: Oh, absolutely. I mean, yes,

14   there is no way to tell.

15   DR. VENITZ: So, this might then

16   contradict one of the statements that you made

17   later on because you are saying that test and

18   reference in the replicate design studies--

19   DR. DAVIT: For those two products.

20   DR. VENITZ: Right, for those two products

21   it could well be that the test product has higher

22   variability than the reference product.

23   DR. DAVIT: For this product, yes, it is a

24   possibility.

25   DR. VENITZ: But all the replicate design

 1   studies that you looked at--

 2   DR. DAVIT: Which was only two.

 3   DR. VENITZ: Right, you found for those

 4   two at least that test and reference had the same

 5   intra-individual variability.

 6   DR. DAVIT: Yes.

 7   DR. VENITZ: How does that compare to the

 8   overall experience, going back beyond your survey?

 9   Do you have any idea? Because I know they talked

10   about this in 2001 the last time we met.

11   DR. DAVIT: You know, that is a really

12   good question and we didn't have the time for this

13   presentation. We were only able to collect data

14   from last year. We do have a lot of replicate

15   design data from 2000, 2001 and I guess some from

16   2002 and I think we would like to expand this study

17   and go back a number of years because we would have

18   more replicate design studies to compare test and

19   reference variability. Yes, this is all we have,

20   unfortunately.

21   DR. BENET: First of all, what you

22   presented is very interesting but it wasn't what I

23   asked for. So, let me make clear what I think the

24   committee could use. There is an issue about the

25   point estimate. In 1999 Commissioner Heaney

 1   published in JAMA an article where she looked at

 2   all the drugs approved in '97, showed the content

 3   uniformity and the Cmax and AUC with the means and

 4   the standard deviations. What I am asking you to

 5   do is to go back and give the committee information

 6   on the point estimates. Where are the point

 7   estimates on all those studies? How much

 8   variability? Are you going to do that?

 9   DR. YU: That is actually going to be

10   presented by the next speaker.

11   DR. BENET: You set me up. Barbara said

12   she was answering my question! Many of you saw the

13   MDS abstract at the AAPS in November of 2002. If

14   you didn't, I have two slides here that I talk

15   about all the time. MDS looked at 800 fasting

16   studies in terms of approval or non-approval. Of

17   course, you can have a highly variable drug that 12

18   people pass because sometimes statistics work.

19   I think the most interesting piece of data

20   from that is that they looked at the number of

21   subjects enrolled and how many studies failed.

22   When they looked at 49-60 subjects enrolled in a

23   study, 68 percent of the studies failed. When they

24   looked at greater than 60 subjects 12 percent of

25   the studies failed.

```
 1              Now, why is that?  It has nothing to do

 2    with statistics.  It has nothing to do with going

 3    back and saying how are you going to run the study.

 4    It has to do with generic companies CEOs, and I

 5    have seen it many times.  The scientists say to the

 6    company "we have run the preliminary study.  We ran

 7    six.  We need 96 people to make sure that we meet

 8    the confidence intervals," and the president says,

 9    "96 people?  Do you know how much that costs?  I am

10    feeling lucky, run 24."  And, that is exactly what

11    happens.  If the 24 they get it.  If the 24 doesn't

12    pass, they either give up or they run another

13    study.  So, you can't conclude anything from the

14    data that you are seeing here in terms of

15    variability and the ability to pass.  I want to

16    warn you on that.  I think it is really important

17    to realize that until you start to see all the

18    data, which you will now, you really can't make

19    comments about whether highly variable drugs can

20    pass or whether you could have a progesterone study

21    that passed based on 50 subjects.  You could

22    easily; you just have to be lucky and lots of

23    people are lucky.

24              DR. DAVIT:  Oh, I agree.  I thought the

25    exact same thing when I looked at all these studies
```

 1   with the number of subjects and number 24 and 25

 2   came up again and again and I wondered if it was

 3   something like that.

 4   DR. KIBBE: I just have a question about

 5   the data. You had 212 studies you analyzed but

 6   that wasn't for 212 different compounds--

 7   DR. DAVIT: Right.

 8   DR. KIBBE: --there were multiple

 9   submissions for the same compound.

10   DR. DAVIT: Right.

11   DR. KIBBE: So, the question that I come

12   back to is on that early slide where you showed

13   five studies had AUC and Cmax problems, which

14   represented 2.5 percent. How many drugs was that?

15   DR. DAVIT: Oh, that was five different

16   drugs.

17   DR. KIBBE: Five different drugs, not just

18   five studies by different companies?

19   DR. DAVIT: Right, it was five different

20   drugs.

21   DR. KIBBE: That isn't the same though for

22   the 33 with AUC or Cmax?

23   DR. DAVIT: Correct.

24   DR. KIBBE: There would be cases where you

25   had studies where there were multiple studies

 1   showing the same drug having variability in each

 2   one of the studies?

 3   DR. DAVIT: Right. I actually had a slide

 4   like that at one point and I took it out. But the

 5   answer to your question is yes.

 6   DR. DELUCA: I noticed that your data is

 7   just for the approved drugs.

 8   DR. DAVIT: Yes.

 9   DR. DELUCA: But I had a question. Maybe

10   Les--with the data he just mentioned because he has

11   data there of approved and non-approved, you have

12   212 here, is there a feel in relation to how many

13   drugs were not approved that did not meet the

14   specs? Maybe the industry or the data that Les has

15   might be able to give an estimate of what that

16   might be.

17   DR. BENET: Well, this is something that

18   Laszlo said. I mean, the MDS data obviously--you

19   know, what they showed was that if you had CVs less

20   than 30 percent, only like one-quarter of the

21   studies failed. If you had CVs greater than 30

22   percent, 62 percent failed. And, Laszlo was giving

23   you the data for greater than 35 percent and all of

24   them failed. But, again, these could have easily

25   been under-powered. I think most of these are

 1   under-powered in terms of the studies that MDS ran

 2   but it is 800 studies. I mean, they got data from

 3   800 studies.

 4   DR. SINGPURWALLA: I want to respond to

 5   Dr. Benet again before he goes away.

 6   [Laughter]

 7   Now, you raised this dichotomy of the

 8   surprise that the test passed and then it failed,

 9   or something like that. I am not sure exactly how

10   you said it. But there is a procedure in

11   statistics called sequential analysis which I am

12   sure you are aware of. The government, not the FDA

13   but the Department of Defense uses this procedure

14   for acceptance sampling of products, whatever

15   product they are interested in. The whole idea

16   behind that is you test one item at a time and you

17   make a decision either to accept or to reject. If

18   you cannot make a decision to accept or to reject,

19   you take another sample. You keep taking a sample

20   until you make a decision, let's say, to accept.

21   The government then buys tons and tons of

22   transistors or whatever it is based on this nice,

23   little sequential test, codified an put out as

24   military standard 414, version C, which is how I

25   last remember it.

 1   Now, if you use that particular procedure

 2   and let's say the procedure says accept and, for

 3   fun, you don't accept and go on testing more, guess

 4   what happens. The procedure leads to rejection.

 5   So, an early acceptance could be a bad thing had no

 6   tested more. It seems that the same phenomenon is

 7   happening here. The culprit there again is this

 8   concept of type 1 and type 2 errors that come into

 9   play. These procedures have been discussed and

10   shown to be incoherent. I suspect similar things

11   are happening here. Thank you.

12   DR. KIBBE: Paul?

13   DR. FACKLER: I have a couple of comments.

14   Ordinarily I agree with Les but I think he might

15   have over-simplified the generic industry.

16   Admittedly, a study with 96 subjects costs a lot of

17   money and there is a statistical probability that

18   with a highly variable drug you will pass with 10

19   or 12 subjects. Decisions are made based on a lot

20   of factors. Part of it is the probability of

21   passing. Part of it is the economics of what a

22   product might bring back to a generic company. I

23   will leave it at that.

24   As far as the analysis that the FDA has

25   done, the generic industry has been asked to submit

 1   failed studies and I believe it is almost part of

 2   the Federal Register now that those are required.

 3   But those are failed studies on products that are

 4   submitted to FDA. There are a number of products

 5   that the generic industry works on that never come

 6   to FDA because the BE studies haven't been able to

 7   be passed. So, MDS have a larger data bank of

 8   studies than FDA but, of course, it is confidential

 9   information and MDS can't really share all of the

10   details about that with FDA.

11   A couple of other comments, the one slide

12   that showed the two products that had differing

13   root mean squares, you suggested it might be

14   formulation differences that caused the difference

15   in the variabilities. I am not sure that you can

16   draw that conclusion. You did qualify it by saying

17   that there could be other reasons for those errors.

18   It could be as simple as different populations of

19   patients or subjects in these cases. We have seen

20   examples where doing a highly variable product by

21   one CRO can give a dramatically different

22   variability than another CRO just because of the

23   variability of the subject population that the CROs

24   are able to gather. A CRO in the inner city is

25   going to have a dramatically different patient

 1   population than a CRO in the country in the

 2   northern part of a very isolated corner of the

 3   United States.

 4   Then, I wanted to make the same comment

 5   about the slide that showed only five studies with

 6   more than 50 subjects. The studies with 50, 60,

 7   70, 80 and 90 subjects often fail and FDA never

 8   becomes aware of those. Those projects are often

 9   dropped after two or three failures because there

10   doesn't seem to be a way to meet the 0.8 to 1.25

11   confidence intervals.

12   I would suggest, if the resources are

13   there, the FDA go back and look at all those

14   replicate design studies that were submitted two

15   and three years ago when we were looking at IBE as

16   a possibility and scaled bioequivalence. I think

17   you will find that the variability between test

18   product and test product is really not different

19   than the variability you see between the reference

20   product in those replicate design studies.

21   DR. KIBBE: Anybody else? Ajaz?

22   DR. HUSSAIN: I think I just want to put

23   some issues back, important issues back on the

24   table. I think one of the reasons we wanted Gordon

25   Amidon to come and speak here I think was to focus

 1   on what the root causes of variability are.

 2   Because often we have these discussions, and so

 3   forth, and we get so bogged down in the numbers and

 4   the statistics that we forget what the real

 5   questions are that we were really asking. So, I

 6   just want to remind us.

 7   DR. KIBBE: Anybody else? No? Thank you.

 8   Now Dr. Sam Haidar.

 9   FDA Perspectives

10   DR. HAIDAR: Good morning, everyone.

11   [Slide]

12   For my talk I will present regulatory

13   perspectives on the issue of bioequivalence of

14   highly variable drugs.

15   [Slide]

16   We are interested in this issue because it

17   has several potential benefits, including reduction

18   in regulatory burden and easier market access for

19   drugs which are safe and effective but also highly

20   variable.

21   [Slide]

22   Initially I would like to present a quick

23   overview of the regulatory requirements if

24   different agencies including the FDA. For example,

25   Health Canada, CPMP in Europe and the FDA

 1   equivalent in Japan.

 2   [Slide]

 3   The FDA criteria for bioequivalence has

 4   been more precisely defined earlier so I will just

 5   repeat that we have 80-125 percent limits on the 90

 6   percent confidence interval for both AUC and Cmax.

 7   These criteria are applied to drugs of low and high

 8   variability.

 9   [Slide]

10   In contrast, Health Canada has the same

11   criterion on AUC, the 80-125, however, no

12   confidence interval criteria for Cmax. They just

13   have a constraint on the point estimate test to

14   fall between 80 and 125. In June of last year,

15   these criteria were judged flexible enough to

16   handle highly variable drugs by an expert advisory

17   committee meeting.

18   [Slide]

19   In Europe they have the same limits on the

20   confidence interval for AUC and Cmax, however, they

21   do make an exception in certain cases with regard

22   to Cmax where wider limits are acceptable and they

23   cite the 75-133 as an example.

24   [Slide]

25   In Japan also they have the 80-125 percent

1   limits for AUC and Cmax, however, in cases of

2   failure they do allow for add-on studies.

3   [Slide]

4   From this, we conclude that major

5   regulatory agencies do have some flexibility in

6   their regulations to handle special cases of the

7   highly variable drugs. To evaluate the performance

8   of the FDA criteria a survey was taken of ANDA

9   submissions between 1996 and 2001. I will present

10   the point estimate distribution for Cmax and AUC.

11   [Slide]

12   This is the point estimate distribution

13   for AUC and we have the percent of total studies

14   submitted. We can see that there is a clustering

15   around the ratio of 1.0 and with a closer look we

16   saw that for 95 percent of the studies--the in vivo

17   bioequivalence studies, 95 percent were within

18   plus/minus 10 percent.

19   [Slide]

20   For Cmax, which is a more variable

21   parameter, it is expressed with a wider

22   distribution. However, we also see a clustering

23   around the ratio of 1.0. In the case of Cmax, 85

24   percent of the studies were within plus/minus 10

25   percent.

 1   [Slide]

 2   From this data set we created a subset

 3   that included highly variable drugs and highly

 4   variable drug products. We see a somewhat similar

 5   distribution, also clustering around a ratio of 1.0

 6   for the AUC.

 7   [Slide]

 8   The same is true for Cmax but also to a

 9   lesser extent as expressed by the greater

10   distribution.

11   [Slide]

12   From this we conclude that although the

13   FDA criteria allow for a mean difference of

14   plus/minus 20 percent, the vast majority of the

15   submissions were within plus/minus 10 percent.

16   This was also observed for highly variable drugs.

17   [Slide]

18   In dealing with the special case of highly

19   variable drugs there are several options, including

20   a scaling approach based on intra-subject

21   variability in Cmax and AUC, or direct expansion of

22   the regulatory limits.

23   [Slide]

24   For scaling approaches, they would result

25   in a reduction in sample size. The limits are not

 1   fixed but they are defined as a function of the

 2   variability. There may also be a need for a point

 3   estimate constraint.

 4   [Slide]

 5   In contrast, direct expansion of the

 6   limits, which may be applied only to Cmax or Cmax

 7   and AUC, the limits are fixed, for example 70 to

 8   143, for drugs which are considered highly variable

 9   or are classified as highly variable. There may

10   also be a need for a point estimate constraint in

11   this approach as well.

12   A major concern with this method for drugs

13   which are borderline around the 30 percent cut-off

14   is how do we classify those drugs, and who does it?

15   Because, obviously, there are major commercial

16   advantages with a drug being classified as highly

17   variable under those circumstances.

18   [Slide]

19   A study conducted by Walter Hauck, which

20   was supported by the FDA when the food effect

21   guidance was under development--they wanted to look

22   at the impact of expanded limits around Cmax on

23   study design since fed studies in general tend to

24   be more highly variable. The interval test

25   evaluated was 70-143 around Cmax. The outcome was

1   60 percent reduction in sample size on average. A

2   concern was expressed in that study that Cmax

3   ratios of up to 128 percent still passed using this

4   limit.

5   [Slide]

6   Finally, if a decision is made to modify

7   the regulations to accommodate highly variable

8   drugs, we feel like either approach would result in

9   a significant reduction in sample size although an

10 additional regulatory criterion might be needed

11 constraining the point estimate. However, based on

12 our previous experience, it is very likely that a

13 clustering around a ratio of 1.0 would still be

14 observed although, in theory, it could fluctuate to

15 a greater extent.

16   [Slide]

17   Now Dr. Dale Conner would chair the

18 question and answer session.

19   Bioequivalence of Highly Variable Drugs Q&A

20   DR. CONNER: Good morning. I was asked to

21 simply not have a presentation but come up and

22 field questions. You know, anything on this topic

23 is fair game I think, although you can try and get

24 some other ones in if you like. However, I decided

25 to start it off to get the ball rolling by making a

 1   few remarks. First off, I can truly say when I sit

 2   through a lot of advisory committee topics and

 3   discussions I am not extremely stimulated by them.

 4   I hate to admit that but sometimes some of the

 5   topics to me, personally, are not very exciting.

 6   This one however I found extremely exciting from

 7   beginning to end, and perhaps that is just because

 8   it is bioequivalence; it is what I do all the time

 9   and it is a problem that has been discussed for a

10   long time and, due to the experts and this

11   committee, we are finally starting to make some

12   progress towards doing something about it.

13   So, I would like to thank both the

14   committee and all the excellent speakers who really

15   gave us quite a lot to think about and discuss.

16   Because there were so many issues, I sat there with

17   my little list of points that I was going to make

18   which, hopefully, wouldn't have taken very long but

19   it started to expand at a very alarming rate with

20   each of the speakers and the excellent points they

21   were making. I consider it kind of a scaling

22   effect that my points were expanding with the

23   variability and quality of the speakers. So, I

24   will try and keep it to a minimum and perhaps be a

25   little Procrustean in cutting off both ends.

1   These comments, these points I am making

2   are my own take on it so one shouldn't necessarily

3   interpret this as FDA policy or even FDA thinking,

4   but I tend to deal with these types of questions on

5   a day-to-day basis in a practical sense and it

6   really seems to me, and what should have come out

7   of this if you get down to the real issue, what we

8   are looking at here for the most part is an

9   economic issue. In other words, from the drug

10   company's point of view it is really economics.

11   These studies cost too much.

12   When I want to develop this drug--if I am

13   a generic company and I want to develop this drug

14   and, as has been stated before, my statistician

15   comes back and say you have to do 120 subjects, I

16   am sure that the bean counters at the firm are very

17   alarmed and saying, "my God, I'm used to paying for

18   a 24-subject trial and you've just told me it's

19   five times as expensive." For a small company that

20   could mean three or four other products that I

21   don't have the funds to develop. So, they have to

22   make a choice. Is this product worth all that

23   money to spend or should I do four or five other

24   ones and forget about this?

25   It doesn't necessarily mean those products

1   aren't going to be developed by someone and be on

2   the market but it will decrease the players. Only

3   those with deep pockets will be able to develop it.

4   So, of course, in the marketplace you will have

5   very much lower competition, which is not good for

6   the consumer.

7   So, there is a variety of economic

8   considerations that this brings into play and if we

9   consistent somehow, using scientifically valid,

10   good regulatory methods, alleviate some of that,

11   that would be good. The FDA has a motivation as

12   well. As has been mentioned, we have a mandate to

13   eliminate or decrease unnecessary or excessive

14   human testing so we have a motivation as well. Our

15   motivation isn't strictly economic but we don't

16   want to expose normal subjects or patients in these

17   trials anymore than we have to because although

18   most of these trials are very low risk, they are

19   not no risk. So, it is up to us to develop

20   scientifically valid ways to determine

21   bioequivalence with confidence, yet efficiently

22   with the least number of subjects we can get away

23   with. That is our motivation.

24   So, you could simply say from the firm's

25   point of view because of this criterion, because of

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1   this inflexible criterion I am having to do an

2   unreasonable or excessive number of subjects. Now,

3   what is that? I mean, how do you define

4   "unreasonable" or "excessive?" I am sure that some

5   people say that anything above 24 is unreasonable

6   and if I asked everybody in this room what is an

7   unreasonable number of subjects, what is the

8   maximum number of subject you think you should have

9   to do in any bioequivalence study for any product,

10 I would probably get as many answers as there are

11 people in this room.

12   So, one of the ways you could start is

13 simply empirically saying, okay, I am going to set

14 a number of samples that I don't want to go above,

15 no matter what. A very simple way would be to work

16 your way backward from that number. Say, 60 was

17 the highest you ever wanted to do, work your way

18 back saying, well, this is the variability I am

19 looking at. This is the allowable true mean

20 difference. This is the power I want. Work your

21 way back and through simulation you get a set of

22 criteria that would achieve that goal, static

23 criteria. You could do something like that.

24   Static criteria, I think as the last

25 couple of talks have outlined, in this case has

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 1   some problems because you have boundary conditions,

 2   things where a drug product in one CRO's hands is

 3   highly variable. You know, you go to another CRO

 4   and it is not highly variable. So, who gets the

 5   benefit of your highly variable technique? When

 6   you look at creating a method to deal with this you

 7   don't want to reward highly variable. You don't

 8   want sponsors, whether they intend to or not, to

 9   force themselves into the highly variable state

10   just to get the benefit of whatever techniques you

11   are dealing with. So, you want to adequately deal

12   with the problem without, whether unintentionally,

13   encouraging bad or highly variable formulations.

14   What was mentioned by Les in the

15   individual bioequivalence, that was an attempt to

16   promise the fact that system would encourage firms

17   to make lower variability products that still

18   matched and fit within the accepted criteria,

19   therapeutic criteria that were established in the

20   NDA. Even if we are not able to do that, we

21   certainly don't want to do the opposite. We

22   certainly don't want to unintentionally encourage

23   people to make their products or do their studies

24   in a more variable manner just to get a benefit and

25   an easier pass. So, just keep that in mind when

1   you are considering anything. You don't want to be

2   counterproductive. You know, help people in one

3   way and then be counterproductive in another way

4   and, therefore, decrease the quality of the generic

5   and maybe even the innovator products that we are

6   putting out. So, that is something that always has

7   to be kept in mind.

8   The topic that also worries me--I again

9   said in these scientific discussions--I will make

10   another admission, a portion of my mind is always

11   on the scientific discussions and a portion of my

12   mind is, you know, on the practical sense of how

13   the heck am I going to implement this. Because the

14   scientists in industry, the firms and the review

15   staff at the FDA are the ones that are going to

16   have to live with this, are going to have to find a

17   way to implement these techniques, to make them

18   work, and a lot of times the little details that we

19   don't talk about in rooms like this are the things

20   that kill you, that make this an almost unworkable

21   system.

22   For example, we can all agree and discuss

23   that we like 30 percent as the cut-off but, again,

24   now do you determine that 30 percent? Is it

25   determined before you do any studies, from pilot

 1   studies? Is it determined from the literature? Is

 2   it determined from the NDA? What happens when the

 3   entire literature and available information says

 4   that something is 28 percent and somebody does a

 5   study and it is 34 on that one product? Every

 6   other product that is done, similar product, is

 7   still 29, what do you do in that case? Or the

 8   opposite? You know, every other study has been 32,

 9   33, 34. It is considered a highly variable drug.

10   Somehow you do one study, have one formulation and

11   it is 28. What do you do then? So, that really is

12   a very practical thing. These things that are on

13   the borderline could have the benefit or the remedy

14   applied to them or not applied to them depending

15   how their data comes out. It is probably an

16   advantage for a proper scaling method rather than

17   simply increasing the study confidence intervals.

18   With that said, I will field the questions

19   if there are any.

20   DR. KIBBE: Shall we start? Les wants to

21   ask a question.

22   DR. CONNER: Les gets very antsy unless he

23   talks about every ten minutes.

24   DR. KIBBE: If you do all the paperwork,

25   Les, you can sit at the table.

1   DR. BENET: That is exactly why I am not

2   sitting at the table.

3   [Laughter]

4   Dale, going back to Sam's data and just

5   following up exactly what you said, you have some

6   products that passed where the point estimate on

7   Cmax was 1.2 and they were supposed to be in the

8   highly variable group. Have you gone back and

9   looked at that data? Was it a huge number of

10   subjects or was there no variability on that study?

11   DR. CONNER: Usually with that type there

12   are only like one or two instances. I mean, we

13   have done all sorts of periods and done that data,

14   and I actually like that way of presenting it

15   rather than the Heaney article--

16   DR. BENET: I like that way too.

17   DR. CONNER: --and subsequent article

18   which just gave point estimates. I always expect,

19   you know, that I am going to see that are out at

20   1.8 or 1.9 or, you know, kind of close to the edge

21   but not quite there, and I always react with horror

22   when I see that particular data point. When we

23   really go in--I am not really sure; I would

24   actually have to direct it to Sam to put that

25   together because it doesn't make sense to me that

 1   something could have a point estimate that far out

 2   and be highly variable unless they used a lot of

 3   subjects--I mean a lot. So, I will direct it to

 4   him but, on its face, it doesn't seem to make sense

 5   because I have seen that type of data presented in

 6   other ways and when I looked into it, it was a low

 7   variability product. It was something that just

 8   squeaked by, had low variability and they used

 9   sufficient subjects so even the alarmingly close

10   point estimate was still okay by our criteria.

11   DR. KIBBE: We are recording the activity

12   so you have to talk into a microphone.

13   DR. HAIDAR: I will have to go back and

14   look at that study but based on what I have seen

15   there were maybe one or two studies that were above

16   1.20, and the reasons could be large number of

17   subjects or just purely by chance.

18   DR. BENET: I agree they passed but I

19   think it would be instructive to go back and look

20   at those boundary conditions and see what are the

21   characteristics of those studies. I am sort of

22   thinking back to the generic drug scandal, you

23   know, where we saw some unbelievably low standard

24   deviations that nobody else ever saw at any other

25   time and I just think we ought to look at that data

 1   carefully.

 2   DR. CONNER: Sometimes you can get low

 3   standard deviations when you study the same drug

 4   against the same drug.

 5   DR. FACKLER: Can I address that point?

 6   DR. KIBBE: Please, go ahead.

 7   DR. FACKLER: Confidence intervals weren't

 8   required for fed studies prior to 2002.

 9   DR. DAVIT: I was just going to say the

10   same thing.

11   DR. FACKLER: A lot of the fed studies

12   from '96 to 2002 only needed a point estimate to

13   pass so 1.20 was perfectly within FDA's

14   acceptability criteria.

15   DR. BENET: I am aware of that too but you

16   didn't separate them out, Sam? Those were both fed

17   and fasted conditions?

18   DR. DAVIT: It is everything.

19   DR. BENET: I think we need to separate

20   them out.

21   DR. HAIDAR: They were not separated.

22   This was our initial look.

23   DR. DAVIT: I would like to say too that

24   probably we didn't start seeing consistently fed

25   studies that passed confidence interval criteria

 1   until about six months ago. So, before that all

 2   the fed studies were point estimate criteria.

 3   DR. CONNER: So, we are doing an unusual

 4   analysis. We are taking that data and calculating

 5   confidence intervals but it was never designed or

 6   powered to do that. So, in a way we are being

 7   unfair to the data although, I mean, it is still

 8   useful to look at it but, you know, to expect it to

 9   pass confidence intervals when that was never the

10   intent and the statisticians that designed them

11   never powered it that way.

12   DR. BENET: Right, I can understand that.

13   If it was really true, then my recommendation would

14   be impossible so that is why I want to see data

15   that looks at that. I think you do too, or the

16   committee should too.

17   DR. CONNER: It is also important to

18   remember that point estimates--you know, people

19   like to look at them because they are easy and they

20   seem to be the mean but you have to really look at

21   them very carefully because the say the statistics

22   work that isn't the true mean of the product. That

23   is simply an estimate of the center of the data of

24   your small sample of the universe. So, although it

25   is interesting to look at them and they can be a

1   good indicator, you have to be very careful when

2   you look at point estimates because it is not the

3   true mean.

4   DR. KIBBE: Ajaz?

5   DR. HUSSAIN: I think Dale mentioned

6   something which I think is important and I want to

7   sort of repeat that because I think the whole

8   aspect of bioequivalence is to confirm that two

9   pharmaceutically equal products would behave as we

10   would expect them to behave. And, I think we keep

11   missing that discussion and I think this discussion

12   also will not get to that but I want to keep

13   pounding on that. If there are differences in the

14   variability of the product in terms of rate and

15   extent of absorption, that is the concern. That is

16   a regulatory decision that has to be evaluated,

17   whether a high level of variability compared to a

18   lower level of variability in the innovator product

19   is acceptable or not.

20   But the key aspect here is differences in

21   the two products of the same drug. The drug is the

22   same here. The formulation is different. That is

23   the focus of our entire discussion and, again, we

24   get into the discussion on numbers and so forth but

25   we never ask the question--since generally drug

 1 approval is evaluation of the chemistry

 2 manufacturing controls and then there is the

 3 bioequivalence study which is one study. If we

 4 remember the clay feet of the bioequivalence

 5 argument that Prof. Levy has always argued, the

 6 connection never gets discussed and somehow we have

 7 to rethink that process.

 8   DR. KIBBE: Nozer?

 9   DR. SINGPURWALLA: First I would like to

10 comment on vocabulary. I prefer that you use the

11 word within-subject versus between subject instead

12 of this inter- and intra-, whatever it is.

13   DR. CONNER: I agree. I always get mixed

14 up by that too.

15   DR. SINGPURWALLA: I think that is a minor

16 comment. But the significant comment is in the

17 handout questions on your last slide.

18   DR. CONNER: Those aren't really my

19 questions. Those are the questions for the

20 committee.

21   DR. SINGPURWALLA: Right, but are we ready

22 to talk about these?

23   DR. KIBBE: We are ready if you are.

24   DR. SINGPURWALLA: Right, I am. Now, this

25 whole morning's presentation, which I agree with

1   you was not boring but very interesting, makes one

2   point clear, that this problem of bioequivalence

3   and highly variable products calls for an

4   application of risk-based decision-making. The FDA

5   should serve as a benevolent decision-maker and

6   formulate the problem as one of decision-making

7   under uncertainty, keeping in mind the interests of

8   the population, of the subjects; keeping in mind

9   the interests of the drug companies or the

10 pharmaceutical companies and balancing and trading

11 off those risks.

12   You can retain the technology of scaling.

13 You can retain the investigation of causes of

14 variability. There is nothing in the framework

15 that denies those things. But what is really

16 needed is a change of mind set and a shift in the

17 paradigm. You have to get away from the notion of

18 confidence intervals which have, I am told, just

19 been introduced two or three years ago, and move on

20 into a paradigm of decision-making under certainty,

21 bringing in utilities, bringing in those kinds of

22 considerations into this problem, otherwise you are

23 just spinning your head against the wheel. That is

24 my comment.

25   DR. KIBBE: Anybody? Marvin?

1   DR. MEYER: If we go with the static

2   change, 70-143 for example, that smacks a bit of

3   being arbitrary which is a problem to defend and,

4   without a point estimate, allows, according to

5   Walter Hauck, 128 percent to pass. That can be

6   taken care of by a point estimate such as Les

7   suggested. So, the arbitrariness of that bothers

8   me.

9   But if we go to what I think is more

10   scientific-based, based on the variability of the

11   reference, albeit necessary to do a replicate at

12   least on the reference, then you have a situation

13   where you have confidence limits varying by study,

14   by sponsor, by whatever else and then the

15   marketplace becomes chaotic because I am sure you

16   will have people arguing, well, our confidence

17   limits are narrower than their confidence limits

18   and we have, therefore, a better product. Of

19   course, then you will send out a letter and say you

20   can't say that. So, I don't know--I guess I would

21   favor the scale because it has some elements of

22   being tied to real data, and then somehow figure

23   out--I think Les said don't worry about what people

24   think in some sense. So, if the confidence limit

25   ranged within two sponsors, maybe it isn't going to

 1   be a big issue once people understand what you did.

 2   Those are just some comments really.

 3   DR. CONNER: Over the years I have been in

 4   many meetings, internal and external, where we have

 5   discussed widening or tightening the confidence

 6   interval depending on the topic and the drug under

 7   discussion. The tendency that always disturbs me,

 8   and still disturbs me to this day, is people say,

 9   oh well, it is more variable so we should widen the

10   confidence intervals; let's do 70, let's do

11   plus/minus 30. You query where did you get this

12   number. Well, it is wider. Well, how do you

13   support that? What makes you think that is wide

14   enough to deal with the problem? Maybe you have

15   gone too far. Or tightening the confidence

16   interval limits, static limits are the same. I

17   mean, what makes you think that is tight enough to

18   deal with the perceived problem? People tend to

19   just jump to the next--you know, they say it is

20   going to be wider and they go to the next five or

21   ten. But we rarely ever have anyone come in and

22   support that with data. Maybe it is just because

23   the data is hard to come by but it disturbs me to

24   this day that most of these discussions are not

25   supported by any kind of scientific support that

 1   this change is truly going to be able to perceive

 2   the problem.

 3   You know there are decisions and there are

 4   problems with scaling methods, especially if you do

 5   mixed scaling where you have a transition point

 6   where it goes from a constant or static limit to a

 7   scaled limit, which we saw proposed in individual

 8   bioequivalence. There are some boundary problems

 9   around that transition point. Again, you know,

10   which side do I fit? Where do I get a better deal?

11   That type of situation. But I don't really think

12   it is as big a problem. You know several different

13   sponsors might have slightly different limits

14   because those limits are determined by their own

15   data, their study, their data. If, say, one CRO is

16   a little more sloppy--I don't mean necessarily

17   negatively, and their variability of doing their

18   study is a little bit higher, that scaling would

19   account for that because you would have that across

20   the board for both reference and test. I mean,

21   scaling does have some properties that if it is

22   properly done it is probably a little more elegant

23   way to deal with this problem. Still, you have to

24   do it properly and you have to think it through

25   very carefully. You can't just jump into a method

1   without careful study.

2   DR. KIBBE: Jurgen?

3   DR. VENITZ: I am trying to get us to

4   start working on question number one, and it has to

5   do with the comment that I made earlier. Gordon

6   talked about mechanisms. We heard Ajaz talking

7   about the need to understand where the variability

8   comes from, and that really is something that I

9   personally am missing. And, I won't even get into

10   my pet peeve about what is the clinical relevance

11   of all of this.

12   But if I can identify, and I think I am in

13   agreement with Nozer that we have to use risk-based

14   assessment. Well, risk to me means I have to

15   understand where are the key variability sources

16   that I am impacting on. What if the variability is

17   primarily driven by systemic metabolism, then the

18   area under the curve and Cmax do not reflect

19   primarily product performance. They reflect

20   something else which presumably is not affected by

21   changing products. So, is there any way that you

22   can incorporate that in some kind of algorithm,

23   some kind of decision tree where you decide what

24   rules you are going to use depending on what you

25   know about the drug? Maybe I am not as strongly

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 1   statistically Bayesian as you are, but I do believe

 2   that the current system disregards anything that we

 3   know about the product. It just says compare

 4   product A to product B and roll the dice. It

 5   ignores everything that we know about the

 6   pharmaceutic characteristics of the drug substance

 7   and what we might know about a specific product in

 8   question, whether it is extended or immediate

 9   release classification.

10   So, I would like for the FDA to think

11   about how you could come up with an algorithm, a

12   decision tree where you would incorporate that in

13   the early stages and then, by the time that you get

14   to the end of your tree, there are different rules

15   but those rules are then based on what you know

16   about the drug, not about something

17   arbitrary--well, in order for me to avoid a large

18   number; in order for me to pass some arbitrary

19   criteria I have to do this. To me, it is the tail

20   wagging the dog as opposed to trying to use the

21   understanding that we have and a lot of those

22   products that you are looking at have been out for

23   a long time so we know a lot about them but we

24   ignore that when it comes to the bioequivalence

25   assessment.

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 1              As far as scaling is concerned, the way I

 2    understand it right now I am still wary about the

 3    scaling and I really haven't formed an opinion yet.

 4    In order to do the average bioequivalence scaling,

 5    right now what you need and probably the most

 6    important problem I guess is within-subject

 7    variability in the reference product.  How would

 8    you get that?  You couldn't get it from a 2 X 2

 9    study design.  So, whose responsibility then is it

10    to provide that information?  Because it presumably

11    requires either a replicate design study or a

12    specific study just to identify the within-subject

13    variability in the innovator product.  Whose

14    responsibility is that?  Is the FDA going to pay

15    for all those studies?

16              DR. CONNER:  Usually it is the sponsor's.

17              DR. VENITZ:  Okay, so the generic company

18    has to do at least two studies or a replicate

19    design study.

20              DR. CONNER:  With that approach, if that

21    is the type of scaling you designed requiring

22    replicate designs as we tried to do in the past,

23    probably a replicate design would be in order.

24    But, you know, there are a variety of things in the

25    literature and other proposals where that may or
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1   may not be necessary. But if you did pick that

2   type of approach, yes, the sponsors would end up

3   probably doing some type of replicate design.

4   DR. KIBBE: Lawrence?

5   DR. YU: I want to make a comment. I

6   guess a lot of speakers, especially FDA speakers

7   from the Office of Generic Drugs, paid a lot of

8   attention this morning to the generic application.

9   Yes, it is absolutely necessary that a part of the

10   requirement for generic approval for the market.

11   But I want to remind you that we are developing an

12   FDA policy to equally apply for innovator

13   manufacturers. What I specifically mean is that I

14   think we have data to show that innovators, during

15   the drug development process, during the approval

16   process or postmarketing, will make significant

17   changes, for example in excipients, formulation and

18   manufacturing facilities, and so on and so forth.

19   They will be required to conduct a bioequivalence

20   study to make sure they are equal. Therefore, for

21   highly variable drugs it is also equally applied

22   for the innovator, not just simply the generic

23   companies. I want to make sure that is

24   understandable.

25   Secondly, in terms of if we go forward, we

 1   are seeking your advice on which approach we should

 2   take so that we can spend time on the right track

 3   and then come back to you with recommendations on

 4   what approach we should take. If the committee

 5   advises us to move forward with the reference

 6   scaling how do we determine within-subject

 7   variability? That is an excellent question.

 8   Certainly it would be very difficult to get a

 9   two-way crossover study. We would have to go to

10   the three-way crossover study at least a

11   replicative design from the reference list product

12   to get the number.   Thank you.

13   DR. KIBBE: Marv?

14   DR. MEYER: To kind of follow-up on

15   Jurgen's comment about what we know about the drug,

16   I think there are a couple of simple yardsticks.

17   If you can give a patient an intravenous and then

18   transfer them to IR, or if you can give them IR and

19   transfer them to CR, or back and forth, there is

20   probably no issue with Cmax there. If the product

21   is only available in one strength, 200 mg, and I

22   take it and small people take it and old people

23   take it once a day or twice a day, there is

24   probably no real issue with AUC or Cmax so you

25   could have somewhat less stringent requirements for

 1   those kinds of drugs.

 2   One other comment, add-in designs--it has

 3   shown up here and there but we haven't really

 4   addressed it and, to me, that seemed to be one

 5   approach, provided that there are some constraints

 6   on that and you don't just keep on adding three

 7   subjects until you get it right. Add-ons have some

 8   capability of eliminating excessive use of

 9   subjects.

10   DR. CONNER: By add-on, I think you mean

11   sequential.

12   DR. MEYER: Yes.

13   DR. CONNER: In other words, you do the

14   first group, you look at the results, you make a

15   decision whether to go on or not.

16   DR. MEYER: Right, the point estimate

17   looks good--

18   DR. CONNER: What we refer to as add-on

19   is, you know, you plan to do 24 subjects and you

20   get a whole lot of dropouts. You haven't looked at

21   the data; you have no decision based on the results

22   but you realize you are going to come up short so

23   you get some alternates, recruit some more and put

24   them in. That is what we consider an add-on. So,

25   there is no real decision based on results.

 1   Whereas a sequential design is a plan ahead of time

 2   to do a certain number and generally, as has been

 3   mentioned before, the true sequential design where

 4   you do one sample at a time is really not very

 5   practical in these types of studies. It would take

 6   you years maybe to do the right trial.

 7   So, what we are talking about is a partial

 8   sequential where you do groups. If you were going

 9   to plan an overall 36, you were going to do 12 at a

10   time or 18 at a time, look at the results, make a

11   decision--you know, a correct statistical penalty

12   for that look and that decision and then go on. We

13   don't currently accept that but we are working on

14   it. In several venues, PQRI and otherwise, we have

15   some working groups looking at that very carefully

16   and the proper statistics to do on that. So, we

17   hope to have some results on that pretty soon.

18   DR. KIBBE: Ajaz?

19   DR. HUSSAIN: No, I think I just wanted to

20   say a couple of things after Jurgen's comment.

21   From what he discussed, I think there are a

22   probably a few questions which are not on the

23   screen. So, are we asking the right question also

24   is the topic and I totally agree with him in a

25   sense because we continue to use the black box

1   approach. We don't know anything about it so we

2   have to pass through this goalpost and the goalpost

3   often tends to be arbitrary to start with.

4   Then also, I think we essentially move

5   towards a check box exercise because that is easy

6   to implement, and so forth. Clearly, I think you

7   have to balance the ease of the process of doing

8   something and the scientific rigor and so forth.

9   So, I think clearly as we move forward we will be

10   looking at what are the right questions also and

11   what are the right opportunities.

12   Two things that I think will open this up

13   further and new opportunities will come is the

14   prior knowledge. For example, currently if you

15   look at an ANDA submission or even an NDA

16   submission you don't have much information to make

17   decisions with respect to formulation, process and

18   so forth, what are the critical variables. In

19   ICH-Q8 we have essentially moved forward with

20   pharmaceutical development as a basis for making

21   more scientific, mechanistic based decisions. So,

22   I think we are trying to bring that know-how into

23   the agency to do that.

24   Also, I look at submissions of all

25   studies, all bio studies done as an opportunity to

 1 use all that knowledge to make more rational

 2 decisions and set more appropriate specifications,

 3 and so forth. So, clearly, I think there is

 4 opportunity that is opening up and what you see in

 5 front of you are questions of trying to make

 6 decisions in the current mode and the future might

 7 be quite different.

 8   DR. KIBBE: Let me just throw out some

 9 thoughts from listening to everyone. We have been

10 trying to take a complicated situation and make an

11 easy rule, a simple rule. I think Jurgen hit one

12 of the points dead-on, and that is, I think we

13 really need a decision tree that looks at the

14 characteristics of the product we are dealing with

15 and the therapeutic ranges that it is effective in.

16 We have lots of data on a lot of these products in

17 terms of their therapeutic concentrations in the

18 body and how wide that can be and still get

19 reasonably safe therapeutic effects.

20   To make a rule that only responds to the

21 fact that the product is variable and doesn't have

22 a basis for why we are allowing that variability or

23 why we shouldn't allow that variability just

24 doesn't sound good to me. The thought of going

25 outside the box with some solutions to some of

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 1   these problems, instead of going straight to

 2   another bio study and redesigning a bio study--and

 3   Gordon said, you know, what is wrong with designing

 4   better dissolution testing? One thing no one ever

 5   said is, well, what is wrong with a different

 6   animal model? You know, I have had quite a bit of

 7   success with the pig. The pig is a good animal

 8   model for human absorption in the GI tract and that

 9   is really what we are caring about--and the

10   controls, the negative controls are always tasty.

11   [Laughter]

12   The question here is too complicated for a

13   simple answer and whether we have enough data to

14   get really a quality answer today is problematic.

15   I am intrigued by scaling but only when the

16   supportive data makes sense that we should scale to

17   allow something to happen.

18   I love three-way and four-way studies

19   because they get at what we have been trying to get

20   at for years, which is how variable is the product

21   and how variable are the people we test it on.

22   I worked for a couple of years in a

23   contract research lab. We did ten bio studies a

24   month and I will tell you that I don't think the

25   agency gets to see 40 percent of what we do, and I

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 1   think a lot of the companies, when they find that

 2   they can't successfully formulate, they kill it and

 3   none of those studies show up. You might get some

 4   useful qualitative information from the contract

 5   research labs by just simply asking them to tell

 6   you how many studies they do that never make it to

 7   the agency so you have a handle on the denominator,

 8   if you will.

 9   I think you have a real bear by the tail

10   here and I wish I had as much confidence in

11   Bayesian that would answer every question as my

12   colleague does, but I think really we have to

13   apply--we have to be willing for the agency not to

14   have a rule that everybody can look at in one

15   sentence and say I meet that rule or I don't meet

16   that rule. We have to be willing to say good

17   science supports my product, good science doesn't

18   support my product, and the agency can make a

19   decision based on a whole set of criteria.

20   The last thing is that there is lots of

21   information I would love to learn about the

22   process, supporting Gordon's idea of really

23   understanding the variables and understanding what

24   is going on so I can make better decisions and I am

25   stuck with the single question of who is going to

 1   pay for that, and I don't see everybody rushing to

 2   the forefront to throw millions of dollars for

 3   understanding it when what they really want to do

 4   is get the product on the market.

 5   DR. MEYER: A really quick follow-up to

 6   Art, maybe there is a way for the innovator firms

 7   to have a little expansion of exclusivity if they

 8   seek answers to some of the questions you would

 9   really like to know about mechanisms. It wouldn't

10   cost you a cent. It would cost the American public

11   a little bit but the return might be good.

12   DR. SINGPURWALLA: Well, I was very

13   pleased to hear Art talk about using decision trees

14   but was a little concerned when he said he doesn't

15   have that much faith in Bayesian methods. Well,

16   the two are isomorphic, my friend.

17   DR. KIBBE: Pat?

18   DR. DELUCA: Just a comment, it seems to

19   me that the innovator wants a drug approved so it

20   should be incumbent upon the innovator to seek

21   answers to why there is that high variability. I

22   don't know if we need to give any more exclusivity,

23   I think it ought to be incumbent upon them to do

24   this and to see whether that high variability is a

25   formulation or a physical property, as Gordon had

 1   outlined.

 2   DR. MEYER: Pat, when I was talking about

 3   exclusivity I was talking about something already

 4   approved, much like the pediatric carrot--if you do

 5   pediatric studies you get an extra six months; if

 6   you do mechanism studies you get another three

 7   months, or whatever. And, if you are making a

 8   million a day that is a pretty good incentive.

 9   DR. KIBBE: I don't know where the

10   incentive is for the company. If I am an innovator

11   with an approved product on the market which has a

12   lot of variability but is still approved and it is

13   clinically effective, and it has been sold and now

14   I am producing X billion dollars worth of product

15   every year, do I really want to carefully define

16   that product so someone else can copy it? Or, do I

17   want to keep claiming that the trace elements in it

18   that come from the natural source are so important

19   if they have to be assays so that I don't have to

20   have the problem? I mean, I think Marvin is right,

21   you have to have an incentive for them to get that

22   data for you.

23   DR. HUSSAIN: I just want to point out

24   what Dr. Benet and Jurgen also pointed out, that I

25   think as you go through an approval decision to

 1   approve a new drug product, the basis of it is

 2   safety and efficacy and the risk/benefit decision

 3   that is made. Often when you go through that

 4   process what results is that it is a safe and

 5   efficacious product.

 6   Now, PK variability, yes, we can measure

 7   it. We know it is there and it may not have any

 8   bearing on that and that is what Dr. Benet started

 9   discussing, and so forth. So, keep in mind--Jurgen

10   keeps raising his hand again--what is the clinical

11   relevance. If we can measure it and it is highly

12   variable, if it is not relevant we should probably

13   not be measuring it.

14   DR. KIBBE: Paul, go ahead.

15   DR. FACKLER: I was just going to make a

16   comment along the same lines. We are aware of some

17   NDAs that have been approved without the BE studies

18   having to meet the traditional confidence intervals

19   on both Cmax and AUC--

20   DR. HUSSAIN: Yes, it is done all the

21   time. It is a clinical decision; it is not a PK

22   decision.

23   DR. FACKLER: Right, where the Division

24   can say, you know, the Cmax isn't that relevant to

25   this therapeutic endpoint and, of course, then the

 1   generic industry still has to meet Cmax even when

 2   reference versus reference can't possibly pass it.

 3   So, I think it is a real problem for the generic

 4   industry. Lawrence is right, these rules apply to

 5   new drugs but the divisions have the authority I

 6   suppose to waive a particular data requirement.

 7   You know, as far as granting extra

 8   exclusivity to find the variability in a new drug,

 9   I don't think the generic industry is opposed to

10   doing replicate design studies, doing four-way

11   studies, to define the variability of the reference

12   product and I am guessing that the Division of

13   Bioequivalence would be interested to know the

14   variability in the test product they are

15   considering. So, I am sure there are lots of ways

16   of getting the information one needs to make a

17   decision about whether a product is highly

18   variable. I just wanted to point out that there

19   are products approved for which there is no way for

20   a generic product to gain approval without

21   reference scaling, wider goalposts, whatever the

22   committee decides to recommend. There needs to be

23   a process for a certain fraction of products that

24   are on the market today in the U.S.

25   DR. KIBBE: And I would hope that the FDA

 1   staffers will go away and give us a decision tree

 2   with some understanding of the therapeutic outcomes

 3   and the risk/benefit of that product, how narrow

 4   the therapeutic range has to be, how variable it

 5   is, and then the goalposts can move based on a

 6   decision tree and not have us reestablish another

 7   set that are just ticked. I think we have lived

 8   quite well with 80-125 but it was still picked.

 9   Someone came up and put that down.

10   The other point I just wanted to emphasize

11   is what Les said about how this plays out in the

12   public and among healthcare professionals, and his

13   concept of adding the point determination with what

14   would appear to be to them a narrower range or

15   allowable range might be something also to look

16   into.

17   DR. YU: I guess we will have to look into

18   long-term solutions, the short-term solutions,

19   long-term objectives and short-term objectives. I

20   think mechanisms understanding of the causes of

21   variability and having some kind of decision tree

22   which you imagine is a great idea. I think that is

23   long-term we ought to be looking for. We ought to

24   be looking at moving in this direction. We also

25   have to balance the short-term objectives. If we

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 1   have not seen what the decision tree will look

 2   like, how to implement them right now basically the

 3   policy for the short-term is 80-125 percent

 4   confidence interval, and you have already heard

 5   that some drugs may be difficult to meet, maybe

 6   never to be put on the market. So, I guess this is

 7   a question put to the committee we will have to

 8   discuss. In other words, we are waiting to also

 9   develop the great idea of long-term objective

10   decision trees and then put basically, given this

11   short-term period for the next decade, you will not

12   have those products. So, that is a decision for

13   which we are seeking your advice. Thank you.

14   DR. CONNER: One comment, I mean, you

15   mentioned that we should come forward with a number

16   of sets of data, including the therapeutic range of

17   the product. Now, having been involved in at least

18   one working group where we were looking at NTI

19   drugs and saying, well, can we have a definition,

20   you know, that can always be supported for a given

21   drug or new drug to say what its therapeutic window

22   or therapeutic range is, we spent I think about

23   four or five years and realized we couldn't do it

24   because the data, even in an NDA, does not really

25   tell the true therapeutic range. I mean, they have

1   some indicators that if I go up above a certain

2   point, you know, I don't get anymore efficacy and I

3   start to get something with disturbing side effects

4   but, you know, they usually don't have a full

5   characterization of therapeutic range. Plus, the

6   definition of what indicators I look for and, you

7   know, do I take a ratio and do I look at this

8   versus that, you know, for any given drug it is

9   just not there. Even if you had infinite amount of

10 data, it is very hard to decide what I should look

11 at and what I should use. So, it is easy to say I

12 want to know about the therapeutic range but the

13 data to determine it so that everyone will agree on

14 it, and determine it with certainty just isn't

15 there. We spent a long time really trying to do

16 that and finally gave up, unfortunately. We are

17 still interested in the topic but, you know, we

18 realize that it is a lot harder to do than most

19 people realize.

20   DR. KIBBE: Marvin?

21   DR. MEYER: Since it is in the interest of

22 everyone who is trying to sell a highly variable

23 drug, it would seem to me that a number of

24 companies would give a release to MDS, if asked, to

25 just have a disguised set of data--you don't even

1   have to say class of drugs.

2   I kind of favor number two, reference

3   scaling with a test of a reference stipulation, but

4   I would be interested in seeing the 66 percent of

5   studies that failed and what would you have to do

6   to your limits in order to get them to pass and

7   work with real data. Right now it is somewhat

8   hypothetical.

9   DR. CONNER: Well, that could be done and

10   it would provide more evidence and information

11   about the immediate problem but I don't think that

12   partial knowledge of those would get at the root

13   cause, which is what some members have said they

14   want to see. I mean, you really have to know what

15   the nature of those drug substances is and how they

16   are formulated. You have to know a lot of factors

17   and relate that to what you saw in trying to get at

18   the problem and its root causes.

19   DR. MEYER: Yes, that is a laudable goal

20   but I thought we wanted an answer while we are

21   still alive.

22   [Laughter]

23   DR. CONNER: I expect you will be around

24   for quite a while.

25   DR. KIBBE: Gary?

 1   DR. BUEHLER: We do want an answer while

 2   you are still alive, Marvin. This is a big issue

 3   for us. I am one that always says that we have to

 4   bring difficult issues to the advisory committee

 5   and, you know, we bring sort of soft balls to you.

 6   I really made the point that this is a very

 7   difficult scientific issue. It is an economic

 8   issue. As was brought up today, clearly it is an

 9   economic issue but the Office of Generic Drugs is

10   an economically driven office that makes scientific

11   decisions and makes these economic decisions in a

12   scientific way. We have products out there that we

13   can't get generics of, and that was made evident by

14   Dr. Fackler, from Teva, and he knows that probably

15   better than I do. But generic drugs are a big

16   political issue. They are a big, passionate issue

17   with the American public today. People see

18   generics as an answer to the high cost of

19   prescription drugs today.

20   So, what we are bringing to you today--I

21   am not saying that a decision tree is not a good

22   idea; I think it is a great idea, but I agree with

23   my colleagues from the Office of Generic Drugs that

24   a decision tree can be an awfully long process to

25   put together and to gather the data from all the

 1   various drugs, and I am not sure I have the staff

 2   to be able to do that within the next millennium or

 3   so. So, what we would like from you today is some

 4   direction as to which way to go. If you would be

 5   able to provide that to us somehow, we would

 6   appreciate that.

 7   DR. KIBBE: I think we have heard from Dr.

 8   Meyer that he prefers scaling. How many of us

 9   think that that is an option for situations that

10   seem to be highly variable and need an evaluation

11   outside of the current rules?

12   DR. SINGPURWALLA: I am sorry, I think one

13   has to put things sometimes rather bluntly. I feel

14   that those questions that you have asked are the

15   wrong questions, or there should be additional

16   questions, namely, what are the alternatives? The

17   decision tree, as Jurgen puts it, is a very good

18   alternative.

19   The second point is the scaling. The

20   scaling has been talked, and talked, and talked

21   about. There is a simple reason why you do the

22   scaling. The scaling is a transformation which

23   tries to bring the variability down. If the

24   scaling does not bring the variability down no

25   statistician will do it. Its main purpose is

 1   two-fold, to make everything look approximately

 2   normal and, in the process, bring the variability

 3   down. So, the scaling is a technical exercise

 4   which nobody should question or criticize whenever

 5   it is appropriate and it is not a debatable issue.

 6   The issue that is really debatable is are

 7   those the right kind of questions and do we want to

 8   pursue that line of questioning. What I would like

 9   to do, if Mr. Chairman would allow me sometime

10   later in the afternoon, is to ask everyone around

11   the table what do they mean by confidence limits;

12   what is its interpretation; and how is it

13   understood. And, I will make a bet that fifty

14   percent will get the answer wrong, at least. Thank

15   you.

16   DR. KIBBE: It is against federal

17   regulation to gamble in Washington, D.C.

18   [Laughter]

19   There will be no betting going on!

20   Jurgen, what do you think?

21   DR. VENITZ: I think it is time for lunch.

22   DR. KIBBE: No, no, no one is going to

23   lunch until we answer his question. What do we do

24   in the short term?

25   DR. VENITZ: Well, in the short term I

 1   don't think there is anything wrong with reference

 2   scaling the way I understand it. I had some

 3   question about how you are going to get the

 4   estimate for your within-subject reference

 5   variability but if that is part of a replicate

 6   design study or separate study, I think I can live

 7   with that. I still think, as I said before with

 8   Les, you should have additional constraints on the

 9   point estimates, and it might just be for public

10   consumption so everybody on the outside that is the

11   recipient of whatever we come up with today feels

12   comfortable, yes, the rules are not being bent to

13   make bad products look good or, you know, highly

14   variable drugs look good. But other than that, I

15   can live with this as a band aid. I do think you

16   should start working on the long-term strategy,

17   which comes back to the decision aspects.

18   DR. KIBBE: Gordon, what do you think?

19   DR. AMIDON: I would agree with the

20   scaling. Again, the question of how you get the

21   reference scaling, I think the last point on the

22   reference scaling is a good starting point to look

23   at in trying to make that in a concrete decision

24   rule. I still think that the mechanism, you know,

25   what is going on with highly variable drugs, where

1   the problems are, that is the real long-term

2   solution, understanding what the problem is and the

3   FDA should in some way put some resources into

4   that, and I think Marvin Meyer's suggestion is an

5   excellent one. You know, just provide some

6   incentive for industry to fund research into what

7   is happening with these drugs.

8   DR. KIBBE: Judy?

9   DR. BOEHLERT: I have thought about this a

10   lot and I also would agree with using the scaling

11   factors but I think you are still going to be in a

12   position of having to make decisions and having

13   some kind of decision tree, even if it is not

14   formal because Dr. Davit presented data this

15   morning that showed that the same product with two

16   different laboratories had different values. So,

17   you are going to be in that situation where one

18   manufacturer uses scaling and the other one doesn't

19   so you are going to have to make some decisions

20   around those issues. It is not so straightforward,

21   particularly when you get around that 30 percent

22   number.

23   DR. BUEHLER: Making decisions is "an

24   understood" for me so I can accept that. But I

25   echo Jurgen. We have to make sure that whatever we

 1   decide will provide a good scientific method so

 2   that the generic products that go on the market as

 3   a result of this are unequivocally bioequivalent

 4   and, of course, safe and effective.

 5   DR. KIBBE: My colleague who hardly ever

 6   speaks?

 7   DR. SELASSIE: I agree with what Jurgen

 8   said because I think that there needs to be a

 9   mechanistic basis as to what type of scaling

10   factors you use, and it seems to me that that is

11   really important and we need to understand the

12   physicochemical parameters that are involved in

13   dissolution and it seems like that is missing and

14   is arbitrary in trying to set some scaling factor,

15   and we are not taking those types of phenomena into

16   consideration. So, I think a decision tree in the

17   long-term would be a good idea but I guess in the

18   interim you can use something like reference

19   scaling.

20   DR. KIBBE: Marc?

21   DR. SWADENER: I think it is a little bit

22   naive to think that all of us here, at every stage

23   along the line, don't use a decision tree of some

24   sort. Formalizing it to the stage that people are

25   talking about here is a little diplomatic but we

 1   all have a decision tree that we use. Whether I

 2   came here to this meeting or not, I used one.

 3   Whether it was formalized or not is a different

 4   question.

 5   I do know enough about statistics to know

 6   you can't believe them all the time. You have to

 7   be very, very careful about them. So, I think I

 8   would encourage looking at a decision tree not as

 9   the short term as it will take time, and do the

10   best you can. I do agree with Jurgen, you really

11   have to look at what are the real fundamental

12   questions you are dealing with too. With my

13   representation on this committee, the public just

14   needs to know that what they are getting is safe

15   and will do what it says it will do. Now, that is

16   a very simple approach but they don't know all this

17   stuff and they are relying on you to do the best

18   you can. I don't see that you are not doing that.

19   DR. KIBBE: Dr. Koch?

20   DR. KOCH: Yes, I would agree with the

21   summary that you came up with and certainly stay

22   with the reference scaling short term but something

23   has to be put together to address the decision tree

24   approach.

25   DR. COONEY: I think that the change in

 1   limits is not acceptable because it is very

 2   arbitrary and if there are options I think the use

 3   of reference scaling makes fundamental sense.

 4   Furthermore, a decision to do that is a decision

 5   down the path of a decision tree so it is a logical

 6   step to take and I want to underscore the

 7   importance of continuing to gather the data and

 8   establish the criteria around which these

 9   individual decisions are made and you will be in a

10   better position to do this goring forward.

11   DR. KIBBE: Pat?

12   DR. DELUCA: I am certainly an advocate of

13   getting those drugs that are safe and effective to

14   the market. Certainly, the public would benefit

15   from those. I guess I favor in the short term--I

16   think in the long term something more substantial

17   has to be done with regards to decision making, but

18   reference scaling I think is very important here.

19   Again, I don't like the arbitrary nature of

20   widening the limits but if that is something that

21   can be approached in the short term, then I would

22   be for it.

23   I still think that we need to encourage

24   the innovator to finance for the high variability

25   that exists. Whether it is offering incentives in

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 1   some way, so be it but certainly an incentive if

 2   they can reduce the variability. It seems to me

 3   they gain something when the generic has to go into

 4   the reference scaling, they have improved the

 5   product so I think that is also an incentive to do

 6   it.

 7   DR. KIBBE: Our industry representatives

 8   have a comment one way or the other? I would just

 9   like to wrap up and go to lunch but with one

10   comment. I think if we go ahead and make a change

11   in the way we approve highly variable drugs, then I

12   think we ought to consider seriously also Les'

13   other point which is to come up with something that

14   is going to reassure the public that the changes we

15   are making are not getting drugs that can vary by

16   50 percent on the marketplace but, rather, that

17   they really are tighter than that so they

18   understand it better. So, I would end with that.

19   With that said and no one else waving frantically

20   to get my attention, we will break for lunch and we

21   will be back at 1:40.

22   [Whereupon, at 12:40 p.m. the proceedings

23   were recessed for lunch, to resume at 1:40 p.m.]

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

2   [Because the Chairman reconvened the

3   proceedings before 1:40 p.m., part of the text is missing.

4   There were no speakers who wished to speak

5   during the open public hearing but there was a public

6   submission from Zeb Horowitz, M.D.]

7   Bioinequivalence: Concept and Definition

8   [Slide]

9   DR. YU: ...bioavailability is rate and

10   extent of absorption and it is the site of drug

11   action. So, normally you give a drug to a healthy

12   volunteer or patient and measure the plasma

13   concentration against time, as shown in this

14   figure. Then you get a Cmax here; you get the AUC,

15   AUC is area under the curve. Cmax is a surrogate

16   for the rate of drug absorption; AUC is basically

17   for the extent of absorption so this is defined as

18   bioavailability.

19   [Slide]

20   Bioequivalence basically is defined as the

21   absence of a significant difference in the rate and

22   extent to which the active ingredient or active

23   moiety in the pharmaceutical equivalents or

 1   pharmaceutical alternatives become available at the

 2   site of drug action when administered at the same

 3   molar dose under similar conditions in the

 4   appropriately designed study. So, this basically

 5   is the Federal Register Notice definition. So,

 6   bioequivalence basically means the absence of a

 7   significant difference in the rate and extent of

 8   drug absorption.

 9   [Slide]

10   This morning we discussed bioequivalence

11   and we said a 90 percent confidence interval for

12   the extent or AUC for the rate as a surrogate or

13   Cmax 80-125 percent. Now, passing or meeting the

14   bioequivalence standards allows marketing access

15   basically as one of the standards for approval of

16   the applications. Of course, you have to meet

17   very many other requirements, especially with

18   respect to the chemistry, manufacturing controls

19   with respect to quality of the products. So,

20   demonstration of bioequivalence makes the generic

21   to be approved and the innovator basically

22   demonstrates that the marketed formulation is

23   equivalent to the clinical formulation.

24   [Slide]

25   The question is why do we define the

 1   bioinequivalence concept? What are you talking

 2   about here? Why do you define this? It is because

 3   FDA receives studies that attempt to reverse a

 4   previous finding of bioequivalence. In other

 5   words, you approve a product to put on the market

 6   when some manufacturer conducts a study to show or

 7   fails to show the bioequivalence. Also, in the

 8   public literature there are claims of

 9   bioinequivalence. In reality, it is simply a

10   failure to demonstrate bioequivalence. So, there

11   is a concept you need to clarify, what is called

12   bioequivalence and what is called bioinequivalence.

13   What is the difference when you fail to demonstrate

14   bioequivalence and bioinequivalence?

15   [Slide]

16   There are many reasons, as we discussed

17   this morning, for high variability--under-powered

18   study designs, study samples, many, many reasons

19   that can make a study fail. Of course, the easiest

20   way, as we discussed this morning, is to use a

21   small number of subjects. So, it is easy to fail

22   to show bioequivalence by a small number of

23   subjects and, certainly, there will be other

24   considerations like study design, study sample,

25   data analysis. There are many, many other reasons

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 1   and these are just several of them.

 2   [Slide]

 3   What should bioequivalence mean if we

 4   define a definition for bioinequivalence? As we

 5   said, bioequivalence leads to market access.

 6   Basically a study that demonstrates bioequivalence

 7   is clear and convincing evidence of equivalence.

 8   Bioinequivalence may lead to market exclusion. Of

 9   course, we have to consider many, many other

10   factors too as we discussed this morning--safety,

11   efficacy, pharmacokinetics, pharmacodynamic

12   relationship and so on. But a bioequivalence study

13   demonstrated by equivalence is clear and convincing

14   evidence of potential problem for the specific

15   product.

16   [Slide]

17   So what do we specifically mean here? I

18   want to spend a little time on this slide. When

19   you conduct a study, if a study is properly

20   designed, the 90 percent confidence interval is

21   between 80 to 125 percent. Now, if this study is

22   under-powered and if this study has a small number

23   of subjects, there is a greater possibility that it

24   fails to demonstrate bioequivalence. What this

25   specifically means is simply that the manufacturer

 1   or sponsor does not use enough subjects for

 2   example, of course, among many other reasons, to

 3   conduct a study. If the study is powered enough,

 4   there is a greater possibility that you can narrow

 5   the confidence interval and make this a passing,

 6   successful study. Coming back to so-called

 7   inequivalence is to make sure that the test product

 8   has a difference more than 20 percent or, for

 9   example is underneath the 80 percent or above 125

10   percent. Of course, there is also the failure to

11   demonstrate a bioequivalence study because simply

12   the top limit above 80 or, on the other side of the

13   lower limit it may be below 125.

14   I think it is in the best interest of the

15   public and us, for clarification, that we want to

16   define the bioequivalence, bioinequivalence,

17   failure to demonstrate bioequivalence and failure

18   to demonstrate bioinequivalence. This is a concept

19   that we have to be very clear about because in many

20   cases in the published literature or studies

21   submitted to the Food and Drug Administration are

22   simply that. For example, the top limit is above

23   125 percent or the lower limit is below 80 percent

24   if you use enough power and increase the subjects

25   of the studies the study will become a successful,

 1   passing study instead of failure to demonstrate

 2   bioequivalence.

 3   Yet, because of confusion because there is

 4   no clear definition with respect to bioequivalence,

 5   in the end any study, whether the lower limit is

 6   below 80 and upper limit is above 125, the sponsor

 7   or other parties will have bioinequivalence. The

 8   reality is simply to fail to demonstrate

 9   bioequivalence. In other words, the true

10   difference is acceptable, however, the study is not

11   properly designed because it is under-powered, or

12   many, many other reasons where the confidence

13   interval does not meet the regulatory criteria,

14   which is 80-125 percent. At the end, the claim is

15   basically bioinequivalence and in reality, as I

16   said, is a failure to demonstrate bioequivalence.

17   So, I want to make it clear, I want to clarify the

18   concept.

19   [Slide]

20   So, the objective at FDA is to develop

21   bioinequivalence criteria that are scientifically

22   sound, statistically valid and fair to all parties

23   and, hopefully, easy to use.

24   With this introduction, I want to turn the

25   podium to Don and I am sure a lot of people know

 1   him. He is the developer of the original 80-125

 2   percent criteria for FDA standards. He will be

 3   speaking about how to statistically establish

 4   bioinequivalence.

 5   DR. MEYER: A real quick question, I don't

 6   quite catch the fail to demonstrate

 7   bioinequivalence for the one where the right-hand

 8   tail is barely across 80 but the point estimate is

 9   well to the left of 80. It seems to me that still

10   is a bioinequivalent product.

11   DR. YU: This one?

12   DR. MEYER: Yes, with the point estimate

13   falling well to the left. It seems to me changing

14   the N won't help that one. It will just make the

15   confidence limits fall, totally bioinequivalent.

16   DR. YU: Yes, most likely if this study is

17   powered--to increase, for example, the power of

18   this study this product is bioinequivalent. This

19   time it is because the confidence interval above 80

20   statistically speaking, as Don can clarify, failed

21   to demonstrate whether it is truly bioinequivalent

22   or not. I think that Don is the better person to

23   answer the question.

24   Statistical Demonstrations of Bioinequivalence

25   MR. SCHUIRMANN: One clarification to what

1   Lawrence said, I did not have anything to do with

2   choosing 80-125 as the limits for bioequivalence.

3   [Laughter]

4   [Slide]

5   This presentation is joint work with

6   colleagues in the Quantitative Methods and Research

7   staff of the Office of Biostatistics and also in

8   the Office of Generic Drugs, and the bulk of the

9   presentation was put together by my colleague, Dr.

10   Qian Li, who originally was scheduled to give this

11   presentation but she just recently had a baby so

12   she is having a little deserved maternity leave.

13   [Slide]

14   We hope to go over the definition of

15   bioinequivalence, comments on claiming

16   bioinequivalence if you fail to show

17   bioequivalence, proposing a criterion to use for

18   one PK endpoint--PK is pharmacokinetic, and talk

19   briefly about strategies when you are looking at

20   three pharmacokinetic endpoints.

21   [Slide]

22   The usual definition of the bioequivalence

23   interval on the ratio of the population geometric

24   mean of the test product over the population

25   geometric mean of the reference product is that it

 1   should fall within the limits of 80 percent to 125

 2   percent. That is what is called the bioequivalence

 3   interval. It is never correct to refer to that as

 4   a confidence interval. So, it is obvious to define

 5   the bioinequivalence region as just the complement.

 6   If you are not in the bioequivalence interval, then

 7   you are in the bioinequivalence region which

 8   consists of the two disjoint regions.

 9   [Slide]

10   So, the question that I first want to look

11   at is, is it appropriate to claim bioinequivalence

12   if a study fails to show bioequivalence? Two

13   products may, in fact, be bioequivalent but they

14   may not be shown to be bioequivalent by the study.

15   The primary reason for that is inadequate power.

16   There could possibly be other reasons.

17   [Slide]

18   In doing our standard testing for

19   bioequivalence, it is an application of statistical

20   hypotheses testing where we have a null hypothesis

21   that says either the ratio of geometric means is

22   too low, below 80 percent, or else it is too high,

23   above 125 percent, and we test that against the

24   alternative hypothesis that the ratio of geometric

25   means is within the interval. The way that we have

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 1   typically tested this statistical hypothesis is by

 2   doing two one-sided statistical tests, and each of

 3   those tests is carried out at the alpha equals 0.05

 4   level of significance.

 5   Now, it turns out that doing these two

 6   one-sided tests--it is an example of what is called

 7   intersection union test--is algebraically

 8   equivalent to calculating a two-sided 90 percent

 9   confidence interval and seeing whether it falls

10   within the equivalence interval. So, that is why

11   you hear a lot of talk about confidence intervals

12   today even though we are not using the confidence

13   interval as a confidence interval; we are using the

14   endpoints of the confidence interval as test

15   statistics. What we are doing here is statistical

16   hypothesis testing. As I said, the type 1

17   error--we have to reject both one-sided null

18   hypotheses, both H-nought 1 and H-nought 2. If we

19   reject both one-sided null hypotheses, then we

20   conclude that this alternative is true, that is,

21   that we have average bioequivalence.

22   [Slide]

23   So, we need to reject the hypothesis of

24   inequivalence with high confidence and the

25   rejection region is selected to make the chance of

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 1   doing that incorrectly to be small, and that is the

 2   level of significance which, as I said, is alpha

 3   equals 0.05.

 4   [Slide]

 5   So, what is the error associated with

 6   claiming inequivalence if you don't claim

 7   equivalence? Well, if you are looking for a

 8   procedure for testing to see if you have

 9   inequivalence, then we need to control the error

10   wrongfully rejecting equivalence to be small. If

11   you are going to base it on the equivalence test,

12   that means you want the equivalence test to have

13   large power. However, the power for the

14   bioequivalence test, as you will in a moment, may

15   not be large overall values of the geometric mean

16   ratio in the equivalence region.

17   The testing for bioequivalence focuses on

18   controlling the type 1 error and then other aspects

19   of the test, such as high power if the alternative

20   is true, are gotten, if they can be. So, we may

21   not have adequate power to claim bioequivalence

22   even when bioequivalence is true.

23   [Slide]

24   Here is an example. If we had a product

25   and we are going to design a two-period, two

 1   sequence bioequivalence trial, and we assume we

 2   have within-subject variance of 0.04, that is to

 3   say within-subject standard deviation of 0.2, and

 4   we are willing to assume that the ratio of

 5   geometric means deviates from 1 by no more than 5

 6   percentage points and, if that is true, we want to

 7   be at least 85 percent sure that we will reach a

 8   conclusion of equivalence, you can then crank the

 9   numbers and you come up with the sample size of 22

10   subjects.

11   Well, if you have 85 percent power, that

12   means you are 85 percent sure of concluding that

13   the products are equivalent. That means you could

14   have as much as a 15 percent chance of not

15   concluding that they are equivalent. So, even with

16   this design study you could have products that are

17   equivalent but you have as much as a 15 percent

18   chance, or even more, of failing to conclude that

19   they are equivalent. In fact, if the variance,

20   unbeknown to you, is higher than you thought or if

21   the geometric mean ratio deviates from 1 by more

22   than 5 percentage points, the power will be lower

23   so the chance of not concluding bioequivalence will

24   be higher. So, it should be apparent that that is

25   not a basis for concluding inequivalence.

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 1              [Slide]

 2              The rejection region for the

 3   bioequivalence test--what do I mean by rejection?

 4   I mean rejecting the hypothesis of inequivalence

 5   and concluding equivalence--is determined by the

 6   variability associated with the point estimate of

 7   the geometric mean ratio, which is illustrated here

 8   on the log scale.  The higher that standard

 9   deviation of the estimator is, the further away

10   from the actual limits--delta-2 here is 1.25;

11   delta-1 is 0.8--the narrower that rejection region

12   will be and the lower the power will be.  So, it

13   isn't enough for the point estimate to be within

14   the equivalence interval.  It has to be comfortably

15   away from the edges of the equivalence interval in

16   order to conclude equivalence.

17              [Slide]

18              This is an example of power curves for the

19   test for equivalence.  The blue lines correspond to

20   a standard deviation on the log scale of 0.5.  The

21   red lines correspond to a standard deviation of 0.3

22   and the green lines correspond to a standard

23   deviation of 0.1.  The solid lines are for a study

24   with 60 subjects.  The corresponding dashed lines

25   are for a study with 30 subjects.
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 1              Let's take this example, a 60-subject

 2    study but the standard deviation is 0.5, even if

 3    you are exactly equivalent, you are identical,

 4    there is a very good chance that you will not

 5    conclude equivalence so that is no basis for

 6    concluding inequivalence.

 7              [Slide]

 8              So, instead of trying to use the

 9    equivalence test as a means for establishing

10    inequivalence, we need to develop a testing

11    procedure aimed specifically at inequivalence.

12    Here we have done that by reversing the hypotheses.

13    Now the null hypothesis, in statistical jargon, is

14    that the geometric mean ratio is within the

15    interval.  The alternative is that it is either

16    below 80 percent or else it is above 125 percent.

17    So, once again try to test this hypothesis by doing

18    two one-sided tests, each at a level of 0.05, and

19    in the case of equivalence we had to reject both of

20    the one-sided hypotheses but in this case we have

21    to reject one or the other.  So, we will reject

22    bioequivalence and conclude bioinequivalence if one

23    of these two one-sided hypotheses is rejected.  It

24    says here under certain conditions and, in fact,

25    under most conditions the overall level of that
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1   procedure will not be appreciably different from

2   0.05, however, we can find mathematically cases

3   where it could be higher. It could be as high as

4   0.1.

5   [Slide]

6   Before I showed you the region for

7   concluding equivalence and that is these lines,

8   here. Now the region for concluding inequivalence

9   is given by this line and this line. You have to

10 fall higher than this with the point estimate or

11 you have to fall lower than that in order to

12 conclude inequivalence. So, once more you need to

13 be comfortably away from the actual boundary before

14 you reach your conclusion.

15   [Slide]

16   This is what the power of that test looks

17 like. The color scheme and the solid and dashed

18 line scheme is the same before. These vertical

19 lines are the 0.8 to 1.25 lines and so if you are

20 in the interval, 0.8 to 1.25, the probability never

21 gets higher noticeably than 0.05. But if you are

22 outside of the interval, then you have a greater

23 chance of concluding bioinequivalence. I might add

24 that it is symmetric in the reciprocal of the

25 ratio. In other words, here is a ratio of 0.5 and

 1   it has a certain high probability of concluding

 2   inequivalence. To have the same probability over

 3   on the other side, it would have to be equal to 2,

 4   which is the reciprocal of 0.5.

 5   [Slide]

 6   We are going to try to control that error

 7   to 0.05. It is a function of what in this slide is

 8   designated sigma-T, which is the standard deviation

 9   of the estimator that is used as the basis for the

10   test statistic. As that sigma-T gets larger you

11   could possibly have more than a 5 percent chance of

12   wrongfully concluding inequivalence.

13   [Slide]

14   Well, how big would the variance have to

15   be? Dr. Li ran some calculations. In this

16   example, here, N equals 10. A bioequivalence study

17   with only 10 subjects I don't think would even be

18   allowed. These studies tend to be considerably

19   larger than 10 subjects. But it just illustrates

20   the fact that even for that tiny sample size the

21   standard deviation, which is on the log scale, has

22   to be quite large before the chance of making the

23   wrong decision, that is to say concluding

24   inequivalence when, in fact, the products are

25   equivalent gets unacceptably high. If you have a

1   more reasonable number of subjects it has to be

2   astronomically high before you start running into

3   that problem.

4   There could be cases perhaps with a

5   parallel design of a highly variable drug where we

6   might have to do some adjustment to the

7   significance level, and there do exist methods in

8   the literature to do that.

9   [Slide]

10   So, that is the corresponding test to the

11 bioequivalence test for one parameter, but

12 generally we assess bioequivalence studies with

13 respect to three endpoints--I said parameter,

14 didn't I? Pharmacokineticists love to use the word

15 "parameter" to describe AUC and Cmax; statisticians

16 don't. Typically, we require for an equivalent

17 study you have to show equivalence for area under

18 the curve to the last sampling time; area under the

19 curve extrapolated to infinity; and maximum

20 observed concentration. What are we going to do

21 about bioinequivalence? In concept the products

22 are bioinequivalent if they are bioinequivalent

23 with respect to just one of these three.

24   [Slide]

25   So, what statistical criteria shall we

 1   use? We are looking at a number of strategies.

 2   Strategy one is to say, well, if you conclude

 3   bioequivalence with respect to just one of the

 4   three pharmacokinetic endpoints, then you will

 5   reach a conclusion of bioinequivalence. The things

 6   in favor of that is that it is quite intuitive.

 7   The arguments against it are that you now have

 8   three chances--if you have a case where the

 9   products are close to being inequivalent but they

10   aren't inequivalent, then you have three chances to

11   make a mistake and you may inflate the overall type

12   1 error rate.

13   [Slide]

14   So, if you are worried about that, here is

15   another strategy which says, well, you have to show

16   that it is inequivalent with respect to all three

17   of the PK endpoints. Then you can tightly control

18   the type 1 error rate. Type 1 error in this case

19   means concluding inequivalence when, in fact, the

20   products are equivalent. But the argument against

21   this strategy is that it is not going to have

22   reasonable power against alternatives of interest.

23   [Slide]

24   Another possibility would be to say, well,

25   you need to prespecify which endpoint you are going

1   to look at. In the slide here AUC was used as an

2   example. Possibly Cmax would be another choice.

3   This will control the type 1 error but if the

4   endpoint you chose is not the endpoint for which

5   the products are inequivalent, then you are not

6   going to have a reasonable chance of reaching a

7   proper conclusion.

8   [Slide]

9   Other strategies require that you show

10 equivalence for all three but you adjust the alpha

11 levels so the overall level is maintained but you

12 have more power for each individual test. A method

13 to do this which doesn't require the levels to be

14 the same for all three endpoints is currently under

15 development in QMR.

16   Other possibilities--one that occurred to

17 me is you might say, well, before you can conclude

18 that the products are inequivalent with respect to

19 AUC you have to show inequivalence for both AUC to

20 the last time point and also for AUC to infinity

21 but we will look at Cmax separately. But there

22 could be regulation complications in all of these

23 proposals.

24   [Slide]

25   So, the main focus of this presentation

 1 was on power to make the right decision and what we

 2 are calling error, which is making the wrong

 3 decision and controlling the probability of making

 4 a wrong decision. There could be other statistical

 5 issues as well. Thank you.

 6   DR. KIBBE: We will open it up for

 7 questions from the panel. Marvin, go ahead.

 8   DR. MEYER: Don, a practical example of

 9 what would happen with strategy one if the type 1

10 error were inflated and the three PK endpoints are

11 now highly correlated--

12   MR. SCHUIRMANN: I apologize, Dr. Meyer, I

13 didn't bring those numbers with me--

14   DR. MEYER: Just conceptually.

15   MR. SCHUIRMANN: Suppose you had a product

16 for which the ratio of the population of the

17 geometric means was something like 124 percent for

18 all three parameters. Then, the chance that you

19 will conclude inequivalence for at least one of

20 them could be something like 15 percent, in that

21 neighborhood, depending on the sample size;

22 depending on how tightly correlated the AUC is with

23 the Cmax. I can't give you a very quick answer.

24 In some of the simulations that Dr. Li did about 15

25 percent was the highest I saw. So, it depends on

1   whether you are interested in controlling that

2   overall level or whether you are merely interested

3   the level in each individual endpoint.

4   DR. BENET: Since this would be a test to

5   take a drug approved off the market, have you

6   considered that maybe we need more than one study?

7   Have you talked about that? Have you thought about

8   that in your thinking about it?

9   MR. SCHUIRMANN: I can't speak for the

10 Center. I have not thought about that much.

11   DR. BENET: Well, I was reacting to

12 Barbara's data where you looked at the two

13 different studies with two people running it with

14 significantly different variance in the two

15 different studies, and that could be an issue here.

16 You know, I think it is a statistical issue but it

17 is also a policy issue in terms of, you know, is

18 one study going to be adequate? No matter which of

19 these terrible suggestions you pick, is one study

20 going to be adequate?

21   MR. SCHUIRMANN: On the one hand,

22 requiring two studies would bring it more in line

23 with what we require for Phase III clinical trials

24 where we want a reproducible result so you have to

25 show us more than once. On the other hand, we

 1 approve generic drugs with only one bioequivalence

 2 study. So, what would be the basis for requiring

 3 two studies for the opposite claim?

 4   DR. VENITZ: But you already have two

 5 studies. Don't you have a prior study that led to

 6 its approval as a bioequivalent generic and now you

 7 have a study to disprove it. So, my question is

 8 somewhat related to what Les is asking, how do you

 9 incorporate the prior information that you have

10 from the fact that your drug got approved based on

11 a bioequivalence study? Because you now have one

12 study done God knows how long ago--

13   MR. SCHUIRMANN: Yes.

14   DR. VENITZ: --but it passed

15 bioequivalence. Now you have done a study, no

16 matter what method you use, that shows

17 bioinequivalence. Are you going to pool the

18 studies? Are you going to use Bayesian to

19 incorporate your prior information or are you

20 completely ignoring the fact that in order to get

21 approval it must have passed a bioequivalence

22 study? And this is not a question to you but to

23 everybody.

24   DR. BUEHLER: Usually when we get a

25 challenge study now we will inform the generic

 1   sponsor of the generic application that their

 2   bioequivalence has been challenged, and that they

 3   can come back to us with additional data, usually

 4   another study, which would refute the study that

 5   came in. We usually review the study extensively,

 6   the challenge study extensively to make sure that

 7   the study was conducted properly. We review it as

 8   far as it was powered correctly, etc. Then we give

 9   the generic firm that was challenged the

10   opportunity to come back to us with a study or else

11   face being downgraded in the "Orange Book."

12   DR. VENITZ: But if they don't come back

13   do you ignore the fact that they must have done a

14   study in the first place that demonstrated

15   bioequivalence?

16   DR. BUEHLER: No, we don't ignore that

17   fact. That is why we leave them on the market

18   while they get the additional data to us. I mean,

19   they did submit a study to us that showed their

20   product to be bioequivalent. Now, whatever

21   happened along the way, you know, whatever water

22   flowed under the bridge between then and the time

23   when we have had the challenge study, you know,

24   sometimes it is a long time. Sometimes

25   formulations change or reference listed drugs

 1   change so we give them the opportunity to come back

 2   to us with another study to show that they are

 3   still bioequivalent.

 4   DR. KIBBE: Go ahead, Marc.

 5   DR. SWADENER: Is my intuitive notion that

 6   these strategies one, two and three could result in

 7   failure to agree on the hypothesis that it turns

 8   out that is not inequivalent doesn't necessarily

 9   say that it is equivalent? Aren't there parts

10   where it is really not equivalent?

11   MR. SCHUIRMANN: We are talking about

12   studies here and there is such a thing as an

13   inconclusive study, a study that does not establish

14   that two products are equivalent and the study also

15   does not establish that the two products are not

16   equivalent.

17   DR. SWADENER: Exactly.

18   MR. SCHUIRMANN: That isn't to be confused

19   with the actual reality unknown to any human being

20   whether they are or aren't equivalent. With these

21   strategies, depending upon how stringent you make

22   it, you could very well have data that, as a

23   clinical, you look at and it worries you--"gosh,

24   these products sure differed a lot in this

25   study"--but it is not conclusive that they are

 1   inequivalent. So, yes, you could have that

 2   situation very easily.

 3   DR. KIBBE: Marvin?

 4   DR. MEYER: Gary, did I understand you to

 5   say that if in the initial study the generic

 6   product came in, let's say, at 80-125, just hit the

 7   upper and lower limit, and then the challenge study

 8   came in at 79-125 the generic would have to redo

 9   their study?

10   DR. BUEHLER: No. That is part of the

11   reason for this exercise, that is, we do face

12   situations like that where we will get very

13   marginal challenge studies submitted and where a

14   reasonable person could say, gee, you if threw

15   another six patients or subjects into that study

16   and you probably would have been 80 or 81. So,

17   what we are looking for here is to try to set up

18   some guidelines as to what will be acceptable as a

19   challenge to the bioequivalence.

20   DR. KIBBE: Let me ask Jurgen's question,

21   which is when the challenge comes in is there any

22   thought to how clinically significant it is what

23   the challenge study shows? I mean, is it

24   clinically significant relative to the use of the

25   drug itself?

1   DR. BUEHLER: The challenge study is

2 reviewed and we make an assessment as to whether

3 the challenge study, as I said, was conducted

4 properly and powered properly. If the condition is

5 that we believe that more subjects, you know, would

6 have thrown it over the line we normally make the

7 generic do another study to prove their

8 bioequivalence. Now, that is a value judgment with

9 respect to what to do. Again, that is one of the

10 reasons we are here right now. We would like to

11 have a little more certainty in making this

12 decision as to when a generic has to repeat their

13 study.

14   DR. KIBBE: Gordon, go ahead.

15   DR. AMIDON: Yes, I think we are, again,

16 treating the BE test just as a simple empirical

17 test, yes or no. I think there have to be other

18 underlying reasons for why there is now a large

19 difference in the performance of the dosage form in

20 vivo, things such as dissolution. I think one

21 should look at other data and have other facts or

22 information supplied by a company saying that it

23 has attempted the bioinequivalence study that they

24 come up with something that suggests that it is

25 bioinequivalent. There should be other facts that

 1   support that conclusion, in particular dissolution

 2   methodology. So, you should look for more

 3   information.

 4   DR. YU: That is correct. Of course, when

 5   we receive such challenge studies we have to make

 6   sure that the study is properly designed and

 7   conducted and the conclusion is valid. Secondly,

 8   we look at the quality of the sample used to

 9   conduct the studies. From the cGMP perspective,

10   from the quality perspective we look at the

11   dissolution of the stability and potency, and so

12   on, all the quality standard samples. Certainly,

13   we also look at the process. As I said, in

14   bioinequivalence we want evidence to show

15   inequivalence and we certainly look at many, many

16   other factors. In other words, we want to say that

17   the decision we are making is a systematic decision

18   instead of being based on one parameter.

19   DR. KIBBE: Nozer?

20   DR. SINGPURWALLA: Yes, C, subscript t,

21   and C subscript infinity--

22   MR. SCHUIRMANN: You mean AUC subscript--

23   DR. SINGPURWALLA: Yes, is that the time

24   index?

25   MR. SCHUIRMANN: It is not an estimate of

1   the time.

2   DR. SINGPURWALLA: It is some index?

3   MR. SCHUIRMANN: When you do these studies

4   you give the products to subjects and then you

5   start taking blood samples from them at specified

6   sampling times, at however many hours, and one of

7   those has to be the last one. Maybe it is 24

8   hours. It would depend on the drug product. So,

9   you can calculate the area under the blood level

10   time curve up to that last blood sampling time for

11   that subject. You have the data for each sampling

12   time and the trapezoidal rule is used to calculate

13   the area. So, that is AUC sub t.

14   Now, there is a way of taking the last

15   several blood concentrations when you are in what

16   is called the terminal elimination phase, and

17   estimate the elimination rate, and to use that

18   estimated elimination rate to extrapolate that

19   calculated area to theoretical infinite time. That

20   is the AUC infinity.

21   DR. SINGPURWALLA: I got the message that

22   AUC infinity is when t goes to infinity.

23   MR. SCHUIRMANN: Yes.

24   DR. SINGPURWALLA: I am not sure that this

25   question is germane, but is there a danger or a

 1   pleasure, depending on which side of the fence you

 2   are, that you may make a certain decision for a

 3   certain time t and your decision would be reversed

 4   about your hypothesis had t been something else?

 5   MR. SCHUIRMANN: That is really not a

 6   question that I am qualified to address. I am sure

 7   there could be aspects of the profile, the blood

 8   concentration over time profile where the action is

 9   in a certain time interval, and if that happened to

10   be the last time you sampled--

11   DR. SINGPURWALLA: In other words, how

12   sensitive is your hypothesis?

13   MR. SCHUIRMANN: I would yield to the

14   pharmacokineticists in the room for that question.

15   DR. KIBBE: Les?

16   DR BENET: There is definitely that

17   possibility. There was a famous brochure that the

18   Upjohn Company--so that is how long this is--put

19   out comparing two different drugs and they showed

20   equivalence making that error of picking an early

21   time point so that they actually had very

22   different--if they had gone to infinity they had

23   very different times. So, that is very critical

24   and usually what the agency will do or what anyone

25   will do, you want to know that the area under the

 1   curve up to t is a very high percentage of your

 2   total area under the curve infinity or you would

 3   not qualify this as a reasonable study to make a

 4   judgment on.

 5   DR. SINGPURWALLA: I have a follow-up, a

 6   word of caution, are you familiar with the filer

 7   problem?

 8   MR. SCHUIRMANN: Yes

 9   DR. SINGPURWALLA: Do you think you would

10   be a victim of that particular problem here?

11   MR. SCHUIRMANN: There are in

12   bioequivalence assessments but usually not with

13   pharmacokinetic bioequivalence assessments. We

14   sometimes are not doing the analysis on the log

15   transformed endpoints but, instead, there are other

16   types of bioequivalence studies where we are

17   analyzing the untransformed endpoints and we do,

18   indeed, do two one-sided tests based on linear

19   inequalities like mu-T minus 1.25 times mu-R and

20   you will reject those two one-sided hypotheses if,

21   and only if the 90 percent filer's confidence

22   interval falls within the interval. So, we use

23   that method. Which aspect of the problem are you

24   referring to?

25   DR. SINGPURWALLA: Well, the filer's

 1   problem is the following, that when you have two

 2   normal distributions with unknown means and when

 3   you take the ratio of their means, then it is

 4   possible to get confidence limits which are from

 5   minus infinity to plus infinity but with the

 6   coverage probability less than 1.

 7   MR. SCHUIRMANN: I am aware of that. If

 8   your data is such that that would happen, then you

 9   would not reject the two one-sided tests and you

10   would not reach a conclusion of equivalence.

11   DR. SINGPURWALLA: But then we would have

12   addressed the comment my colleague made that you

13   will have an inconclusive answer.

14   DR. SWADENER: My question really related

15   to rejecting the case that it is non-equivalent.

16   That doesn't mean that it is equivalent. Right?

17   Because there are some outliers; there are places

18   between the two.

19   MR. SCHUIRMANN: There are experimental

20   outcomes that are inconclusive. If you reject

21   equivalence, then you conclude inequivalence. If

22   you reject inequivalence, then you conclude

23   equivalence. But there are data sets for which you

24   would not reject either.

25   DR. SWADENER: But I thought you said the

1   rationale for trying to define inequivalence,

2   rejecting equivalence doesn't mean inequivalence.

3   MR. SCHUIRMANN: No, I said failing to

4   conclude equivalence doesn't necessarily mean

5   inequivalence. Perhaps that sounds like word games

6   to you but I assure you it isn't.

7   DR. SINGPURWALLA: I think you are facing

8   a statistician.

9   DR. SWADENER: No question about it,

10   right.

11   [Laughter]

12   DR. KIBBE: And a frequentist statistician

13   at that.

14   DR. SINGPURWALLA: It pains my heart!

15   MR. SCHUIRMANN: The take-home message of

16   my presentation was it is not reasonable to

17   conclude bioinequivalence if you do a

18   bioequivalence test and don't conclude

19   bioequivalence. You have to aim a test

20   specifically at seeing whether you can show

21   bioinequivalence.

22   DR. KIBBE: Thank you, Don. Ajaz wants to

23   say something and I guess, Lawrence, you want to

24   get back to the questions?

25   DR. YU: Yes.

 1   DR. KIBBE: Good.

 2   DR. HUSSAIN: Well, I think this

 3   discussion has been focused primarily on the bio

 4   topic but the principles, concepts and issues go

 5   beyond that and how does this relate to that? Does

 6   somebody have any thoughts on that?

 7   DR. SINGPURWALLA: Actually, I do.

 8   DR. KIBBE: I knew you would!

 9   DR. SINGPURWALLA: Again, a problem like

10   this is a problem which should be cast in the

11   framework of decision making or, in other words, it

12   should be cast in the framework of a Bayesian

13   setup, and that is the way you address this kind of

14   a problem where you may have three decisions, three

15   actions--equivalence, inequivalence or

16   inconclusive. That could be a decision and that

17   provision could be made. Of course, it could also

18   be made in the frequentist framework. But I think

19   this is another example of decision making and it

20   should be cast in the same framework.

21   DR. KIBBE: I think the problem we are

22   facing here is the difference that we have in a

23   court of law between preponderance of evidence and

24   beyond a reasonable doubt, and we accept drugs as

25   equivalent when we have the preponderance of

 1   evidence. Do we now ask for something beyond a

 2   reasonable doubt to reject what we have already

 3   accepted, and I think that is interesting. Paul?

 4   DR. FACKLER: I just wanted to ask a

 5   question, recognizing that there are thousands of

 6   generic products on the market and I understand

 7   that there have been challenges to those, do you

 8   have any idea how many of those have turned out

 9   post-approval to be inequivalent to the innovator?

10   DR. KIBBE: He wants a success rate for

11   challenges.

12   DR. BUEHLER: All right. Well, I have to

13   think. I know we have had at least one that I can

14   remember where we had a challenge and when we

15   threatened to downgrade they removed the product

16   from the market. I know that because that was when

17   I was in the Office of Generic Drugs. I am not

18   sure how many more there have been but I do know

19   that there was at least one.

20   DR. YU: I think we just had one right

21   now. In fact, the study is under-powered so it has

22   come back--

23   DR. BUEHLER: But that wasn't removed from

24   the market.

25   DR. YU: It was not removed.

 1   DR. FACKLER: Could I ask a question then,

 2   how important an issue is this?

 3   DR. BUEHLER: I think the importance of it

 4   depends on the amount of work it generates to the

 5   Office of Generic Drugs with each specific

 6   challenge that we get because I have the

 7   understanding that the challenge studies are sort

 8   of bioequivalence studies, sort of masquerading as

 9   bioequivalence studies but they are really

10   channeled to show bioinequivalence or showing

11   failed bioequivalence. Therefore, we look at them

12   really with a fine-tooth comb and, as Lawrence

13   said, we look at all aspects of the drug product

14   that was used in the challenge study. We go out

15   and actually make site visits to inspect the CRO

16   that conducted the challenge study to make sure

17   that the study was conducted properly. So, it

18   really involves a significant amount of resource

19   allocation when we get one of these challenge

20   studies because we take them very seriously. If

21   someone challenges the bioequivalence of a product

22   that is currently on the market we, in the Office

23   of Generic Drugs, take that challenge very

24   seriously and we do put a lot of resources into

25   making sure that it is either valid or invalid.

 1   Because of that, we would like to have a little bit

 2   better framework under which to sort of, like,

 3   unleash these dogs. You know, if we don't have to

 4   turn the dogs out we really want to but right now

 5   we are.

 6   DR. KIBBE: Do you have a comment?

 7   DR. DAVIT: Yes, I would like to add to

 8   what Gary was just saying. I was directly involved

 9   in a challenge several years ago and it was a

10   tremendous amount of work to sort out what was

11   going on. I was a team leader at the time. I

12   pretty much had my entire team working on it. We

13   had project managers working on it. We got the

14   clinical division involved; we had the

15   statisticians involved. We looked at the

16   dissolution. We looked at the RLD. We made many

17   visits to the clinical division to discuss what was

18   going on. We sent an inspection out to the site

19   where the challenge study was conducted. We had

20   meetings with the generic company. So, it was

21   very, very involved. And, the outcome of that

22   particular situation was positive but it took many,

23   many man hours of work from many different people

24   to sort things out.

25   DR. YU: In other words, the effort we put

 1   in to clarify some of the concept is well worth it.

 2   DR. KIBBE: Do you think we should

 3   approach it like they do with a challenge flag in a

 4   football game? That if they uphold the challenge

 5   they still keep their time outs? And, if the

 6   challenge hasn't been upheld they lose their time

 7   outs? So, if a company wants to challenge they

 8   have to put a bond up to pay for the expense of FDA

 9   adjudicating the challenge?

10   DR. BUEHLER: That would be okay!

11   DR. YU: Basically, in many cases if a

12   study comes back it fails to demonstrate

13   bioequivalence instead of bioinequivalence study.

14   As Don has very clearly pointed out, if you test

15   for bioequivalence you simply fail to show

16   bioinequivalence. So with a guidance, if you do

17   want to show that it is bioinequivalence, here you

18   are, this is how to conduct a study so there is no

19   confusion or ambiguity. It is a very clear

20   definition, clear evidence for agency to take

21   action so we can spend all the time to approve

22   generic applications. We received over 500 this

23   year.

24   DR. KIBBE: Marc?

25   DR. SWADENER: Have you thought about

 1   whether if, in fact, you clearly defined

 2   inequivalence it is going to increase your

 3   challenges? Will it, in fact, make your life

 4   easier?

 5   DR. YU: I think my life would be a lot

 6   easier. There is no doubt about it; I am very

 7   confident.

 8   DR. SWADENER: It may double the number of

 9   challenges, or triple.

10   DR. YU: That is certainly a hypothetical

11   question and I am very confident.

12   DR. KIBBE: Jurgen?

13   DR. VENITZ: I am trying to get back to

14   the questions that you want us to answer, Lawrence.

15   I would say you have demonstrated to me that it is

16   different whether you prove equivalence or you

17   prove inequivalence. In other words, they are two

18   different objectives, meaning they require two

19   different studies. So, failing to show

20   bioequivalence is not the same as demonstrating

21   bioinequivalence, which I think is what your first

22   question is all about.

23   DR. YU: Thank you very much--

24   DR. VENITZ: Well, that is my personal

25   answer; I can't speak for the committee. The

 1   second one, as far as the challenge study is

 2   concerned, in order to demonstrate bioinequivalence

 3   which, as I said, is not the same as failing to

 4   show bioequivalence, you have to have an adequate

 5   and well-controlled study to do that, which

 6   includes all the characteristics that you are

 7   familiar with. From my perspective, in addition to

 8   that you have to have preexisting information

 9   suggesting that the drug is bioequivalent because

10   that is what is being challenged in the first

11   place. So, in my mind, the burden of proof is upon

12   the challenger t have an adequate and

13   well-controlled study demonstrating beyond any

14   reasonable doubt, to use Dr. Kibbe's terminology,

15   that they are truly bioinequivalent. So, among the

16   strategies that you are proposing I would use the

17   most conservative one, which I think is number two,

18   meaning that all three endpoints have to

19   demonstrate bioinequivalence. Only underlying

20   those circumstances would you move to the next step

21   which would be removing, I guess, the generic from

22   the market.

23   DR. YU: And some others too.

24   DR. VENITZ: I am sorry?

25   DR. YU: Assuming the quality--

 1   DR. VENITZ: Right, just speaking about

 2 the testing procedures. I am sure there are other

 3 things that you look at.

 4   DR. YU: Yes.

 5   DR. VENITZ: So, I would say number one is

 6 the difference between showing bioequivalence and

 7 showing bioinequivalence. Number two, a study to

 8 demonstrate bioinequivalence has to be adequately

 9 well-controlled, or the equivalent thereof. Number

10 three, the burden of proof is on the challenge

11 sponsor to demonstrate that, and I would suggest

12 strategy two as the most conservative one.

13   DR. YU: Thank you.

14   DR. KIBBE: Anybody else? Marvin?

15   DR. MEYER: I agree with part one, that

16 this is needed. I think, just from a conceptual

17 point of view, if approval means everything has to

18 be between 80 and 125, then for inequivalence

19 everything needs to be less than 80 percent or

20 above, as you have drawn it on your little diagram.

21   I don't know that it is fair to require

22 all three to fail. I think any one should be

23 enough because, after all, it is not fair to expect

24 AUC to always fail along with Cmax. Sometimes AUC

25 is fairly stable and Cmax isn't. So, I would say

 1   number one rather than all three.

 2   DR. VENITZ: Can I just give you the

 3   reason why I disagree with you on that?

 4   DR. KIBBE: Please, go ahead.

 5   DR. VENITZ: Because you already have a

 6   study that demonstrated bioequivalence in the first

 7   place. Otherwise, I would be in agreement with

 8   you. But it is not like the study stands on its

 9   own. You are basically trying to meta-analyze two

10   studies.

11   DR. MEYER: But I would argue that you are

12   just setting it up for the inequivalence people to

13   fail by requiring all three.

14   DR. VENITZ: But I think there is another

15   study demonstrating that there is bioequivalence.

16   DR. KIBBE: And we are waiting for Les to

17   clarify everything for us--

18   [Laughter]

19   --but I think the first point is true,

20   that we need to have the study design to show

21   bioinequivalence, not just that you do a

22   bioequivalency study and if it fails that doesn't

23   work. That is clear. But the argument over

24   whether you want all three items or not, I think we

25   need to fall back on what is the clinical relevance

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 1   of the thing failing the Cmax component of the

 2   bioinequivalency study to a drug that has a large

 3   therapeutic index. I think you probably need to

 4   put more emphasis in terms of area under the curve

 5   if you are going to pick one instead of three. So,

 6   I would be inclined to go with my colleague Jurgen

 7   and say let me see all three out of whack and then

 8   I am ready to get the generic company to do

 9   additional studies to balance out what we are

10   doing. Les?

11   DR. BENET: I would like to make a

12   comment--

13   DR. KIBBE: Good.

14   DR. BENET: --and it is something I have

15   worried about for a long time, and that is the

16   stability of the innovator's product from study to

17   study. It sort of gets to Ajaz' question. I have

18   always been concerned about the innovator or

19   generic, at the end of the shelf life, is the

20   product equivalent to the product when it was first

21   approved? So, I think in this criteria there needs

22   to be something that is an evaluation of the data

23   of the innovator product, that it is, in fact,

24   representative of what the agency knows. Because I

25   know that there are situations where you could have

 1   end of the shelf life drugs that would fail versus

 2   when they are first manufactured. So, I could see

 3   how this could easily be manipulated, if I was a

 4   manipulative person which I am not, right--

 5   [Laughter]

 6   --to make a failed study. I don't think

 7   it would be that difficult with some drugs. So, I

 8   think there needs to be an additional criteria,

 9   again no matter which of these three you pick, that

10   the agency has confidence that the innovator data

11   is, in fact, representative in this study. Maybe

12   that is already true, Gary. I don't know.

13   DR. BUEHLER: As part of the review of the

14   study I believe we do look at that parameter.

15   DR. KIBBE: Anybody else?

16   DR. COONEY: Just one point to come back

17   to, in trying to resolve the distinction between

18   one, two or three PK parameters to make the

19   decision on, the issue of clinical relevance that

20   several of you have spoken to strikes me as the

21   most important part of that part of the question.

22   So, my question is it doesn't matter what decision

23   is made, whether it is one, two or three of these

24   parameters, how do you factor into the analysis

25   that you are doing that you have chosen the

 1   parameters that, in fact, are clinically relevant

 2   for each individual case?

 3   DR. KIBBE: Do you want to give an answer?

 4   DR. YU: Instead of giving an answer, I

 5   guess we have to make some kind of recommendation

 6   that, indeed, when we look at those challenge

 7   studies the clinical division is heavily involved.

 8   We are working as a team in resolving some of the

 9   challenge studies, instead of pharmacologists or

10   chemists acting alone.

11   DR. COONEY: Then the question becomes how

12   do you factor that working into the recommendation

13   that is being made so that it isn't just an

14   arbitrary one, two or three or the parameters but

15   that a judgment call is clearly defined in the

16   decision process?

17   DR. YU: That is, indeed, a challenge. We

18   will certainly look at case by case but we do want

19   some kind of clarification so that people know what

20   is going on and what to do.

21   DR. KIBBE: Marvin?

22   DR. MEYER: Two comments. One, I know a

23   body in the street is not a good measure but if the

24   generic product has been out there and has sold

25   five million units, it is probably not that bad if

 1   your adverse reaction reports aren't alarming.

 2   Secondly, I think the approach of having

 3   the inequivalence confidence limit be totally to

 4   the left of the right of 80 or 125 is a fairly

 5   rigorous kind of assessment because your point

 6   estimate then has to be well to the left or right

 7   of the upper limit, in other words, quite a ways

 8   away. So, I think one is probably all you need,

 9   Cmax or AUC.

10   DR. KIBBE: And, if you are going to go

11   with one I would go with AUC. Gordon?

12   DR. AMIDON: I can readily see how a

13   contention of bioinequivalence could generate an

14   awful lot of work for the agency, and it could be

15   done almost frivolously. Therefore, I would be in

16   favor of requiring that it be all three parameters

17   to be bioinequivalent, plus other supporting data

18   like dissolution data to support that there is

19   something really to go after here and that would

20   merit the action and activity, investigation by the

21   agency. Yes, I am all in favor of having a bond

22   posted. If you don't pass, then you lose your

23   money. It is not gambling, is it?

24   [Laughter]

25   DR. KIBBE: That is not legal. But this

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 1   is, so it couldn't be gambling.

 2   DR. BENET: I support that, Art.

 3   DR. KIBBE: Les is going to comment. Go

 4   ahead.

 5   DR. BENET: Thank you. I want to support

 6   Marvin's position because this is, as is the

 7   difficulty of the correction now--I mean we have

 8   very good criteria for approving bioequivalence.

 9   The way you have defined bioinequivalence is very

10   difficult criteria that has to be outside the

11   boundary and the confidence interval has to be

12   outside the boundary. For sure, that is going to

13   be so hard to do, and if there is one, then it is

14   real and I think that if one of those three

15   parameters is outside I would go for the one. I

16   think Marvin's argument is a very good argument.

17   DR. MEYER: You agreed with me before.

18   DR. KIBBE: I want somebody to make note

19   of the historical events that Marvin and Les have

20   been agreeing everywhere.

21   [Laughter]

22   If you and I are going to have to back

23   off, then I suggest you look seriously at the area

24   under the curve, more seriously than Cmax. I

25   think, if anything that might actually meet this

 1   criteria where the other two wouldn't, it would be

 2   the Cmax. It is the most open to pushing one way

 3   or the other.

 4   DR. AMIDON: I think I am still a little

 5   confused, Les and Marvin. You want to do one

 6   parameter. You want to do a test and if any one

 7   parameter falls--what is the correct statistical

 8   language?--doesn't show bioequivalence or shows

 9   bioinequivalence as opposed to all three must

10   showit--it depends on how you word it, all three

11   must show bioinequivalence, that would be tougher,

12   right? That is what I am saying and it is what you

13   are saying. You are saying, Les and Marvin, that

14   is too tough. I am not sure. It makes the agency

15   look like they are trying to sweep everything

16   possible under the rug by having such criteria that

17   it will almost never happen.

18   DR. KIBBE: But the bioequivalence

19   criteria is that way. It requires, you know, both

20   Cmax and AUC to be--

21   DR. MEYER: But if one fails, it fails;

22   not all three. I mean, if Cmax fails it doesn't

23   matter what the AUC was, you failed.

24   DR. KIBBE: We can go around and around on

25   this. One of the nice things about an advisory

 1   committee is that we give advice and the agency can

 2   just ignore us if they want, and they can look at

 3   everybody's advice and when the committee is split

 4   they can take the input of each member of the

 5   committee and weigh one against the other and do a

 6   Bayesian analysis of it and pick the right

 7   decision. All I am saying is that if you are going

 8   to accept that the study has shown inequivalence

 9   because it has shown inequivalence in one of the

10   three parameters, then I would be careful to make

11   sure it was the area under the curve parameter and

12   not a Cmax. I would have less confidence in that

13   personally and I am sure that is biased.

14   DR. SINGPURWALLA: Mr. Chairman, the point

15   you raise has to have one thing in mind. Are these

16   three criteria interdependent? If they are, it

17   makes a big difference. If they are not, it makes

18   another difference. I suspect they are

19   interdependent and that is what you should keep in

20   mind. So, rejecting one is as good as rejecting

21   all if they are interdependent. If they are not,

22   then the kind of things you mentioned do become

23   serious, or the kind of things that Marvin

24   mentioned do become serious. I am asking the

25   question are they interdependent in your judgment.

1   DR. VENITZ: I think they are

2   interdependent and I think the differences between

3   the two strategies are marginal. In other words,

4   if you reject AUC infinity you are likely to reject

5   AUC-t as well. There is a little less

6   interdependence between the Cmax and the area

7   estimates. So, you are really splitting the

8   difference that is very small.

9   DR. SINGPURWALLA: Did I agree with you?

10   DR. KIBBE: I don't know. I need a

11 decision tree to find out whether we agree or not.

12 Has anybody got anything else? Lawrence, do you

13 need anything else from us or have we given you

14 enough information to help you go forward?

15   DR. YU: I think so.

16   DR. KIBBE: Then I propose that we take

17 our break. We have two more topics to cover after

18 break. We are breaking right on schedule. We will

19 be back to do topical bioequivalence at a few

20 minutes before 3:00.

21   [Brier recess]

22   DR. KIBBE: We have a cadre of taxis

23 waiting at 4:30. We want to be finished. We want

24 to have time for topical bioequivalence, such a

25 wonderful topic and Lawrence again is going to

 1   start off, only he has no slides.

 2   Update--Topical Bioequivalence

 3   DR. YU: The October, 2003 advisory

 4   committee meetings report and, in fact, manuscript

 5   have reviews and systematic reviews of the

 6   challenges in developing pharmaceutical or

 7   bioequivalence criteria for topical products. I

 8   think we sent it to you one month ago and this is

 9   the work that was developed in collaboration with

10   Dr. Jonathan Wilkin. It also further developed the

11   Q3 concept.

12   So, today we want to share with you and

13   seek your feedback. For example, are we on the

14   right track? We will publish this manuscript very

15   soon to initiate a dialogue and then bring back to

16   you the formal proposal. We will have Dr.

17   Lionberger give you an overview of this paper.

18   Rob?

19   Establishing Bioequivalence of Topical

20   Dermatological Products

21   DR. LIONBERGER: Today I am going to give

22   you an update on our current efforts to develop

23   methods to demonstrate bioequivalence of topical

24   dermatological products.

25   [Slide]

 1   The current state of topical

 2 bioequivalence is that for almost all products, for

 3 almost all locally acting dermatological products

 4 clinical trials are necessary to demonstrate

 5 bioequivalence. So, I am just going to give you

 6 some quick examples of the kind of clinical trials

 7 that are actually needed for this demonstration.

 8 These are just recent submissions to the Office of

 9 Generic Drugs.

10   [Slide]

11   As you can see here, the number of

12 subjects used in these comparisons--these are all

13 for topical antifungals, there were three-arm test

14 references placebo studies in patients. They used

15 700, 400 and 400 subjects. Here is just the

16 percent cure rate for the test and the reference

17 product. The reference product is the RLD. Then,

18 the 90 percent confidence interval on the

19 difference between the test and reference cure

20 rate. The goal for this is to be within minus 20

21 to plus 20.

22   So, you can see that even with these large

23 numbers of subjects these studies still came close

24 to failure. So, if you retrospectively looked at

25 the power of these studies, you would find that

 1   these studies probably had at least a 50 percent

 2   chance to fail even with that large number of

 3   subjects.

 4   [Slide]

 5   So, there are consequences to having this

 6   cost to demonstrating bioequivalence. It is a

 7   barrier to product improvement and also the access

 8   of generic products to the market. Innovator

 9   products need to use bioequivalence studies after a

10   formulation change. These clinical endpoints have

11   high variability and so, if you think of what the

12   purpose of bioequivalence is, it is to demonstrate

13   formulation similarity and these are just clinical

14   endpoint and there are just not good methods to do

15   that. Also, these lead to possibly unnecessary

16   human testing in these studies that have hundreds

17   of patients to say unapproved products.

18   [Slide]

19   So, based on this, some of the goals that

20   we have are to identify when clinical studies are

21   not necessary to demonstrate bioequivalence of

22   topical products and to provide some alternative

23   methods that will still assure product quality.

24   [Slide]

25   In this talk I am going to outline and

1   give you an update on a strategy to reach these

2   goals. Our bioequivalence strategy starts with a

3   mechanistic understanding of the topical drug

4   absorption process. Then we will identify the key

5   parameters that affect bioavailability. You heard

6   a similar approach in Prof. Amidon's talk this

7   morning where he talked about the mechanistic basis

8   for oral absorption and how that led to a

9   biopharmaceutical classification system, and the

10 possibility for bio waivers based on an

11 understanding of the mechanistic processes

12 involved.

13   So, once these key parameters are

14 identified, then we can choose the in vitro and in

15 vivo tests that best measure and detect differences

16 in these key parameters. As part of the selection,

17 we are going to look at classification of

18 formulation similarity. If two formulations have

19 exactly the same components, exactly the same

20 compositions we might focus a different set of

21 tests than if they had different excipients and

22 vastly different formulations.

23   This talk is just giving you the first

24 step to presenting a decision tree that will allow

25 us to decide when we might not need clinical

 1   studies to demonstrate bioequivalence. This

 2   decision tree will be specific for different sites

 3   of action. So first we will look today primarily

 4   at products that are targeting the very top layer

 5   of the skin, the stratum corneum. Finally, I will

 6   talk about some of the external research projects

 7   that we have under way to support development of

 8   this decision tree.

 9   [Slide]

10   So, the first thing I am going to talk

11   about is just an overview of the topical drug

12   absorption process. Here I have a schematic of the

13   skin showing different layers. If you think about

14   what happens when you apply a topical product,

15   first the vehicle is applied to the skin and then

16   the drug must dissolve in the vehicle, if it is not

17   already dissolved, and fused to the surface of the

18   skin.

19   So, the top layer of the skin is the

20   stratum corneum and this is a very dense layer,

21   about ten microns thick, and it is the primary

22   barrier to keep things outside of the body. There

23   are two paths across the stratum corneum, either

24   the drug can partition from the vehicle which is

25   placed on the surface of the skin into the stratum

 1   corneum and diffused through the stratum corneum,

 2   or there is the possibility that drugs applied to

 3   the surface of the skin can travel through the hair

 4   follicles and bypass the stratum corneum.

 5   If we look at sort of the various areas

 6   available for transport by these two mechanisms and

 7   we assume that there is no bias in the drug

 8   choosing one path over the other, the flux through

 9   the stratum corneum will be about 30 times more

10   than the transport through the hair follicles if

11   there is no bias between the two pathways, if the

12   drug is equally likely to go into one path or the

13   other.

14   Once the drug gets across the stratum

15   corneum, then the tissue behind that is much less

16   dense. The drugs can fuse much faster; this is

17   much less of a barrier to the drug finally reaching

18   the systemic circulation.

19   [Slide]

20   So, as we think about this process we have

21   to remember that we are looking at bioequivalence

22   and the goal of bioequivalence is to detect

23   differences in the formulations. It is not really

24   about how complicated this absorption process is

25   and how well we can understand that. It is really

 1   how well we can detect differences in the

 2   formulations that have already been demonstrated to

 3   contain drugs that work in clinical trials.

 4   [Slide]

 5   Again, as Lawrence has said and we have

 6   heard many times today, bioequivalence is defined

 7   as no significant difference in the rate and extent

 8   of absorption at the site of action. So, if we are

 9   looking at products where the site of action is

10   this top layer of the skin, the two sort of rates

11   that can possibly important for determining this

12   are, first the rate at which the drug might leave

13   the formulation and, second, the rate at which the

14   drug might cross this barrier of the stratum

15   corneum. So, if we understand those two rates,

16   then we can understand what rate is actually

17   controlling the rate at which the drug actually

18   reaches the site of action. That is the thing that

19   we are after in bioequivalence, to demonstrate that

20   the two formulations will perform the same.

21   [Slide]

22   Usually, in almost all cases, the stratum

23   corneum is the limiting resistance and we

24   characterize this limiting resistance by

25   permeability. The permeability just includes

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 1   contributes from the diffusion of the drug through

 2   the stratum corneum, the thickness of this layer

 3   and the partition between the vehicle and the

 4   stratum corneum. So, we can write an expression.

 5   The J is the total flux. That is the sort of rate

 6   at which drug is reaching the body and that is what

 7   we are interested in when we are making our

 8   comparison of bioequivalence. This is related to

 9   the permeability times the area that is available

10   times the concentration of the drug that is present

11   in the vehicle. We can sort of do a little bit of

12   manipulation with this partition coefficient here,

13   where S is just the solubility of the drug either

14   in the membrane stratum corneum or the vehicle.

15   So, this is sort of split up into

16   contributions that are just properties of the skin

17   and just properties of the formulation. From this,

18   you can see it is the thermodynamic activity, the

19   ratio of the concentration to the solubility in the

20   vehicle that is the driving force for what the flux

21   is. So, if the membranes were the same between two

22   products and presumably if they were applied to the

23   same person it is the same skin and you would think

24   that these two products would be the same, and it

25   is just essentially this activity in the

 1   formulation that would determine how fast the drug

 2   arrives at the site of action.

 3   But the most sort of important

 4   complication here and the thing that we are sort of

 5   worried about when we are looking at what methods

 6   are best to develop, bioequivalence methods, is

 7   that properties of the formulation can alter the

 8   barrier properties of the skin. So, if by applying

 9   the formulation, either the formulation itself or

10   the excipients in it, if they can alter the

11   properties of the skin they will change this flux

12   independent of what is happening in the

13   formulation. There is a whole technology and

14   design in topical formulations to, say, improve

15   bioavailability where there are lots of adjuvants

16   that are known to reduce the barrier and increase

17   the flux. This is not just hypothetical

18   possibility but a known situation that can happen.

19   [Slide]

20   Once we recognize tat this is sort of the

21   key mechanism. Then we can sort of identify what

22   are possible causes of bioequivalence for products

23   that have the same drug content. So at different

24   stages in the absorption process we can identify

25   things that possibly can go on.

1   First of all, at the application stage if

2   the two products spread differently on the

3   skin--say, the viscosity or the rheology is

4   different, you could have different outcomes in

5   terms of how they contact the skin, the amount of

6   area each product has if they are applied

7   similarly. If we look into the formulation we can

8   imagine a case where, well, what if a drug doesn't

9   leave the formulation at all? Say, the drug is

10   present in the formulation as suspended particles

11   and these particles just don't dissolve, the drug

12   never leaves the formulation so, even though you

13   have the same amount of drug in the formulation but

14   it doesn't get out of the formulation, the two

15   products might not be equivalent.

16   Again, the thermodynamic activity in the

17   vehicle might be different. In one case the drug

18   might be dissolved into a cream and partitioned

19   between the oil and water phases and you have one

20   concentration of drug, one free concentration of

21   drug in the vehicle. If you had a suspension where

22   the particles were dissolving the dissolution rate

23   might control what the free drug concentration is.

24   And, this could happen if you had the same overall

25   drug content.

1   Finally, when you reach stratum corneum,

2   again as I said, formulations might have different

3   effects on the stratum corneum or you might have

4   one formulation preferring the follicular pathway.

5   This is particularly known to happen when you have

6   particles of certain sizes that might bias toward

7   this particular transport pathway. So, that is

8   primarily a concern when you have the drug present

9   in the formulation as a suspension.

10   So, if you we think about the mechanism

11   and possible reasons why products might not be

12   equivalent, that leads us to think about how can,

13   or is it possible that in vivo or in vitro tests of

14   the formulation can measure these differences

15   adequately enough to replace clinical trials.

16   [Slide]

17   So, I just quickly want to point out two

18   sort of most important in vitro tests that are

19   relevant to these types of products. The first is

20   diffusion cell. Just a quick description of what

21   that it is, in a diffusion cell it measures the

22   rate at which the drug leaves the formulation and

23   crosses an artificial in vitro membrane into

24   receptor fluids. So, in most implementations of

25   diffusion cells the membrane in the diffusion cell

 1   is very permeable to the drug so the membrane is

 2   not the limiting resistance. In this case, this

 3   really measures how fast the drug is actually

 4   released from the formulation or diffused from the

 5   formulation, and also the rate of release and

 6   diffusion is also proportional to the fraction of

 7   the free drug. So, it gives you a sense of whether

 8   or not the drug is actually bound to the

 9   formulation or is free to transport into the skin.

10   Because of this fact that these devices

11   are usually used with highly permeable membranes

12   they are not very predictive of bioavailability in

13   vivo because in vivo bioavailability is usually

14   controlled by the resistance due to the stratum

15   corneum itself. But these tests have been shown to

16   be very sensitive to formulation differences.

17   There is also an important safety role for

18   this test. If you imagine applying a topical

19   product to damaged skin where the barrier function

20   of the stratum corneum has been breached for some

21   reason, perhaps by disease, then the drug release

22   to the patient is going to be determined by how

23   fast it is released in the formulation, which is

24   exactly what is measured in this type of test.

25   The other key in vitro test is a measure

 1   of the rheology or how the formulation flows. This

 2   would determine how vehicle spreads on the skin.

 3   This type of characterization is also important to

 4   classifying the proper dosage form for the

 5   formulation. At the last advisory committee

 6   meeting you heard about a decision tree to classify

 7   different topical semi-solid dosage forms, and part

 8   of that decision tree involved evaluating rheology

 9   or how easy it was to make a formulation flow. So,

10   that is part of the testing that is already

11   involved in these products.

12   [Slide]

13   If you have a drug present in a suspension

14   form you have additional tests that might be very

15   relevant to apply. It might be direct measurements

16   of particle size in the formulation or measurements

17   of the dissolution rate in the vehicle as well.

18   [Slide]

19   There are also in vivo tests that can be

20   used to characterize topical formulations. The two

21   most important ones in this case are a skin

22   stripping method where you apply the formulation to

23   the skin, after a certain amount of time remove it,

24   then remove the layers of skin and assay them for

25   the actual drug content in the skin layers, or

 1 microdialysis techniques where you insert a

 2 capillary under the skin and you measure the

 3 concentration that passes through the skin into the

 4 lower layers of the dermis.

 5   There have been experimental reports in

 6 the literature on how they are used. But in this

 7 context, please remember that the important role of

 8 in vivo tests is to quantify the effect of the

 9 formulation on the skin itself. If we didn't

10 believe that there is any possibility that the

11 formulation would change the barrier properties of

12 the skin we would be much more confident that just

13 assays of the in vitro performance would be

14 sufficient to determine whether or not two products

15 were bioequivalent. But since we have reason to

16 believe that formulations can affect the skin

17 properties, then we would like to at least have our

18 battery of tests in some way to measure this

19 effect. So, the role of these in vivo tests is

20 sort of very specific.

21   They tell you a lot more information than

22 this. They tell you about the amount of

23 experience, concentration, presence of different

24 aspects of the skin as well. We are specifically

25 here looking formulation effects since we are

 1   looking to determine bioequivalence.

 2   [Slide]

 3   Now that we have sort of identified the

 4   whole list of tests, the question is how do you

 5   decide which tests should be relevant to which

 6   types of products. So, again, here we are going to

 7   be talking specifically about using formulation

 8   similarity as part of that classification. So,

 9   here we define Q1 similarity as products that have

10   the same components. Q2 similar products have the

11   same components but also present at exactly the

12   same amounts. So, Q3 means we have the same

13   component and the same amount, but they also have

14   the same arrangement of matter or microstructure of

15   the material so that they are sort of identical not

16   just in composition but also in the arrangement of

17   the material. So, based on classification of the

18   formulation difference between test and reference,

19   we want to choose the appropriate in vivo or in

20   vitro test.

21   So, in all the following discussions,

22   since we are talking about bioequivalence we are

23   really talking in the beginning, before we even

24   talk about bioequivalence, about products that are

25   pharmaceutically equivalent and that means they

 1   have the same active ingredient in the same dosage

 2   form so we are comparing a cream versus a cream,

 3   not a cream versus an ointment or versus a

 4   solution, at the same strength, the same dosage

 5   form of the active ingredient and also targeting

 6   the stratum corneum. So, again, all those things

 7   are sort of prerequisites to determining if the

 8   products are bioequivalent.

 9   [Slide]

10   So, if we start at the sort of highest

11   degree of similarity, if we know the products are

12   Q3 similar and have the same composition, the same

13   structure, you might regard them as identical and,

14   by definition, bioequivalent.

15   One example in sort of a regulatory scheme

16   where this comes up is for topical solutions. If

17   it is a solution it is in thermodynamic

18   equilibrium. If you know that it is Q1 and Q2, has

19   the same composition, then because it is in

20   thermodynamic equilibrium you know it has the same

21   arrangement of matter as well. So, we often give

22   bio waivers for products that are true solutions.

23   Unfortunately, for formulations that are

24   more complex than simple solutions it is harder to

25   directly tell that they are exactly identical in

 1   their formulation, and possibly manufacturing

 2   differences might result in products that have the

 3   same composition having different arrangements of

 4   matter. A simple example of that might be a case

 5   where you have the same composition but in one

 6   formulation your particle size is different from

 7   the other one. So, that is something that is a

 8   non-equilibrium state and usually comes from

 9   differences in the manufacturing process of the raw

10   materials. So, those are sort of the origins of

11   cases where products might have the same

12   composition but have differences in their Q3

13   identity.

14   [Slide]

15   Now if we step down a little bit and look

16   at products where we just know that they are Q1 and

17   Q2 identical, we want to sort of identify what kind

18   of differences they could possibly have. So, here

19   it is sort of thinking if you deliberately took

20   products with the same composition and you tried to

21   manufacture them in a way where you actually get

22   differences in product formulation, what kind of

23   things would you have to do?

24   So, one of those is that rheology might be

25   different. The flow maybe might be different. If

 1   you take a cream or some sort of emulsion and you

 2   changed the particle size of the droplets you might

 3   actually change dramatically how the material

 4   flows. It might adhere to the skin differently and

 5   you would end up with different performance even

 6   though the products have exactly the same

 7   composition. By having some non-equilibrium

 8   formulation in manufacturing, you might be able to

 9   change the solubility of the free drug by

10   increasing the sort of surface area of, say, an oil

11   phase. You know that in these products you have

12   the same excipients. Presumably they should have

13   mostly the same effect on changing the barrier

14   products of the skin. But you might have a case

15   where in one formulation the excipients might be

16   released at a different rate and if you have

17   suspensions, as mentioned before in the particle

18   size example.

19   If we think about these things, these are

20   all sort of manufacturing differences and the

21   question we want to ask is are the in vitro tests

22   that we have able to detect these types of

23   manufacturing differences? So, again, the rheology

24   we can measure directly. In vitro release is a

25   very sensitive measure of are things diffusing

 1   through the formulation at the same rate; will

 2   there be any differences in how sort of excipients

 3   or drug reach the skin itself from the formulation.

 4   Those two can be directly measured.

 5   So, the question that sort of hinges on

 6   this is for products where you know that they are

 7   pharmaceutically equivalent, you know they have

 8   exactly the same composition, in this case are in

 9   vitro tests sufficient to ensure bioequivalence?

10   Again, all of these differences, all these possible

11   differences are really due to manufacturing

12   processes. As I said before, in vitro tests are

13   probably the most sensitive and best evaluation

14   methods for detecting manufacturing differences

15   rather than relying on clinical trials, which are

16   very insensitive to those types of differences.

17   [Slide]

18   If we sort of step down the level one more

19   time and we look at products that are just Q1

20   identical, they just have the same components but

21   maybe in different amounts, in this case we might

22   be more concerned that the different amounts of,

23   say, excipients in the formulation might have

24   different effects on the skin barrier. They might

25   change the solubility of the drug in the

 1   formulation. So, in these cases we might be more

 2   likely to say that in this category you might want

 3   to do some sort of in vitro test to ensure that the

 4   change in the formulation does not have a

 5   significant effect on the barrier properties.

 6   [Slide]

 7   Finally, if you go down to products that

 8   are Q1 different, which means they might have a

 9   different excipient between test and reference

10   products, again similar discussion to the previous

11   tests for the in vitro tests, but here it seems

12   that you would always want to do some sort of in

13   vitro test to make sure that the new excipients are

14   not having a different effect on the skin barrier

15   process.

16   [Slide]

17   Just summarizing sort of a little bit of

18   our current thinking, we go to the beginning of the

19   process of developing this type of decision tree

20   and looking at classifications based on formulation

21   similarity and the level of in vitro and in vivo

22   testing that you might want to do in those

23   different categories.

24   [Slide]

25   So, as we were sort of developing this, we

1   sort of identified key problems that we wanted to

2   look at. So, we have sort of two ongoing external

3   research projects, one which with Colorado School

4   of Mines where we are looking at the in vivo skin

5   stripping method, specifically looking to reduce

6   variability and also accuracy of the method to

7   measure both the diffusion coefficient and the

8   partition into the formulation, so measuring

9   effects of the formulation on the stratum corneum

10   and its partition in it. The key aspect there is

11   as you are doing the skin stripping, measuring the

12   thickness of skin removed via transepidermal water

13   loss.

14   We also have another project going on.

15   So, we have emphasized sort of in vitro

16   characterization and its ability to detect

17   manufacturing differences. We have a project with

18   the University of Kentucky where they are

19   manufacturing different formulations that are Q1

20   and Q2 identical, so exactly the same composition

21   but using different manufacturing processes,

22   primarily for cream formulations so oil and water

23   emulsions, and then looking at these known

24   differences and seeing how much difference can we

25   manufacture looking at the ability of the

1   rheological and in vitro release tests to detect

2   these manufacturing differences.

3   With that, I would like to thank you for

4   your attention and answer any questions that you

5   might have.

6   DR. KIBBE: Anybody have any questions?

7   DR. FACKLER: I have one.

8   DR. KIBBE: Good.

9   DR. FACKLER: Looking at the decision tree

10   and then at the examples that you gave at the very

11   beginning, the three examples, to me, showed

12   products that were similarly efficacious and I am

13   wondering if in your decision tree you are

14   suggesting that--I don't know if those products are

15   Q1 and Q2 or Q3--but being that they are similarly

16   efficacious, is it important whether or not the in

17   vitro tests for those products pass?

18   DR. LIONBERGER: Well, I think we are

19   trying to provide an alternative framework so the

20   idea is that, certainly, you can have products that

21   will give similar efficacy and they won't match at

22   all the in vitro tests. It is certainly possible

23   to come up with products that have different

24   viscosities, different in vitro release rates,

25   especially since that is not a limiting step, and

 1   still be bioequivalent in a clinical study. So, we

 2   are trying to provide sort of an alternative

 3   pathway. It is not that sort of this decision tree

 4   will determine bioequivalence; it is sort of an

 5   alternative pathway to doing a clinical study. So,

 6   it is basically up to the sponsor to decide do we

 7   want to try to characterize our product very well

 8   in vitro or just do some sort of clinical study,

 9   and they have to balance the costs to those two

10   different pathways.

11   DR. FACKLER: The only reason I ask is

12   thinking back on the nasal products, there is a

13   requirement for bioequivalence that they pass both

14   the in vitro studies and the clinical study. So, I

15   am wondering if that is the same direction FDA is

16   going in for the topical products.

17   DR. HUSSAIN: I think right now this is

18   simply our current thinking of moving away from ten

19   years on DPT and so forth, and starting fresh.

20   Again, going to a mechanistic basis, here is

21   another highly variable situation and I think the

22   mechanistic basis decision tree up front as an

23   approach to providing all possible alternatives is

24   the direction. But at the same time, I think we

25   need to keep in mind that in many of these cases

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1   some of these attributes are critical variables and

2   they will need to be controlled during

3   manufacturing lot-to-lot anyway.

4   DR. KIBBE: Judy?

5   DR. BOEHLERT: Have you also considered in

6   these studies looking at how creams or ointments,

7   or whatever, age? Because there can be differences

8   that develop that are formulation dependent or not.

9   For example, it comes out a solution; you could get

10   crystal growth if it is not in solution to begin

11   with. So, what seems to be equivalent to start off

12   with may not be as the product ages.

13   DR. LIONBERGER: That would be part of

14   sort of the chemistry manufacturing controls to

15   ensure the stability of the product over its shelf

16   life. Is that what you are talking about?

17   DR. BOEHLERT: Exactly, that is what I am

18   talking about. Over the shelf life of a lot of

19   creams you will get crystal growth and the efficacy

20   of that cream will change because the crystals

21   start to grow and they don't have the same

22   transport property that they did.

23   DR. LIONBERGER: You would want to have in

24   vitro tests for stability to evaluate those

25   differences, if they occurred.

1   DR. KIBBE: Gordon?

2   DR. AMIDON: Yes, Bob, I would like to

3   commend you. I think you have really brought a

4   good focus to how to apply and rationally go about

5   in vitro testing for topicals, which are more

6   complicated than oral, as you have described. That

7   is why I have stayed away from it. The dilution

8   that you get in the stomach is an enormous

9   advantage to regulating oral products, but I think

10 the enumeration of the factors you are really very

11 much on track with, simplifying or quantitating the

12 differences.

13   I like the idea of starting out by looking

14 at formulations that have qualitative similar

15 components because they are maybe going to have

16 similar effects on the permeability; similar

17 effects on the thermodynamic activity; similar

18 evaporation rates of spreading rates--start with

19 something that is manageable and then go off into

20 different excipients where it is more complicated

21 and determine how you might characterize that. I

22 think it is a very difficult process and you are

23 not going to be able to simplify everything but you

24 can simplify some things and at least characterize

25 where we feel confident about the in vitro test and

 1   where in vivo testing is needed. So, I think it is

 2   really an excellent start.

 3   DR. KIBBE: Ajaz?

 4   DR. HUSSAIN: I think this is more focused

 5   on understanding the mechanisms first and then

 6   deciding what is critical and what is not critical,

 7   and how it relates to performance. I totally agree

 8   with you, here is a much more complex system from a

 9   physical-chemical perspective compared to the

10   tablets and how that happens, and here is a highly

11   variable drug situation also. So, this example

12   relates totally to the previous disease that we had

13   on highly variable drug products.

14   DR. KIBBE: Anybody? No? Good.

15   DR. SELASSIE: In terms of your Q1

16   differences, have you looked at the role of

17   hydrophilicity, especially in terms of the

18   different excipients and what effect they have on

19   follicular transport versus stratum corneum?

20   DR. LIONBERGER: Yes. Certainly the

21   partition between sort of the effect of the

22   formulation on different transport paths would be

23   determined by the partition between the two phases.

24   So, I don't think that just sort of changing the

25   excipients will have a big effect on partition

 1 between the two things since they are both

 2 partitioning from the same vehicle phase into

 3 either the stratum corneum of the sebaceous fluid.

 4 So, it is not going to be sort of different unless

 5 you have some sort of mechanism by which it can be

 6 biased toward the follicle, things like

 7 micro-motions or things like that.

 8   DR. KOCH: I just had a question and it is

 9 related but not necessarily. We heard that using

10 this topical evaluation is perhaps more complicated

11 than the dissolution one would have in the stomach.

12 But what about another form, a suppository? Are

13 there methods in place--and obviously it is not

14 exactly what you would call a topical, but are

15 there similar equivalence studies in place that

16 either can be drawn from, particularly as you go

17 into some of the European dosage forms, to validate

18 or add to this particular study?

19   DR. HUSSAIN: I think the key is that we

20 often struggle when the site of action is local.

21 Now, rectal suppositories often are for systemic

22 absorption. If they are for systemic absorption,

23 then our current system handles it fairly nicely.

24 But if they are for local effects, and anything

25 that we have to deal with for localized effects, we

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 1   have challenges, inhalation, topical and so forth,

 2   where the site of action is the tissue adjacent to

 3   where the delivery is.  So, those are sort of the

 4   common challenges we face.

 5            DR. KIBBE:  Pat, do you have something?

 6            DR. DELUCA:  I just wonder if this is

 7   going to extend to the transdermal delivery

 8   devices, the patches, and all?

 9            DR. LIONBERGER:  This is mainly for

10   products that are locally acting so if you can

11   measure concentration in the blood and sort of

12   reduce the standard pharmacokinetic measurements to

13   do bioequivalence.

14            DR. KIBBE:  We are clearly talking about

15   drugs that act in the stratum corneum.  But the

16   direction that drugs move from the applied product

17   is into the stratum corneum and then out.  So, now

18   that begs the question where they go after that,

19   and can we measure it there as a surrogate for it

20   being in the stratum corneum.  I will argue that

21   our ability to measure trace amount of things has

22   gotten better.  I remember the reason we actually

23   even started doing pharmacokinetics is because the

24   Bratton Marshall was invented and we actually could

25   measure sulfa drugs and therapeutic concentrations
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 1   for the first time. So, has anyone thought about

 2   the possibility of looking for trace amounts just

 3   to show that it has crossed and penetrated into the

 4   capillaries?

 5   DR. LIONBERGER: Sometimes there is

 6   concern that the site of action really is the

 7   stratum corneum. You don't know how much is

 8   accumulating there versus other parts of the skin.

 9   DR. HUSSAIN: I think the discussions have

10   always been in terms of two aspects, safety and

11   efficacy aspects. Now, if the site of action is

12   the stratum corneum or the dermis or the follicles,

13   and so forth, clearly that is important from an

14   efficacy perspective. But where it goes next also

15   is important from a safety perspective and often we

16   will have some coverage of that, and so forth.

17   But I think the challenge we have had for

18   the last ten years is that the localized delivery

19   to site of action is the focal point for discussion

20   and looking at systemic circulation because, after

21   topical application, you could look at urinary

22   excretion or even blood levels but that is

23   generally considered from a safety perspective, not

24   to demonstrate bioequivalence because it has

25   crossed over and it is not the site of action.

1   DR. KIBBE: But you recognize that

2   bioequivalence has always been aimed at evaluating

3   the dosage form.

4   DR. HUSSAIN: Yes.

5   DR. KIBBE: So, once it gets into an

6   individual stratum corneum, no matter how long it

7   takes to get out, that is a direct measure of how

8   well it got out of the dosage form, and if you can

9   find it and quantitate it, it is a measure of what

10   happened before. So, I think as we get better with

11   LC, MSMS and we can find them it might even be

12   better for some of these companies rather than

13   doing 728 patients to look at percent cure rate.

14   If you can find it with trace amounts with a lag

15   time of an hour and a half, and look at it for

16   three or four hours, wouldn't that be acceptable?

17   DR. HUSSAIN: It has not been acceptable

18   for the last ten years. That has been the debate

19   because, if you recall the debates that we have had

20   it was the localized concentration that the

21   clinicians wanted. I could actually argue that

22   measuring systemic circulation can actually

23   indirectly give you that assessment, but we haven't

24   been able to convince the rest of the world on that

25   yet, especially the dermatology community. So, I

 1   think that is a challenge. But also I was hoping

 2   that we can also bring a lot of imaging

 3   technologies to bear on this.

 4   DR. KOCH: That is exactly the next point

 5   I was going to make because a lot of the imaging

 6   technologies, as they are now being applied for

 7   physical measurements--I have seen different things

 8   showing up that have to do with--well, just the

 9   thing I mentioned yesterday about studying

10   coatings. Using the same technology we are now

11   able to get below some of those levels down to 100

12   microns or increasing all the time, and the

13   sensitivity is improving. So, at least from an in

14   vitro method, I think a series of imaging

15   technologies should be able to begin showing some

16   value there.

17   DR. HUSSAIN: We just started a process to

18   look at terahertz microscopy, a spatial aspect of

19   looking at chemical distribution within membranes,

20   and so forth. The technology is evolving rather

21   quickly so we may see some solutions out there.

22   DR. KIBBE: Anybody else?

23   DR MEYER: Silence is interpreted as

24   negative. I think you have incorporated almost

25   everything we talked about here that we would like

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1   to do for many things. We would like to know more

2   about the mechanism. We would like simpler, or

3   dissolution tests that meant something, or in vitro

4   tests that mean something. We would like a

5   decision tree. It seems like everything everybody

6   mentioned about some of the other problems you are

7   incorporating. You are testing in vitro, trying to

8   look at manufacturing and effects on topical

9   variability. So, I think you are covering a lot of

10   basis and doing a good job.

11   DR. KIBBE: Yes, I think you are right.

12   The one thing that you need to keep in the back of

13   your mind is that the source of the excipient is

14   going to have a dramatic effect sometimes on their

15   viability and their physical and chemical nature.

16   So, the company ought to have good characterization

17   for all their excipients coming in when you get the

18   chemistry data for the Q1 and Q2 evaluations

19   because they don't really characterize the

20   excipients coming in. It is hard for them to be

21   assured that they have gotten a good, consistent

22   product.

23   DR. COONEY: If I can just add one more

24   point, when I think back on studies that I have

25   done where I have made mistakes, the most common

 1 mistake is not to have looked, really looked at

 2 what I am doing. So, using imaging and microscopy

 3 to visualize what is there should not be

 4 overlooked.

 5   DR. YU: Since the imaging technique has

 6 been mentioned a couple of times, I just want to

 7 update you. In fact, as we are speaking right now

 8 the studies being conducted, hopefully, will have

 9 some results very soon on topical imaging at the

10 University of Kentucky. Thank you.

11   DR. KIBBE: Is the agency happy with the

12 discussion? Okay? Well, we have our last

13 presentation and then Dr. Hussain will summarize.

14   DR. HUSSAIN: As Nakissa is coming over to

15 talk, all the topics that we have discussed are

16 interconnected, and one of the issues that Nakissa

17 wants to bring to your attention is the issue of

18 nanotechnology-based drug delivery systems.

19 Currently, there are a number of issues--confusion

20 to a large degree with respect to nomenclature,

21 definition and so forth. So, as she talks about

22 that, I think you will see what we are trying to do

23 to address some of these.

24   Future Topics--Nanotechnology

25   DR. SADRIEH: Good afternoon.

1   [Slide]

2   The last presentation at this advisory

3   committee meeting will be on nanotechnology. This

4   is an awareness topic so this is going to be a very

5   short presentation.

6   [Slide]

7   Why the interest? Nanotechnology is a

8   rapidly growing area of science. You just have to

9   look at the number of publications with the word

10 nanotechnology in the title. With regards to CDER

11 interests, it is anticipated to lead to the

12 development of novel and sophisticated applications

13 in drug delivery systems. The private sector,

14 academic centers and federal agencies are all

15 developing substantial programs in nanotechnology,

16 and there are significant research dollars being

17 invested in this area. Approximately 3.7 billion

18 dollars have been invested by the U.S. government

19 projected for the next four years. So, this is a

20 major area of research.

21   [Slide]

22   This talk will focus on the regulatory

23 considerations of nanotechnology, and specifically

24 as they apply to CDER products. We have identified

25 four areas that we would like to talk about. The

 1   first one is nomenclature, and quality, safety,

 2   facility/environmental issues. I will just go over

 3   each one of these things right now briefly.

 4   [Slide]

 5   For nomenclature the National Science

 6   Foundation has a definition for nanotechnology

 7   presently, which is anything with a dimension less

 8   than 100 nanometers is considered nanotechnology.

 9   However, for CDER purposes we need to first define

10   what are some of the nomenclature criteria, and

11   then having defined these criteria we will need to

12   develop a definition that will be appropriate for

13   CDER, and then identify the potential

14   nanotechnology applications to CDER.

15   [Slide]

16   Regarding quality, for products that are

17   going to be called nanotechnology we need to

18   consider these five elements here. The first one

19   is characterization of the nanomaterials;

20   description of the critical attributes; assurance

21   of stability; manufacturing and controls; and then

22   drug release and bioequivalence testing issues.

23   These all have to be identified and described.

24   [Slide]

25   For safety, pharmacology and toxicology

1   studies have normally addressed the safety issues.

2   Currently, we believe that the studies that we

3   require for any drug the pharmacology and

4   toxicology are adequate for nanotechnology products

5   also. However, since this is a new area and there

6   might be some unique areas of concern, we might

7   need to think about possibly new testing models and

8   whether they be in vitro or in vivo. So, these

9   issues will have to be discussed and this is purely

10   going to be based on scientific issues.

11   For the environmental aspect the things

12   that we have to consider are facility design and

13   the potential impact of nanotechnology products in

14   the environment, whether they be from an industrial

15   setting or other.

16   [Slide]

17   The last few slides just identify some of

18   the challenges that we anticipate having to address

19   regarding nanotechnology. At CDER we have decided

20   to meet this challenge by crating a

21   multidisciplinary working group. This working

22   group will identify the regulatory challenges

23   related to the timely scientific assessment of drug

24   and drug-device combination products. We have to

25   consider the drug-device combination products in

1   this area because in nanotechnology this might be a

2   very important consideration. Also, this working

3   group will propose solutions to overcome these

4   challenges.

5   Presently, the members for this group are

6   from the Office of Pharmaceutical Science, Office

7   of New Drugs, Office of New Drug Chemistry, Office

8   of Generic Drugs, Over-the-Counter Drugs and Office

9   of Clinical Pharmacology and Biopharmaceutics. The

10   co-chairs of this group are in the Office of

11   Pharmaceutical Science. There is also one member

12   from the Office of the Commissioner because in the

13   Office of the Commissioner there is an interest

14   group for nanotechnology and we would like to

15   maintain a connection between the CDER working

16   group and that Office of the Commissioner interest

17   group so we have that member there to maintain

18   that.

19   [Slide]

20   The goals and objectives basically of this

21   working group are to provide a definition and to

22   craft the terminology; to develop a position paper,

23   a White Paper, possibly in the future; to identify

24   areas of concern and propose suggestions towards

25   the development of regulatory guidance documents;

 1   to identify training and research needs; and to be

 2   involved in the coordination of the above-stated

 3   activities and also collaboration for potential

 4   research activities in the future.

 5   So, having said that, that is the end of

 6   the presentation. I said it was a "nanotalk."

 7   Thank you.

 8   DR. KIBBE: It was a "nanotalk." I like

 9   that. Are there any questions or comments? Go

10   ahead.

11   DR. SINGPURWALLA: I am very curious. I

12   have seen nanotechnology operate at Sandia Labs.

13   What I saw was miniature gears and miniature

14   machines that they were making. So, as far as

15   manufacturing is concerned or building things is

16   concerned, I saw the relevance of nanotechnology.

17   Can you tell us how nanotechnology is relevant to

18   the kind of things that you do?

19   DR. SADRIEH: Are you talking about

20   devices?

21   DR. SINGPURWALLA: I saw little gears

22   being made.

23   DR. SADRIEH: That sounds more like a

24   device. We are going to focus mostly on drugs.

25   So, you know, there might be drug-device

 1   combinations with the gears that you are talking

 2   about, but we specifically are focusing on drug

 3   issues for CDER.

 4   DR. SINGPURWALLA: Right. So, I just need

 5   to get a sense of what you have in mind.

 6   DR. SADRIEH: For example, we have

 7   nanoparticulate drugs or, you know, platforms.

 8   Sometimes somebody designs a platform and it has

 9   several different components in it and there might

10   be an imaging component and a treatment component,

11   a targeting component, and all of this might be

12   within a size that actually would be within the

13   nano range. So, that is more the direction that we

14   are going in.

15   DR. SINGPURWALLA: What advantage do you

16   see in it?

17   DR. HUSSAIN: Before I answer that

18   question direction, I think one of the challenges

19   we face is that we often get calls from higher-ups

20   from everywhere, saying, how many nanotechnology

21   products do you have, and so forth, and it is very

22   difficult to answer that because there are a lot of

23   products which have been in nanoscales for years,

24   and every solid material that goes into solution

25   goes into a nanoscale. So, from one aspect, every

1   product we have is nanotechnology so the definition

2   out there is not really applicable. So, we want to

3   avoid the confusion of what is nanotechnology.

4   The type of products that we have where

5   nanotechnology is being utilized is to reduce

6   particle size to increase bioavailability, and so

7   forth. That is one but that is simply

8   micromization to a nanoscale, right? But other

9   than that, I think you are looking at design of

10   drug delivery systems. These could be nanosomes.

11   These could be other ones which are more target

12   oriented where you want to distribute the drug

13   differently, and so forth. So, these are mostly

14   drug formulation or drug delivery devices in the

15   nanorange. Then, as Nakissa said, you will have

16   combinations where, you know, you have a drug

17   delivery device which is a device, a machine with

18   drug loaded on to that. So, there are many

19   possible combinations. So.

20   DR. KOCH: I was going to add there

21   because I think this committee or working group

22   that you are talking about needs to just take a

23   step back to put on the list those things which may

24   be obvious present products that may go all the way

25   from aerosols through a number of micromization

 1   products but I think that also then takes you into

 2   excipients and things that are related. Then,

 3   there are the proactive ones where you would

 4   actually be involved with, say, nanotubes, etc.,

 5   for sustained release and things like that. So, it

 6   seems like you first need to begin putting

 7   everything on paper that exists and plan as to

 8   proceeding or encouraging.

 9   DR. SADRIEH: But that is what we are

10   doing. We are presently preparing a database of

11   what we have already in-house, what we have already

12   approved.

13   DR. KOCH: So, we will hear that when you

14   get to the micron presentation.

15   [Laughter]

16   DR. SADRIEH: Sure.

17   DR. KIBBE: Gordon?

18   DR. AMIDON: What I can see in the

19   research area are things like polymerized mice

20   cells. You know there are new technology methods

21   being developed and I can see where there are going

22   to be questions what are the things we should be

23   concerned about--oral, topical ophthalmic, rapid

24   dissolving, and I don't know the answer. I think

25   it is being proactive to look at that and, yet we

 1   have systems to go through the nanoparticle size

 2   range today and we are seeing new technologies to

 3   do that and direct use in delivery systems.

 4   Do you have any products or any product

 5   areas that you are initially looking into? Let's

 6   say nanoparticle polymerized oral delivery system

 7   or something like that, to kind of focus on what

 8   issues do we have to address if we are presented

 9   with one of these as an NDA application, or

10   probably earlier during the process of developing a

11   delivery system? Because likely it would be a new

12   material so then you have the drug master file

13   issues, but maybe not. If it is not, then I think,

14   yes--if it is a material that is used in humans but

15   processed differently then you have to ask the

16   question what standards are we going to set for

17   that.

18   DR. HUSSAIN: Let me give you an example.

19   The challenges are in a sense same material that we

20   have always used now nano-sized, and what issues do

21   they raise? One of the things we had to look at

22   was, for example, titanium dioxide and zinc oxide

23   in sunscreen preparations. You bring them down to

24   nanoscale, you have translucence in sunscreen

25   preparations.

1   Traditionally these are USP materials and

2   USP does not have physical attributes as

3   specifications so they are USP. Whether nano or

4   micro it doesn't matter, they are USP. That raises

5   the same set of issues in terms of do we have the

6   characterization methods? Are these stable? Are

7   there photocatalytic issues, and so forth? Also, I

8   think we are sort of working with the NCTR, the

9   National Center for Toxicology Research that has

10   started a program on looking at skin penetration

11   and photocatalytic activity leading to some

12   toxicity issues. So, we have a small program

13   looking at all those things.

14   But from a general perspective, what we

15   have seen happening is physics become more

16   important now from a stability perspective.

17   Generally, if anything, we will focus--because we

18   don't do physics well today with current products,

19   we have to do physics much better in nanotechnology

20   products. That is an area of gap that we want to

21   fill from a characterization perspective.

22   Also, you will see a lot of issues in the

23   press. There are a lot of concerns being raised,

24   and so forth, so we just want to make sure we are

25   rational, science-based with our approaches and

1   proactive in our approaches because, otherwise,

2   this area will get stifled and we don't want to do

3   that.

4   DR. SADRIEH: We currently think that we

5   are addressing the issues pretty well with our

6   existing system. We just want to make sure. This

7   working group is going to consider all the issues

8   and just make sure that we really are; is there

9   anything that we might not have thought about

10   because, as Ajaz said, we get asked a lot of

11   questions. So, I think it is primarily to just

12   make sure.

13   DR. AMIDON: You are right, it may bring

14   new technologies for quality control and stuff, and

15   things that we aren't familiar with within the

16   typical pharmaceutical manufacturing formulation

17   area. Yes, I think this is a good step to be

18   proactive and think about what we may be faced

19   with. In fact, you will be; it is a matter of

20   when.

21   DR. COONEY: I would also like to add my

22   compliments to taking a very proactive view towards

23   this area. I would also suggest that you look at

24   it as a continuum of the activities you have in

25   place now because it is a continuum from interest

 1   in topical application of drugs. It is a continuum

 2   from some of the things that have been looked at in

 3   the drug delivery area. So, it doesn't stand out

 4   by itself but it connects back to so many

 5   activities that are in place.

 6   One of the things that I find very

 7   positive about this is that by anticipation and by

 8   taking this proactive approach you will be able to

 9   put in place the assets, the people, the mind set

10   to be prepared when things come to you and you are

11   not going to be trying to catch up. You will be

12   right on line if not even ahead of the game.

13   DR. SADRIEH: Right.

14   DR. KOCH: If I could add something to

15   that, I think this would be a good opportunity for

16   the MOUS or NSF where NSF is looking to take a role

17   in nano, but to build on what you have already

18   established if you got involved with

19   characterization of tools that would help take the

20   continuum down. I still feel that there is

21   probably in your particle size distributions or

22   registrations an area, as we have talked about,

23   that is called below 400 mesh. That could be a

24   very critical area to what is actually happening in

25   some of the dissolutions and other things. So, it

 1   is a continuum again, but just to move into

 2   perfecting the characterization tools that will

 3   allow you to move forward.

 4   DR. KIBBE: Let me just add a couple of

 5   science fiction items. The rate of technology

 6   change is exponential and has been exponential for

 7   known recorded history. Right now we are at a rate

 8   which is astronomical. There are some people who

 9   have written, really knowledgeable people in terms

10   of science who have written about singularity in

11   the year 2014 and you can't predict what is

12   possible after that because of the rate, and all

13   that. And, it is really good to see the agency,

14   even if it is gradually getting its feet wet in an

15   area that is potentially spectacular in terms of

16   therapeutics which combine what might be called

17   nano devices with drugs or that kind of thing--so,

18   I think some of the issues that you will deal with,

19   and this working group might be the busiest working

20   group in the agency in about five years. So, it is

21   really good to see that. Anybody else have any

22   comments? If not, we get to let Ajaz have the

23   final word; it is kind of the rule around here.

24   Conclusions and Summary Remarks

25   DR. HUSSAIN: Well, I think I have

1   actually thoroughly enjoyed the discussion and I

2   think, especially today, the morning discussion was

3   very useful.

4   But let me go back to day one and try to

5   summarize some of the talks and at least some of my

6   conclusions which I think I was able to reach, and

7   I want to share that internally as we start

8   tomorrow and we get back to our work.

9   On day one we started with the process

10   analytical technology update. We provided you a

11   brief summary that covered history, evolution,

12   current status and next steps. I think the

13   committee was generally satisfied with the progress

14   of this initiative and essentially agreed with the

15   direction in which it is going.

16   I think the suggestions we received from

17   you for this topic were that we need to consider

18   more objective metrics, especially for a training

19   program, to see how effective they are. Look

20   towards international harmonization is another

21   message that we heard and we are pursuing that and

22   will continue to do that. Also, I think Dr. DeLuca

23   pointed out the need to encourage publications and

24   research in this area, and I think this links to

25   nanotechnology. Everything is connected in some

 1   way or form and we will try to do that as much as

 2   possible.

 3   The afternoon discussion was PAT provider

 4   tech. As I sort of summarize the talks here, the

 5   Office of Biotechnology Products is a new office in

 6   the Office of Pharmaceutical Science. They were

 7   not part of the initial team building and the

 8   training and certification program that we had for

 9   our CDER staff members. Since the guidance is a

10   framework guidance, the framework is applicable to

11   any manufacturing. The reason the Office of

12   Biotechnology Products was not included within the

13   scope of the guidance was because they were not

14   part of the training.

15   So, the afternoon discussion was to give

16   our Office of Biotechnology Products and CBER

17   colleagues an opportunity to discuss with you

18   challenges of the complexity they are facing in

19   their area, and how PAT might be applicable to

20   biotechnology products. I think we discussed a

21   number of emergent technologies and then potential

22   applications, not only by the members here but also

23   in open session.

24   I think the question focus primarily in

25   particular was on how should the training program

 1   be structured as we go to the next training

 2   program. The general discussion and what we heard

 3   from the committee was that training needs to be

 4   emphasizing more critical thinking problem solving.

 5   We did not really get a sense that it has to be a

 6   technology focus, and so forth, because we cannot

 7   do that. If we focus on general principles, if we

 8   focus on the concepts and approach that technology

 9   will evolve and we can always gather that

10   information rather quickly.

11   Based on that sort of discussion--I had a

12   chance to talk to Helen also, I think we have an

13   opportunity to think a bit differently than we

14   were. What I am proposing now is that as we move

15   forward, since we already have a mature PAT process

16   within the Office of Pharmaceutical Science and

17   since we never excluded biotechnology products from

18   the PAT guidance because our Office of New Drug

19   Chemistry probably has more biotechnology products

20   than the Office of Biotechnology Products right

21   now, so I don't see a need to exclude our Office of

22   Biotechnology Products from the scope of the

23   guidance that we finalize.

24   The key issue there is that of training

25   and certification. Because of the infrastructure

 1   already in place with our OPS PAT team and others,

 2   through consultation, and so forth, we can actually

 3   build a bridge to that and get the second training

 4   program started but not have to exclude our Office

 5   of Biotechnology Products from the guidance. So,

 6   that is the thought process that sort of evolved,

 7   and I think Helen an I thought this might be a

 8   better approach as we finalize to include them.

 9   So, the guidance will only exclude CBER products

10   because CBER was not on board from that

11   perspective. So, that is how we think we will

12   proceed with that. So, I think the discussion was

13   very useful to make that sort of a decision and I

14   hope you agree with that. If you don't, obviously

15   you will tell us before we leave.

16   I think discussions today were very

17   valuable and I am really pleased with how we sort

18   of came up with a decision with respect to highly

19   variable drug products, at least a sharpened

20   decision. But I do want to sort of emphasize a

21   couple of things. In a sense the discussion was on

22   highly variable drug products because

23   bioequivalence deals with formulation of products;

24   it doesn't deal with the drug. If you inject a

25   drug, a very simple solution of drug into a human

 1   being and you see a lot of variability in the PK

 2   parameters, that is a highly variable drug with

 3   respect to the disposition characteristics--you

 4   know, metabolism, excretion, elimination and so

 5   forth. Now, if you give the same solution orally,

 6   then you add on the variability, the physiologic

 7   variability of gastric emptying, and so forth. So,

 8   that is a highly variable drug by itself. For the

 9   sake of assumptions, it is a simple solution; the

10   formulation is not an effect.

11   But then you put that drug in a solid

12   dosage form, or any other dosage form, or a topical

13   dosage form and you have a set of variabilities

14   there. If the variability is the same as what we

15   had after intravenous administration the

16   formulation really did not add or subtract from

17   that variability. So, it is a highly variable drug

18   and the product did not alter that variability.

19   But you can also have scenarios where the

20   product that you design can increase or actually

21   reduce that variability. For example, I think we

22   have seen more recently some drugs, especially

23   Class II drugs, which have significant food effect

24   when you administer them in a conventional dosage

25   form. If you can design a formulation, for example

 1   a nanoparticle formulation or a cyclodextrin-based

 2   formulation you can actually eliminate the food

 3   effect so you have reduced the variability. So,

 4   here is a formulation design strategy that can

 5   actually reduce the variability.

 6   So, I think the highly variable discussion

 7   really is a focus of discussion of highly variable

 8   drug products. The variability is no different

 9   from the variability of the innovator. That is not

10   an issue. When the variability is higher then that

11   becomes a decision issue, whether it is acceptable

12   or not.

13   But for the last ten years or so that we

14   have discussed that, all the discussion has focused

15   on the statistical criteria and actually trying to

16   clear the check box exercise. The simple answer, I

17   think it is simply an arbitrary number. I hate

18   those check box exercises and it is easy, we can

19   make a decision. So, I am not comfortable with

20   sort of arbitrary numbers defining that. So, I

21   think that is the gap that will remain.

22   But the scaling approach, if we address

23   the arbitrariness of that and make it more

24   comparative scaling to a reference variability is a

25   way forward, and I think that was the general

1   conclusion of this committee and I think you gave

2   us the signal to move forward. I will ask Lawrence

3   next month to have that ready for you.

4   [Laughter]

5   I think that was a very useful discussion

6   and I think we will move forward very quickly to

7   sort of hone in on that. At the same time, I think

8   the decision tree approach is built in there. It

9   is a logical decision tree that will evolve and I

10   think we will move there and I can be assured how

11   it can be done with the topical discussion that

12   followed, and that is a highly, highly variable

13   scenario right there.

14   So, I think the discussion was very useful

15   and helped us move forward in terms of being more

16   confident about the direction we want to move

17   forward in. With Lawrence and his team I am very

18   confident. Probably, if necessary, we can bring

19   our proposal to you in October. That might be an

20   option. I don't want to put pressure on Lawrence

21   but I think we can do it.

22   The topic of bioinequivalence I think is

23   to address currently I think a procedural nightmare

24   that comes from the aspect that our Office of

25   Generic Drugs has to deal with. I think we want a

 1   solution to use our resources more effectively and

 2   so forth. So, Lawrence and the group presented

 3   this proposal and I think generally we came to the

 4   general understanding that it might be very useful

 5   to move forward.

 6   But I do want to sort of remind ourselves

 7   of a couple of things. This is an important

 8   concept. It is not a trivial concept because we

 9   have to really think beyond the application that we

10   discussed today and how it applies to the entire

11   regulatory scenario. For example, out of

12   specification results and how do we deal with those

13   is a major issue, and how does this relate to that

14   discussion I think is a very serious discussion

15   that probably needs to be considered more

16   carefully. One can think about misuse of this in

17   some ways. If a product is out of specification

18   and the company does a bioequivalence study and

19   fails to establish bioequivalence, and they come

20   back and say there is no clinical relevance so why

21   do you want to recall the product? So, all those

22   implications are there, which we did not discuss

23   today. So, it is not a simple matter and how it

24   relates to the big picture needs to be looked at

25   very carefully.

 1   The other positive aspect of this is that

 2   I hope it will force people to ask the question

 3   why, why is it bioinequivalence? That gets to a

 4   road to a mechanism understanding, and I think

 5   without that the numbers game and the check box

 6   exercise will continue. As Helen pointed out in

 7   her opening remarks, we really don't like check box

 8   exercises--at least Helen and I don't like them,

 9   and we want to move away from that and be more

10   science based. But the challenge is when you go

11   towards that without proper training, without a

12   proper quality system for our review staff and

13   review processes, it has the potential of creating

14   more questions and so forth. So, we want to manage

15   that very, very carefully.

16   Now, the other two topics that we

17   discussed, I think topical bioequivalence again is

18   a 10-15 year old saga. We have debated and

19   discussed this, and so forth, and the only solution

20   that we could find was to step away from all that

21   we have done for 15 years and to start fresh.

22   Lawrence and Dr. Lionberger really took the step

23   backwards and said let's rethink this and work with

24   Dr. Wilkin to rethink the mechanism perspective.

25   Again, the misgiving, if I have any, is in

 1   the sense as a professor of pharmaceutics we knew

 2   this 15 years ago. There is nothing new in that.

 3   But it is unfortunate that at FDA we have to now go

 4   back to the basics that we have been teaching. So,

 5   that is a bit of a frustration but I think we have

 6   taken a positive step, in my opinion, in that

 7   direction and with the support of our clinicians I

 8   think we will move forward very quickly.

 9   Now, nanotechnology--I think it is simply

10   a starting point for discussion and we actually

11   have a number of products which companies want to

12   discuss with us, and PAT is actually very well

13   connected to nanotechnology. If you read the

14   guidance, there is a sentence in that and many of

15   the things that we are looking at--particle size

16   reduction, for example, particle size analysis, you

17   cannot just take a sample and send it to the lab

18   and do this. Most of the particle size reductions

19   are based on on-line assessment of particle size.

20   So, every discussion topic was

21   interconnected and I was thinking that, in a sense,

22   I was going to apologize for quality by design of

23   our advisory committee agenda because I think the

24   topics were a bit lighter on day one; we had more

25   time left, and a bit heavy on day two. But the

 1   sequence that we had in mind was if you look at the

 2   discussion of PAT and biotech, and if you look at

 3   the discussion of highly variable drug products,

 4   there was a quality control check right there from

 5   our speakers that we had invited. Everything was

 6   connected. The sequence was there but I think the

 7   material should have been more in depth on day one.

 8   So, we will work on quality by design for our

 9   agenda more. With that, Helen, do you want to say

10   something?

11   MS. WINKLE: I just want to say that I

12   agree with Ajaz. I thought the conversation, both

13   yesterday and today, was excellent. I think that

14   yesterday there was total agreement on the

15   direction we are going with PAT. I think that the

16   committee has been very supportive for what we have

17   been doing in PAT and I think we have moved ahead,

18   and I think it is going to be really a very good

19   undertaking for industry, FDA and the public, and I

20   appreciate the committee's support of that

21   initiative.

22   Today's discussion was especially valuable

23   to us. I think there are a lot of things in the

24   area of bioequivalence as well as inequivalence

25   that we are still learning and still need to make

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 1   changes. It is constantly evolving and I think

 2   today's conversation will help move us forward in

 3   the direction we need to go to in making some of

 4   the really necessary changes that can reduce the

 5   regulatory burden and really get the products out

 6   on the market quicker. So, I appreciate the

 7   conversation on that as well.

 8   DR. KIBBE: Do I get to say we are

 9   adjourned? Good. We are adjourned.

10   [Whereupon, at 4:10 p.m., the proceedings

11   were adjourned.]

12   - - -