

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF
THE ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

8:32 a.m.

Wednesday, June 24, 1998

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Ballroom
Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland

APPEARANCES

COMMITTEE MEMBERS:

ROBERT E. TAYLOR, M.D., PH.D., Chairman
Chairman, Department of Pharmacology
Howard University College of Medicine
520 W Street, N.W., Room 3412
Washington, D.C. 20059

KIMBERLY TOPPER, Executive Secretary
Advisors and Consultants Staff
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-21)
5600 Fishers Lane
Rockville, Maryland 20857

ROBERT A. BRANCH, M.D., F.R.C.P.
Director, Center for Clinical Pharmacology
University of Pittsburgh Medical Center
200 Lothrop Street, 623 Scaife Hall
Pittsburgh, Pennsylvania 15213-2582

GAYLE A. BRAZEAU, PH.D.
Associate Professor
Department of Pharmaceutics
College of Pharmacy, Office of the Dean
Box 100484
Gainesville, Florida 32610-0494

STEPHEN R. BYRN, PH.D.
Charles B. Jordan Professor of
Medicinal Chemistry
School of Pharmacy and
Pharmaceutical Sciences
Purdue University
1336 Robert Heine Pharmacy Building
West Lafayette, Indiana 47907-1336

ARTHUR H. GOLDBERG, PH.D.
Principal Consultant
Pharmaceutical Development Group, Inc.
624 Sand Hill Circle
Menlo Park, California 94025

APPEARANCES (Continued)

COMMITTEE MEMBERS: (Continued)

KATHLEEN R. LAMBORN, PH.D.
Professor, Department of Neurological Surgery
University of California San Francisco
350 Parnassus Street, Room 805, Box 0372
San Francisco, California 94143-0112

MICHAEL MAYERSOHN, PH.D.
Professor
College of Pharmacy
The University of Arizona
Tucson, Arizona 85721

JAMES T. STEWART, PH.D.
Professor and Head
Department of Medicinal Chemistry
University of Georgia College of Pharmacy
D.W. Brooks Drive, Pharmacy Building, Room 371
Athens, Georgia 30602-2352

ROBERT ELDEN VESTAL, M.D.
Associate Chief of Staff for Research
and Development
Veterans Administration Medical Center
500 West Fort Street
Boise, Idaho 83702

DESMAR WALKES, M.D., Consumer Representative
Director of Private Clinic
1011 Chestnut Street
P.O. Box 306
Bastrop, Texas 78602

CHERYL L. ZIMMERMAN, PH.D.
College of Pharmacy
Health Sciences Unit F
University of Minnesota
Minneapolis, Minnesota 55455

APPEARANCES (Continued)

COMMITTEE GUESTS:

LARRY AUGSBURGER, PH.D.
University of Maryland

KEN SEAMON, PH.D.
Immunex

ROGER SCHWEDE
IGPA

THOMAS X. WHITE
Pharmaceutical Research and Manufacturers of America

FOOD AND DRUG ADMINISTRATION STAFF:

YUAN-YUAN CHIU, PH.D.
DOUG ELLSWORTH, PH.D.
DAVID FINBLOOM, M.D.
AJAZ HUSSAIN, PH.D.
BRUCE SCHNEIDER, M.D.
ERIC SHEININ, PH.D.
ROGER L. WILLIAMS, M.D.

ALSO PRESENT:

ROBERT JERUSSI, PH.D.
Jerussi Consulting, Inc.

CHARLES KUMKUMIAN, PH.D.

LEO LUCISANO
Glaxo-Wellcome

CHRISTINE MUNDKUR
Barr Laboratories

DR. GOPI VUDATHALA
Procter & Gamble Pharmaceuticals

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P R O C E E D I N G S

(8:32 a.m.)

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3 DR. TAYLOR: Good morning. I'd like to call to
4 order day two of the Advisory Committee of Pharmaceutical
5 Science for the Center for Drug Evaluation and Research.
6 I'm Dr. Robert Taylor. I'm the Chairman of the committee.

7 We'll move directly to the agenda. We do have
8 some housekeeping items to take care of, and I'll have
9 Kimberly Topper advise you of that.

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

14 Since the issues to be discussed by the
15 committee will not have a unique impact on any particular
16 firm or product, but rather may have widespread
17 implications with respect to entire classes of products, in
18 accordance with 18 U.S.C. 208, waivers have been granted to
19 each member and consultant participating in the committee
20 meeting. A copy of these waiver statements may be obtained
21 by submitting a written request to FDA's Freedom of
22 Information Office, Room 12-A30 of the Parklawn Building.

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

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

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

8 Thank you.

9 DR. TAYLOR: Thank you.

10 For the record, I'd like to have the committee
11 introduce themselves again. I'm Robert Taylor. I'm from
12 Howard University.

13 DR. MAYERSOHN: Good morning. Michael
14 Mayersohn, the College of Pharmacy, University of Arizona.

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

17 DR. VESTAL: Bob Vestal, the Department of
18 Medicine, University of Washington and Mountain States
19 Medical Research Institute.

20 DR. ZIMMERMAN: Cheryl Zimmerman, College of
21 Pharmacy, University of Minnesota.

22 DR. BYRN: Steve Byrn, Industrial Pharmacy,
23 Purdue University.

24 DR. BRANCH: Bob Branch from the University of
25 Pittsburgh.

1 DR. STEWART: Jim Stewart, College of Pharmacy,
2 University of Georgia.

3 DR. GOLDBERG: Arthur Goldberg, independent
4 consultant.

5 DR. LAMBORN: Kathleen Lamborn, University of
6 California, San Francisco.

7 DR. TAYLOR: Thank you very much.

8 The morning session is entitled SUPAC-IR:
9 Update of Guidance. I believe Dr. Eric Sheinin will
10 coordinate this session and make presentations of his
11 group. I would request that we hold the questions for this
12 discussion until after all the presenters have completed
13 their presentations. Thank you.

14 DR. SHEININ: Thank you, Dr. Taylor. Good
15 morning, everyone.

16 In this session, what we would like to do is to
17 present to the advisory committee where we are currently in
18 the area of SUPAC-IR -- that was the first SUPAC that we
19 issued -- and get some guidance on future directions that
20 this document should go as we are attempting to revise it.

21 So, what I would like to do is just give you a
22 very brief overview of SUPAC in general and the philosophy
23 behind SUPAC and then turn it over to the other speakers.
24 There is a slight change in the agenda. Following me will
25 be Ajaz Hussain who will give you some perspective on the

1 revision process and what we would like to do with SUPAC-
2 IR. Hopefully this will be followed by Larry Augsburger
3 who will discuss some of the research that was performed at
4 the University of Maryland that was used to support the
5 development of the initial SUPAC document, and then we'll
6 hear the industrial perspective. Tom White will be
7 presenting the PhRMA view and Roger Schwede the IGPA
8 viewpoint.

9 So, I guess to start, what is the purpose of
10 SUPAC? SUPAC was designed to reduce the regulatory burden
11 on the industry when they're making post-approval changes,
12 but the main thing that it would do, while allowing a
13 reduction in the regulatory burden, would be to maintain
14 the safety, efficacy, and quality of the drug product in
15 question. SUPAC-IR is for immediate release, solid, oral
16 dosage forms. So, that was the first SUPAC that we put
17 out.

18 It also will provide an increased degree of
19 flexibility to the industry in how they go about making
20 those changes.

21 Just to give you a brief history of SUPAC-IR,
22 it was issued as a final guidance in November of 1995. We
23 did a series of in-house training for our reviewers. Then
24 we put on a very large, well-received training session for
25 the industry in February of 1996. This was coordinated

1 with the University of Maryland.

2 Immediately after this SUPAC issued, it was
3 obvious that there were some inconsistencies, there were
4 some things that maybe were not addressed fully to the
5 extent that there were a lot of questions from the
6 industry. We started a series of weekly meetings within
7 the Office of Pharmaceutical Science by the five chemistry
8 division directors. These were the division directors in
9 the Office of New Drug Chemistry and the Office of Generic
10 Drugs, and we attempted to answer questions that came in
11 from the industry on how to apply SUPAC-IR.

12 This led us to put out an industry letter in
13 February of 1997 that clarified some of these issues and
14 also clarified some of the concerns that were raised by the
15 industry and also actually in a way updated SUPAC-IR in
16 terms of what would be allowed under various types of site
17 changes.

18 We continue to get questions about equipment
19 changes. The way all of the SUPACs are set up, equipment
20 changes are based on whether the new equipment is the same
21 design and the same operating principle as the equipment
22 that was being used previously, and whether it falls within
23 that category or whether it's a different design and
24 operating principle would determine the filing mechanism.
25 And we were getting questions from the industry on how do

1 | we file this? Is this equipment the same? Is it not the
2 | same?

3 | It turned out we really had no good sense both
4 | within the center and within the field with the
5 | investigators as to whether or not equipment was the same,
6 | was it the same design, was it the same operating
7 | principle.

8 | So, we turned to the ISPE, the International
9 | Society for Pharmaceutical Engineering, to give us some
10 | assistance in developing a list of equipment by operating
11 | principle and by design so that we would have a handle on
12 | whether or not an equipment change could be done as an
13 | annual report or if it would require a prior approval
14 | supplement.

15 | And that led to the issuance of the
16 | Manufacturing Equipment Addendum in October of 1997, and
17 | this set forth and spelled out various types of equipment,
18 | whether it's, for example, a mixer or a dryer and actually
19 | gives the manufacturers of equipment. It provides
20 | additional guidance to the industry to help with the
21 | interpretation of SUPAC-IR in the area of equipment
22 | changes.

23 | Even with all this, it was obvious, as we went
24 | on with additional SUPAC documents, that there may be the
25 | possibility of further reducing the regulatory burden on

1 | the industry. So, we formed a working group to take a look
2 | at SUPAC-IR and to try and develop a revised guidance that
3 | would provide additional regulatory relief. That's the
4 | main reason why we're here today, is to get input and
5 | feedback from the advisory committee on what direction this
6 | update should take.

7 | Just for your additional information, solid,
8 | oral, immediate release dosage forms include tablets,
9 | chewable tablets, capsules, and soft gelatin capsules. At
10 | this point it does not include things like powders for oral
11 | administration after dissolution.

12 | What is the SUPAC guidance? SUPAC, as with all
13 | our guidances, represents the best judgment or the current
14 | position and thinking of the center at the time that it's
15 | issued. All of our guidances are more or less informal and
16 | they're nonbinding, nonbinding on the industry, meaning
17 | that if a firm wants to take a different approach and can
18 | justify it scientifically, it might be acceptable to us.
19 | What we do ask is that if a firm is going to take a
20 | different approach than is spelled out in any of our
21 | guidances, that they discuss it with the appropriate
22 | chemistry team in the review division where the application
23 | is housed.

24 | It's also not binding on our reviewers
25 | officially, but in reality what we have told our reviewers

1 is the same thing we're telling industry. If you want to
2 ask for something above and beyond what is spelled out in
3 the SUPAC guidance, you have to be able to justify it.
4 There may be certain instances where additional information
5 or additional testing is justified on the basis of the
6 known stability or the known properties of a particular
7 drug product.

8 The types of changes that are covered under
9 SUPAC include changes in the components or composition of
10 the dosage form.

11 The site of manufacture, and this has now been
12 expanded to include analytical testing sites and packaging
13 sites.

14 The scale of manufacturing. This is it can be
15 scaled up or it can be scaled down with a floor of 100,000
16 units.

17 And the manufacturing changes. This could be
18 process changes or the equipment changes that I spoke about
19 previously.

20 The guidance defines -- and all the SUPACs
21 generally take the same approach -- levels of changes, and
22 there are three different levels right now within SUPAC.
23 The recommended testing, chemistry, manufacturing, and
24 controls procedures for each level, and these may be
25 different depending on the various levels.

1 The levels generally start out, level 1 is the
2 easiest type of change, being an annual report, and that
3 would require the least amount of supporting data to be
4 included in the submission, going up to a changes being
5 effected supplement and then to a prior approval
6 supplement, which would be the most stringent type of
7 change.

8 It provides information on when in vitro
9 dissolution testing and when in vivo bioequivalence testing
10 might be required, and this varies with the individual
11 levels.

12 It also talks about what sort of documentation
13 should be included in the submission, whether it's an
14 annual report or a supplement, to support that change.

15 It's all based on probability and the potential
16 impact of the change. So, level 1 is the least stringent
17 change where it's unlikely that the change would have an
18 impact on the identity, strength, quality, and purity of
19 the drug product and any impact would not be detectable.
20 It goes up to level 3 where there's a high likelihood that
21 the change has the potential to impact the identity,
22 strength, quality, or purity of the drug product, and under
23 those conditions, there could be a significant impact.
24 This then is something that the center would want to see
25 ahead of time and have the opportunity to decide whether or

1 not that's an appropriate change, whether there's
2 sufficient supporting information to allow the firm to go
3 ahead and make that change.

4 Some of the major implications that are
5 contained within the SUPAC-IR document, in terms of the
6 component and composition change, a classification system
7 was established that will be used to determine what sort of
8 documentation will be required, and this will be discussed
9 further this morning. In many cases the annual report
10 would be sufficient documentation for some of these
11 changes, and these are generally the level 1 changes.

12 This represented in my mind a rather
13 significant change in the center's position in that in the
14 past, under 314.70 which is the part of the Code of Federal
15 Regulations that deals with post-approval manufacturing
16 changes and other types of changes, annual report changes
17 were generally reserved for what we considered very, very
18 minor types of changes that really do not have much impact
19 on the identity, strength, quality, and purity of the drug
20 product.

21 In certain situations, the manufacturers will
22 be able to make changes in the various areas that SUPAC
23 talks about without prior approval.

24 So, all these represented a reduction in the
25 regulatory burden in taking things that in the past had

1 | been prior approval to a changes being effect supplement
2 | and maybe even all the way down to annual report type
3 | changes.

4 | The guidance defines the levels of change, and
5 | as I said, there are three changes. Unfortunately, in all
6 | cases the information that is required to go along with the
7 | change is not the same for all level 2's and all level 3's.
8 | So, that's one thing that we might look at in the future as
9 | we revise this document, is to have all level 1
10 | documentation the same, all level 2 documentation the same,
11 | all level 3 documentation the same, which would make it
12 | easier on the industry and make it easier on our reviewers.

13 | It provides this information on the recommended
14 | test that should be performed. It may be, like for a level
15 | 1, that all a firm would have to do is demonstrate that it
16 | meets the acceptance criteria that are spelled out in the
17 | new drug application or abbreviated new drug application,
18 | or it may be that they just have to meet what's in the USP,
19 | in the pharmacopeia.

20 | The in vitro and in vivo dissolution testing
21 | are spelled out again in the various documentation, whether
22 | you need to have prior inclusion of stability data at the
23 | time of submission, or whether it's just a commitment to
24 | perform stability on the first batch or maybe three batches
25 | post approval, depending on the type of change and

1 | depending on the manufacturing history and how much history
2 | the firm has with that product.

3 | So, what we would like to achieve today and get
4 | feedback and input from the advisory committee. Direction
5 | for future research. We really feel comfortable with the
6 | SUPACs that are out there now in that there was research
7 | performed that would allow us to justify this reduction in
8 | the regulatory burden.

9 | As we go further and try to refine these
10 | documents and provide additional relief to the industry, is
11 | there additional research that can be performed that would
12 | allow us to have the scientific data and the basis then to
13 | justify reducing that burden or reducing the filing
14 | requirements further.

15 | This ties into the second request. What
16 | direction should the future reductions take? What I've
17 | mentioned today is the various types of changes that are
18 | allowed under SUPAC. There are other changes that a firm
19 | can make to their drug product that are not covered by
20 | SUPAC at this point. Can some of these be brought into a
21 | guidance that would reduce the burden? Can we take the
22 | types of changes that we allow now and further reduce the
23 | filing burden? Is it possible to move more things to
24 | annual report?

25 | Is it possible to move more things to a changes

1 | being effected supplement? The advantages of a changes
2 | being effected supplement over a prior approval supplement
3 | right now is that the changes being effected supplement,
4 | that change can be put into effect immediately upon
5 | submission of the documentation.

6 | Under FDAMA, the Food and Drug Administration
7 | Modernization Act of 1997, those CBE supplements in general
8 | are going to be changed to a 30-day CBE supplement, meaning
9 | the center will have 30 days to decide if the supplement
10 | really is a changes being effected type or should it be a
11 | prior approval, and firms will have to wait 30 days before
12 | they implement. But that's the only difference then
13 | between, in essence, a CBE supplement and an annual report
14 | in terms of when the change can be implemented.

15 | So, are there things that we can move further
16 | down in the regulatory scheme of things?

17 | Finally, we'd like to have a discussion of the
18 | acceptability and the potential use of something called a
19 | comparability protocol. A comparability protocol would be
20 | a protocol that a firm could have included in their
21 | original NDA or ANDA submission or could be submitted after
22 | approval as a prior approval supplement. What this
23 | protocol would do would spell out what sort of testing a
24 | firm would do, what sort of validation a firm would do when
25 | making a change that perhaps might be otherwise classified

1 a prior approval supplement, if they spell out in this
2 protocol what they're going to do to verify, validate, and
3 justify reducing the filing burden on this change, whatever
4 it happens to be.

5 This has the potential of further reducing
6 regulatory burden tremendously on firms, even way above and
7 beyond whatever SUPAC is designed to talk about. So, we
8 would like to have, hopefully either today or in the
9 future, some feedback from the advisory committee on the
10 use of comparability protocols.

11 That concludes my remarks on SUPAC, just to
12 bring you more or less up to date on where we stand with
13 SUPAC-IR. I'll turn it over to Ajaz at this point.

14 DR. HUSSAIN: Good morning. I'll be speaking
15 on behalf of the SUPAC-IR Revision Working Group. My
16 presentation covers some of the thought processes that the
17 working group currently holds and some of the research
18 findings at the University of Maryland, how we intend to
19 use that research.

20 I was expecting Larry Augsburger to speak after
21 me. Since he's not in the audience, I may spend a few
22 minutes more talking about the research too. Professor
23 Augsburger was at the southeastern regional meeting of AAPS
24 yesterday. Hopefully the bad weatherman should not have
25 held him back there.

1 The purpose of the revision process is to
2 accomplish a few issues. One, the major reason for
3 revising is to improve the utility of SUPAC-IR, and there
4 are a number of reasons why the working group felt the
5 SUPAC-IR may not be used as much as it should have been,
6 one being the current recommendation on dissolution tests,
7 specifically the case C dissolution test. The questions
8 that I will raise to you deal with this.

9 To some extent, the definition of these change
10 levels may need to be modified, especially in light of the
11 fact that we plan to introduce multiple changes in this
12 guidance.

13 Also, as Dr. Sheinin pointed out, we had quite
14 a bit of lessons learned from this first attempt at SUPAC.
15 SUPAC-IR was the first of the SUPAC guidances, and there
16 are a number of questions and answers that need to be
17 consolidated into this guidance in the revised version.

18 Let me start with dissolution. You'll recall
19 that for level 2 changes, especially the components and
20 composition changes, SUPAC-IR introduced a classification
21 system, what we now call Biopharmaceutics Classification
22 System, for defining or recommending dissolution test
23 conditions. In this classification system, a drug is
24 classified based on its solubility and permeability
25 characteristics. So, in essence, you have highly soluble,

1 highly permeable drugs. For these drugs, the guidance
2 recommends a dissolution in .1 normal HCl, and if the
3 dissolution is rapid, 85 percent in 15 minutes, one point
4 specification is sufficient to document unchanged quality
5 and performance.

6 However, if the permeability of the drug is
7 low, the guidance recommends a profile comparison,
8 signifying some concern that with low permeability drugs,
9 you would like to control the dissolution more carefully.
10 So, in the application or compendial media, there is a
11 recommendation to compare profiles, not just one point
12 specification.

13 For high permeability drugs but those with low
14 solubility, the guidance recommends a case C dissolution
15 and that may have been too rigorous. The original case C
16 dissolution comes from the AAPS/FDA workshop report. So,
17 that was the origin of that. SUPAC-IR did not recommend a
18 dissolution test to document unchanged performance for low
19 permeability and low solubility drugs.

20 Case C dissolution is dissolution profiles in
21 five media, and the five media that were recommended
22 included water, .1 normal HCl, pH 4.5 buffer, 6.5, and 7.5.
23 The two products, pre- and post-change products, need to
24 show similar dissolution profiles in all these five media.
25 The guidance also introduced the concept of a metric for f2

1 and offered an f2 value of greater or equal to 50 would be
2 judged as being comparable profiles.

3 The number of dissolution tests that need to be
4 done and validated from an analytical perspective is large.
5 For example, if the current application or compendial media
6 are different from this, it may mean that you may have to
7 do six dissolution tests to justify this change.

8 As I mentioned earlier, case C dissolution
9 applies for level 2 component and composition changes for
10 products of low solubility, high permeability drugs. But
11 it also applies for level 2 equipment changes for products
12 of all drugs regardless of the class. So, it impacts these
13 two change definitions.

14 The work at the University of Maryland used six
15 model compounds, and the summary conclusions of the work
16 there was all the formulations that were tested were
17 bioequivalent despite large in vitro dissolution
18 differences. In fact, formulations were developed to fail
19 current application and compendial dissolution tests. Even
20 those products were found to be bioequivalent. So, in a
21 sense what this suggests is the application or compendial
22 media were found to be sensitive to formulation changes for
23 all drugs tested irrespective of BCS class membership.

24 Just to remind you, the drugs we tested were
25 metoprolol, propranolol, highly soluble, highly permeable;

1 ranitidine, highly soluble, low permeability drug; naproxen
2 and sodium salt, and piroxicam were class 2 low solubility,
3 but high permeability. We did not have any model compounds
4 of low solubility and low permeability drugs included in
5 this database.

6 When we look at this and we look at the
7 conclusion of this research database, that application and
8 compendial media may have been sufficient to distinguish
9 between different formulations. However, we have some
10 concerns generalizing this for low solubility drugs for
11 several reasons.

12 One, when the solubility is low, dissolution is
13 likely to be rate-limiting. What that does is, if you look
14 at the literature, when dissolution is rate-limiting,
15 there's a high likelihood of in vitro/in vivo correlation.
16 But the way we develop in vitro/in vivo correlation today
17 is very empirical. You try out different media. You try
18 out different apparatuses until you find one which gives
19 you the correlation. So, there is no a priori method for
20 defining what is the dissolution condition that will
21 satisfy or give you the correlation.

22 But that raises some concern, and connected to
23 that point is that single pH may not be discriminating,
24 especially, to give you an example, when you look at weak
25 acids, say, NSAIDs, ibuprofen, ketoprofen, and so forth,

1 | the current dissolution test conditions are in similar
2 | intestinal conditions, pH 7.4. Solubility of these drugs
3 | is extremely high under those conditions, but the data we
4 | have in house on the new drug side where they have
5 | evaluated different formulations, although the formulation
6 | changes right now would be considered as major level 3, one
7 | media does not discriminate between bioinequivalent
8 | products especially because dissolution is so rapid that
9 | you do not see differences which might have been apparent
10 | if the pH was lower. Furosemide is the prime example.
11 | When the first dissolution USP specification was set, it
12 | was a higher pH. It was later reduced to a lower pH where
13 | the lower pH was found to be more discriminating.

14 | Also keep in mind, we have very limited multi-
15 | media dissolution data. In the past three years, industry
16 | has not used case C dissolution for SUPAC submissions, very
17 | few examples, and we really do not know whether five media
18 | or six media or three media will give you the answer.

19 | So, the options that we have for modifying case
20 | C dissolution is as follows. I think this is what the
21 | working group refers, number one, is to recommend two
22 | media, and the one media would be the application and
23 | compendial media. In addition to that, based on whether
24 | the drug is a weak acid or a weak base, the second media
25 | would be based on that decision. If it's an acidic drug, a

1 pH of 1 or 3 might help. For a weak base, application and
2 compendial media plus a more alkaline pH condition, 6.8 or
3 7.5.

4 To give you another example, if you look at
5 diazepam, it's a weak base with a critical peak ka value.
6 If you look at dissolution of diazepam products in .1
7 normal HCl, they dissolve in less than 5-10 minutes. But
8 we have cases of biofailure because at pH 4.5, you see
9 dramatic differences in those products. So, pH 4.5 for
10 diazepam would have been more discriminating than pH 1 or
11 .1 normal HCl. So, I think that's the basis of
12 recommending the second pH condition at the higher value.

13 Also the second option is obviously to fix the
14 pH media according to critical physiology parameters,
15 gastric, duodenal, and jejunal or intestinal pH conditions.
16 That's another option. But what happens is if we fix pH
17 conditions at 1, sodium naproxen -- there's hardly any
18 dissolution. So, doing a dissolution at 1 may not make
19 sense because you don't see anything there.

20 Also there is some consideration on how to
21 address the situation when the application and compendial
22 media already has a surfactant. I think that is an
23 important point. There are a few drugs where a surfactant
24 is necessary. Should we recommend the surfactant be
25 included in any of these? That's an issue that we are

1 | discussing within the working group right now.

2 | As we move toward multiple changes and also
3 | start looking at the research that we already have done,
4 | there is a desire to reevaluate the change definitions
5 | based on existing research, and also we need to accommodate
6 | multiple changes. The working group right now feels that
7 | the way to do that would be to simply say multiple change
8 | level would be the highest level of an individual change in
9 | a series of changes. Instead of restricting multiple
10 | changes, if we can allow this and adjust the change levels
11 | accordingly, this might be a very simple way of addressing
12 | and make it more flexible.

13 | We are addressing all issues in terms of
14 | components, composition, batch size, equipment, process,
15 | and site. But I just want to bring to your attention a
16 | question on batch size today.

17 | Batch size changes under SUPAC-IR today deal
18 | with two numbers. One, as Dr. Sheinin pointed out, pilot
19 | batch or biobatch is defined as a batch which has 100,000
20 | or more units. We do not allow scale-down below this.

21 | The second boundary for batch size changes is a
22 | scale-up factor of 10. If you can scale up without
23 | changing anything right now by 10X, that's a level 1
24 | change. If you go beyond 10X without changing anything,
25 | it's level 2.

1 The research at the University of Maryland --
2 I'm happy to see Professor Augsburger walked in, so he can
3 talk about it more. The scale-up was done for all drugs or
4 for many drugs, and the scale-up was beyond 10X, 66 times,
5 20 times, depending on the drugs and so forth. And we
6 didn't find that the scale-up factor was really meaningful.
7 However, I need to point out that for that consideration,
8 we used very small batches. We scaled from lab batches,
9 3,000 units, 1 kilogram batch, up to, say, 66 times and so
10 forth. So, that is the concern because that does not match
11 with what we currently practice of 100,000 units.

12 Also, I think you need to keep in mind that
13 changes in batch size are generally associated with changes
14 in equipment and process parameters. That's one reason why
15 SUPAC-IR may not have been used for scale-up changes the
16 way we expected it to be maybe because you really cannot
17 make batch size changes without adjusting your parameters.
18 If you look at the process parameter level 1 change, you
19 have to be within your validated range, and that's too
20 restrictive, at least in the opinion of the working group.

21 What we feel right now is I think change in
22 processing parameter may not be a bad thing. You really
23 need to optimize when you make changes. You need to adjust
24 your mixing times so as to meet your in-process controls
25 and so forth. So, that may not be a bad thing. You need

1 | to allow that flexibility.

2 | So, the question that I would pose to you is
3 | this. Is it appropriate to define batch size as a multiple
4 | equipment and process change? Batch size is a dependent
5 | variable, not an independent variable in this sense. For
6 | example, how this could be accomplished is right now the
7 | proposed level 1 change for batch size could be defined as
8 | batch size change accomplished using equipment of similar
9 | design and the same operating principles and changes in
10 | processing parameters to meet in-process and final product
11 | specification.

12 | Keep in mind that these changes have to be
13 | validated. Also, all products not only have to meet
14 | established specifications, plus the additional test that
15 | we recommend for chemistry and biopharm.

16 | So, just to summarize, I think I would
17 | appreciate it if you could give us some suggestions on two
18 | topics: case C dissolution, reducing the number of media
19 | to two or three; optimizing change levels, especially for
20 | batch size, define batch size as a multiple equipment and
21 | process change or retain the 10X scale-up factor.

22 | My working group is here in the audience, and
23 | I'll leave this. We are thankful to our consultants. This
24 | is the first time I think the working group has assigned
25 | consultants. Allen Rudman and Hank Malinowski from the

1 working group who first developed the SUPAC-IR. Nancy
2 Sager is the contact person for all questions and answers.
3 Professor Augsburger did most of the research at the
4 University of Maryland.

5 Thank you.

6 DR. SHEININ: I see Dr. Augsburger has arrived,
7 so he will next present a summary of some of the research
8 that was done at the University of Maryland.

9 DR. AUGSBURGER: Well, good morning, everyone.
10 I was told I had 10 minutes to do this. How many?

11 DR. HUSSAIN: 20.

12 DR. AUGSBURGER: Oh, 20 minutes. It has been
13 changed. Okay, that's even better still.

14 What I want to try to do this morning is to
15 walk you through some of the research that was conducted at
16 the University of Maryland that provided much of the
17 database that supports SUPAC. We're really looking at this
18 from the point of view of the PQRI drug product technical
19 committee perspective, and some of you may know that while
20 that initiative proposes to do some active research, a
21 large part of what is suggested is that we could do some
22 retrospective investigation looking at research that has
23 already been done or perhaps already published. In this
24 case we're looking at research that has already been done
25 to see if there is justification for making some changes or

1 | updates to the current SUPAC-IR.

2 | In looking at this data, one of the
3 | recommendations that might come forward would be to give
4 | consideration to a downward shifting of the levels that
5 | currently exist in the area of compositional changes,
6 | perhaps going from 1 to 0 if there is a 0, from 2 to 1, and
7 | so forth. The justification stated kind of succinctly is
8 | that after looking at six different drugs in the Maryland
9 | research, which represented classifications 1, 2, and 3, we
10 | found that broad in the in vitro USP-style dissolution
11 | resulting from what most of us would consider major
12 | compositional changes -- in many cases they equaled or
13 | exceeded the current level 2 -- did not translate into
14 | bioavailability differences. That's a fairly potent
15 | statement.

16 | Let's take a look at just a couple of those.
17 | Here, for example, is sodium naproxen. To kind of give you
18 | a little bit of background on this, one of the objectives
19 | of the research was to develop formulations that would have
20 | widely differing dissolution performance, that is, in terms
21 | of USP dissolution. In order to achieve those levels,
22 | those changes of differences in dissolution performance, we
23 | had to make a lot of changes, SUPAC-type changes, mostly
24 | compositional changes in these cases, in order to do that.

25 | What you see on the right-hand side, for

1 | example, for sodium naproxen, which is a class 2 drug,
2 | you'll see the slowest dissolving formulation that we
3 | produced. You'll also see the fastest dissolving
4 | formulation that we produced, and we also have it by
5 | comparison any particular lot that we found of the
6 | innovator product. You can see that our fastest dissolving
7 | product was closely similar to the innovator product.

8 | In order to get that level of difference in
9 | dissolution, you can see that the slow product did not meet
10 | the USP specifications. There were a number of changes
11 | that had to be made in those formulations and you can see
12 | up here the ranges, in this case the change in lubricant
13 | level of magnesium stearate from a half to 2 percent. We
14 | also changed the level of extragranular microcrystalline
15 | cellulose, another excipient in the formulation. In this
16 | particular case, the only SUPAC level that was affected is
17 | the lubricant level, and we far exceeded the current level
18 | 2 limit for that excipient. Yet, when these were studied
19 | in bioavailability studies, we find that these formulations
20 | are bioequivalent to each other as well as to the innovator
21 | product, and these are the Cmax and AUC ratios over here.

22 | Here is naproxen, another class 2 drug. Here
23 | you see our slowest formulation, and it just barely meets
24 | the USP definition of dissolution. The fastest formulation
25 | is almost congruent with a lot of the innovator's product.

1 In this particular case, the formulation was quite
2 different, so there were more things to manipulate to get
3 these differences in dissolution profile. You can see the
4 binder level changing from 1 to 5 percent, lubricant level
5 from .1 to 2 percent, disintegrant level, a super-
6 disintegrant, from 2 to 6 percent. And there were process
7 variable changes, increasing the lubricant blending time,
8 almost doubling it, and the volume of the binder solution
9 was increased by 20 percent.

10 Well, which of those applied to SUPAC? Binder
11 level, lubricant level, and the non-starch disintegrant
12 level? The binder solution volume is not addressed in the
13 original SUPAC. But as you can see, these are the level 2
14 limits or ranges that would define them as level 2 limits,
15 and we've exceeded those. Again, the formulations are
16 bioequivalent to each other as well as to the innovator's
17 product.

18 Here's a class 1 drug, propranolol. Here you
19 can see the slowest formulation we were able to produce
20 would meet USP, but it certainly takes a much different
21 path than the fast one or the innovator product. In order
22 to get that much difference in dissolution performance,
23 again we had to make substantial changes in formulation or
24 process variables. Again, we were pushing or exceeding
25 level 2 limits where they applied, and again the

1 formulations were bioequivalent.

2 Piroxicam, a class 2 drug. The slow
3 formulation did not meet USP dissolution specifications.
4 Here we have a few more things that we were changing, not
5 only the filler level, but in fact we changed it so much we
6 swapped filler. So, now we're looking at a difference not
7 only in technical grade, but a physical chemical type of
8 filler. So, in one case we would have 100 percent lactose,
9 and in another product it's 100 percent microcrystalline
10 cellulose. Lubricant level changing three-fold. Wetting
11 agent, not really addressed in the original SUPAC, I don't
12 think, from 0 to 1 percent. Particle size expressed in
13 terms of fraction of the total piroxicam that was milled.
14 There was about a five-fold difference in specific surface
15 area between the original form of the piroxicam and the
16 milled form. We went from 100 percent unmilled to 100
17 percent milled in these formulations, a substantial
18 difference in particle size. Lubricant blending time from
19 10 to 18 minutes. In terms of SUPAC levels, again for
20 those that apply, we are pushing or exceeding level 2
21 limits, and yet these formulations turned out to be
22 bioequivalent.

23 Ranitidine, a class 3 drug. Sometimes when we
24 talk about this data, we say we failed. In this case we
25 failed to make a bad product in terms of USP dissolution at

1 | least because even the slowest product that we could
2 | produce would meet USP standards. But even to produce this
3 | much of a difference in dissolution profiles, we had to
4 | make a number of changes, again pushing level 2 limits, and
5 | again these formulations are bioequivalent.

6 | Where do these formulations come from in the
7 | first place? We would simply open up the PDR and see what
8 | the list of excipients were, and then we'd build up our
9 | formulations around that.

10 | Metoprolol, one of the most studied drugs in
11 | the University of Maryland research, both for the ER as
12 | well as for the IR projects, a class 1, high solubility,
13 | high permeability drug.

14 | The slow formulation is quite distinctly slower
15 | than any of the others, and certainly does not meet USP
16 | standards. If you look at the innovator product and our
17 | fastest releasing formulation, they were quite comparable.

18 | In order to get these levels of differences, I
19 | should point out there was also another formulation,
20 | intermediate, but I left them off these slides so they
21 | wouldn't be too complicated. They're complicated looking
22 | as it is.

23 | If you look at the variables, we changed the
24 | binder level from 3 to 5 percent, a disintegrant level, a
25 | super-disintegrant, from 3 to 9 percent, not a whole lot of

1 change in the lubricant level in this particular case, but
2 still it was in that level 2 range. Process variables,
3 changing the lubricant blending time. This is a high sheer
4 granulation. We found the impeller speed had a significant
5 effect on dissolution performance. The presence or absence
6 of intragranular microcrystalline cellulose, which is a
7 granulation 8 in this case, also was a factor. Again,
8 these formulations turned out to be bioequivalent to each
9 other as well as to the innovator product.

10 So, that's the database that I think would
11 support some slippage or loosening of the definition of
12 those levels.

13 But I'd like to comment a little bit more about
14 this class 1 series of drugs. We looked at two of them,
15 propranolol and metoprolol. I think serious consideration
16 should be given to reducing the dissolution requirements
17 for class 1 drugs.

18 A general comment, a general observation in our
19 hands at least for those two examples, we find that class 1
20 drugs are very robust with respect to the impact or the
21 possible impact of formulation or process variables. Very
22 little seems to have an effect on them, and regardless of
23 what we have done to change their dissolution performance
24 in terms of USP dissolution, it never seemed to have any
25 impact on bioequivalence.

1 In particular, it's not just this statement
2 here, which is what I led off with, but I would also add
3 this point here, that a requirement of 85 percent
4 dissolution in 15 minutes is simply not justified by the
5 data that we've seen.

6 Here's the metoprolol data that we just looked
7 at a few minutes ago. Here you can see that these two
8 formulations here are dissolving perhaps almost 90 percent,
9 I guess, in 15 minutes. This one dissolves about 30
10 percent in 15 minutes. Yet, these two formulations were
11 bioequivalent. And you get exactly the same pattern if you
12 look at the propranolol data, which also is a class 1 drug.

13 Another recommendation that you could kind of
14 tease out of this data is that serious consideration should
15 be given to removing reference to 10X from the guidance on
16 batch size. Justification for that: Dissolution profiles
17 and bioequivalence did not change upon scale-up using
18 equipment that has the same design and operating principle
19 when scale-up factors were properly considered. General
20 engineering concepts, when you go to larger bowls, what do
21 you do to the rate of rotation of the impeller, for
22 example?

23 Here is metoprolol. Metoprolol turns out to
24 have been one of the drugs that had the broadest range of
25 scale-up experience in this particular project. You can

1 | see that we went from as low as 2 kg size batches up to 66
2 | kg size batches.

3 | These weren't always done in the same site, by
4 | the way. They were moved around to different sites. In
5 | some cases, the formulations were made at Pfizer. In some
6 | cases, they were made at Glaxo. In some cases, they were
7 | made at the University of Maryland. In some cases, parts
8 | of the formulations were made at Niro, who makes the
9 | granulator. So, there's a lot of site change in here.

10 | But I'm not talking about site change. Just
11 | look at the scale changes here, and you can see these are
12 | the USP dissolution profiles for all the scales plotted on
13 | the same graph, and you can see that regardless of the size
14 | batches, size equipment, those profiles would be in
15 | anybody's judgment fairly much the same, pretty much the
16 | same. They're congruent.

17 | Over here in a follow-up biostudy, we took the
18 | 14 kg and 66 kg batches into a bioavailability study, and
19 | we found that comparing those two batch sizes, they were
20 | equivalent. Here are the ratios over here.

21 | We had similar experiences with three other
22 | drugs in the contract, ranitidine, for example. Here is
23 | the dissolution profile for the 5 kg size scale versus a 50
24 | kg size scale. We chose the slowest releasing formulation
25 | of the series. These were obviously very similar profiles

1 and they were bioequivalent.

2 Here is piroxicam, 5 kg, versus 50 kg, and
3 they're bioequivalent.

4 Here is propranolol, funny looking profiles,
5 but they're fairly similar, and they're bioequivalent.

6 Another recommendation that I would like to
7 suggest is that we should take a close look at what we mean
8 by technical grade of excipient and whether or not level 2
9 is the most appropriate level for that kind of a change.
10 Frankly, in the Maryland research, we didn't look a lot at
11 that aspect. There were a few things that we could say we
12 looked at, but not much. Those things that we did see
13 didn't give us a lot of reason for concern about technical
14 grade.

15 I think also, in addition to that, what
16 contributes to this feeling about this recommendation is
17 that if you look at the overall range of dissolution
18 profiles that were found to be bioequivalent, regardless of
19 the classification of drug that we looked at, it's
20 difficult for someone who's experienced in the field to
21 believe that changing the technical grade could have that
22 much of an impact on dissolution or exceed that much impact
23 on dissolution.

24 I do have some things we can talk about. This
25 is a piece of data that probably I haven't shown for a long

1 | time, and I had good reason to kind of draw it out of the
2 | files because we're talking an awful lot about
3 | vegetable/tallow source of magnesium stearates, the
4 | vegetable versus the animal source of magnesium stearates.
5 | There was one particular part of the study when we were
6 | doing piroxicam, one of the earlier runs, when we actually
7 | tried to see if there would be any impact on changing, it
8 | turns out, what we call today the technical grade of
9 | magnesium stearate. You'll see that there were two animal
10 | type -- I think this middle grade is the standard grade.
11 | There were two animal source of magnesium stearates and one
12 | vegetable source. These are all Mallincrodt grades.
13 | Within them, there are also differences in particle size.
14 | So, we thought this would be an interesting exercise.

15 | So, what I've produced here are some bar graphs
16 | showing in this case the percent dissolved in 15 minutes in
17 | USP dissolution for one particular slice through the data.
18 | This happens to be using the unmilled piroxicam, and the
19 | level of lubricant was 1 percent. The lubricant blending
20 | time was 10 minutes. There was 1 percent sodium lauryl
21 | sulfate, and we were using an instrumented Zanasi machine
22 | so we could measure the tamping force and control it for
23 | the study. 300 Newtons was the standardized tamping force
24 | on the powder plugs that were dropped into the capsules.

25 | You can see that we also were changing other

1 | things in this study. This was a typical center composite
2 | type experimental design. You can see that we looked at a
3 | filler that was 100 percent lactose. We looked at a
4 | situation where the filler was 100 percent microcrystalline
5 | cellulose, and a situation where the filler was 50/50
6 | microcrystalline cellulose and lactose.

7 | Now, if you look at these, you would see
8 | immediately that there are differences in the percent
9 | dissolving in 15 minutes, and it changes according to the
10 | filler system. Within any given filler system, though, the
11 | actual differences here are not large, certainly not large
12 | relative to what we've seen to be bioequivalent in our
13 | later bioavailability studies. You can see a difference
14 | here between maybe 62 or 63 percent here and something
15 | around 68 percent. That's not a big difference. For some
16 | products, that's within the normal variation of
17 | dissolution.

18 | Here is, a little bit larger perhaps, a
19 | difference of 56 or so percent to maybe 65 percent, and
20 | again a very small difference here.

21 | Despite those obviously differing trends in
22 | dissolution performance, I don't believe these are
23 | meaningful based on the bioequivalence studies that we did
24 | later on.

25 | If you consider this to be two changes -- let's

1 | say, you're changing the filler system and the lubricant at
2 | the same time -- even if you start to compare between these
3 | different filler systems, these are not super big
4 | differences relative to those differences in dissolution
5 | performance that we saw to be bioequivalent in those later
6 | studies.

7 | Here's the same set of data for 45 minutes. I
8 | think that's the USP standard now. You can see that as you
9 | got later in dissolution, the differences between the
10 | different lubricants become even smaller and not important.
11 | It would not have any impact on USP dissolution, in other
12 | words.

13 | I think that's the last slide that I have. I
14 | hope I did that in about 20 minutes, but that's really a
15 | thumbnail encapsulation of, I think, the salient parts of
16 | the data that would support a reexamination of SUPAC-IR in
17 | the direction of loosening up some of the requirements. I
18 | think the SUPAC-IR, on the basis largely of the Maryland
19 | data, goes beyond the recommendations of workshop 1. Now
20 | that we've had some experience with SUPAC-IR, it's probably
21 | time to think about going beyond the current SUPAC-IR.

22 | Thank you.

23 | DR. SHEININ: Thank you, Larry.

24 | I'd like to ask Tom White now to come up.

25 | MR. WHITE: Good morning. I'm filling in for

1 | Dr. Tim Hagen of Pfizer who could not be here this morning.
2 | PhRMA appreciates the opportunity, the invitation that we
3 | received, to participate and provide some suggestions on
4 | revision of the SUPAC-IR.

5 | I'll be very brief this morning. PhRMA looks
6 | forward to the expected revision to SUPAC-IR guidance.

7 | Even when SUPAC-IR was first issued, it was
8 | greeted with less than wide acclaim. I think probably one
9 | of the reasons for that was that it was a pioneer. It was
10 | the first SUPAC. At the time I referred to it -- and
11 | mainly I was just trying to nail Dr. Williams once in a
12 | while by saying it was a work in progress, and I think
13 | indeed it was a work in progress.

14 | After the training that took place at the
15 | University of Maryland and the early application of the
16 | guidance, the assessment, sort of the background noise that
17 | we would hear at PhRMA -- and I don't know who said this --
18 | was that it would go along like it's not worse off. We're
19 | not really a great deal better off. Only time will tell,
20 | and I think time has told.

21 | That assessment was improved by Dr. Williams'
22 | sort of mid-course correction in early 1997 with his letter
23 | to the industry, and also I think a continuing commitment
24 | by CDER to make it work.

25 | Part of that commitment actually is why we're

1 here this morning because it was a commitment to update and
2 revise SUPAC-IR based on the lessons learned and the
3 experience. PhRMA appreciates all those efforts and the
4 invitation to provide suggestions this morning. I'm able
5 to provide sort of a list of few areas that should be
6 considered in the revision. This is sort of at the macro
7 level.

8 It has been suggested that the elements that
9 were included in Dr. Williams' February 1997 letter be
10 incorporated to the extent that experience has helped in
11 any revised guidance.

12 There have been calls for clearer directions
13 for handling multiple changes. I think that both Dr.
14 Hussain's and Dr. Augsburger's presentations sort of bear
15 that out.

16 Have the revised version provide more clarity
17 regarding the respective roles of the field investigators,
18 field offices, in the SUPAC process.

19 And finally -- and this has also been borne out
20 by Dr. Hussain and Dr. Augsburger. We didn't collaborate
21 before this, but have the revision improve upon and make a
22 better attempt at deregulation and streamlining of the
23 post-approval change process.

24 The original SUPAC process was touted as a
25 reinventing government initiative, and we shouldn't be

1 satisfied until there is a significant further reduction in
2 the need for prior approval supplements. We believe the
3 revised guidance should reflect the concepts that are
4 contained in the manufacturing change provisions of the
5 recently enacted Food and Drug Administration Modernization
6 Act, the so-called FDAMA legislation. We're pleased that
7 FDA intends to factor that new development into the planned
8 revision.

9 PhRMA has an active work group that is
10 developing suggested approaches that could build upon the
11 SUPAC approach and simplify the change process in keeping
12 with the spirit of the FDAMA provisions.

13 We support the consideration of comparability
14 protocols mentioned by Dr. Sheinin. That is actually a
15 tool that I don't think there's any impediment to its use
16 now, that a sponsor prior to approval could include within
17 its original application some kind of protocol that would
18 facilitate a post-approval change process. But to have
19 that incorporated into the thought processes and the
20 system, PhRMA has long believed that that would be a way to
21 take care of a lot of anticipated changes up front.

22 Finally, there's one other aspect that should
23 be kept in mind in the revised guidance and that is the
24 harmonization wherever possible of the post-approval change
25 system with those systems used by drug regulatory

1 | authorities in other parts of the world, notably the
2 | European Union variations system, the Canadian system, the
3 | Australian system. I think that in addition to lessons
4 | learned from SUPAC-IR and the concepts that are
5 | incorporated in the FDAMA manufacturing change provisions,
6 | the harmonization with some other systems that treat this
7 | same issue could also benefit the revisions.

8 | Thank you very much.

9 | DR. SHEININ: Thank you, Tom.

10 | Roger Schwede now will present the viewpoint
11 | from the generic industry side.

12 | MR. SCHWEDE: Good morning. On behalf of the
13 | generic trade associations, I'd like to start off by
14 | thanking the Food and Drug Administration and members of
15 | the Pharmaceutical Science Advisory Committee for the
16 | opportunity to comment on experiences to date with SUPAC-IR
17 | documents.

18 | Listening to the previous presentations, I
19 | could probably shorten my presentation to saying I endorse
20 | all of the previously made recommended changes because
21 | there already seems to be a fair amount of consistency in
22 | what we're sharing with you this morning. Nonetheless,
23 | I'll proceed with my presentation.

24 | As some of you may be aware, I'm also a
25 | substitute speaker for Dr. Seymour Heyden who unfortunately

1 is not able to make this presentation today. While he is
2 recovering, I will attempt to present the collective
3 thoughts of the generic industry and the individuals and
4 the companies that have provided me the input for this
5 presentation.

6 As a bit of historical perspective, I can
7 remember being in a Holiday Inn conference center not too
8 far from the one we're in today several years ago. The
9 presentations were being made to the then Generic Drugs
10 Advisory Committee by members of the generic manufacturing
11 firms, and we were describing the challenges that we
12 encountered in formulating our generic products, securing
13 the sources of active ingredient for products, challenges
14 in validating analytical methods and in validating the
15 processes for our products. For those presentations, that
16 meeting preceded the work that was undertaken as research
17 at the University of Maryland.

18 We also described in those presentations the
19 need for changes to the application post approval because
20 of the experiences that were gained in manufacturing
21 experiences post approval. As I said, that preceded the
22 research that was conducted at the University of Maryland,
23 which we know created the scientific basis for the
24 documents we refer to today as SUPAC-IR guidance.

25 From the generic industry perspective, as long

1 as we use good science as the basis of these guidances, as
2 long as we're not afraid to make changes as opposed to
3 maintaining status quo, and as long as the process to
4 identify and effect changes is open to all of the
5 interested parties and is an interactive process between
6 the industry and the agency, our only concern becomes the
7 speed with which we can accomplish the changes that we set
8 out to make.

9 My comments this morning will be brief. We'll
10 talk about some general concepts of the guidance, some
11 changes that we deem as appropriate, and also some thoughts
12 on where we go from here.

13 First and foremost, the initial reaction to
14 SUPAC-IR almost universally has been positive. I think a
15 good part of that positive reaction, though, is reflective
16 of the process that was used as opposed to its distinct
17 content. We've already talked about the training programs
18 that were used to roll out the SUPAC-IR documents, and that
19 was reflective of something that we really had not seen
20 before. It was a very interactive process and I think it
21 was appreciated by everybody in industry. Although I don't
22 have the numbers on the number of ANDA's that have had
23 supplements that used SUPAC-based recommendations, I know
24 the general reaction has been positive.

25 If one wants to understand why, you can take a

1 | look at the language that is in the guidance and compare it
2 | to the language that was previously used as the basis for
3 | characterizing changes to an approved application. We've
4 | gone from one and a half pages of text in the CFR to five
5 | and a half pages plus in the Federal Register notice.

6 | We've gone from somewhat vague
7 | characterizations of the types of changes, often subject to
8 | interpretation or negotiation between the sponsor and the
9 | FDA reviewer. In a lot of instances, that resulted in
10 | almost a characterization of any change had to go to a
11 | prior approval status.

12 | We now have some pretty well defined and stated
13 | changes and identification of the supportive data that's
14 | necessary. The filing criteria are clearly identified.
15 | Little, if any, is subject to either interpretation or
16 | negotiation, and it clearly spells out what is eligible for
17 | annual progress report changes and changes being effected.
18 | That's the good news.

19 | The bad news, as some would say, is that we've
20 | gone from vague language open to interpretation to black
21 | and white characterization of what is necessary and in some
22 | cases more onerous for some of the changes that are being
23 | effected. As one would expect, making changes to this
24 | document, as significant as they are, you can't keep
25 | everyone happy, but there is some concern that we've lost a

1 little bit of the flexibility and some of the changes that
2 could have been made under the old interpretations are now
3 a little bit more onerous.

4 From a general perspective, there continues to
5 be some disappointment that the full text of the research
6 that was conducted at the University of Maryland has never
7 been fully disclosed or shared. While it's acknowledged,
8 that there have been several poster presentations and
9 podium sessions at annual meetings and published articles,
10 it's also known that the full extent of what was researched
11 is rich with data that has not been shared. As scientists
12 and engineers that work with this type of data on a regular
13 basis, the desire to see all of the data still exists.

14 As Dr. Augsburger stated, some of the PQRI
15 initiatives may rely on more of a retrospective
16 reevaluation of the data that does still exist in those
17 files, and I guess that pretty much characterizes what I've
18 just stated. We know there's additional data, and as the
19 industry that pretty much prompted the research, it would
20 be interesting to have all of that data shared.

21 The second general observation deals with the
22 guidance's reliance on the drug being characterized by
23 solubility and permeability, when in fact with a fair
24 number of the drugs that we work with, these two aspects
25 are not fully understood. Level 2 and level 3 changes that

1 | involve the components or the composition of a product
2 | require this characterization and pretty much dictate the
3 | filing requirements. In the absence of having that type of
4 | information on a drug, SUPAC-IR is just a document for
5 | highly soluble, highly permeable drugs, unless you
6 | automatically assume worst case scenarios for the type of
7 | supplement. In those instances, no efficiency is gained.

8 | The next general area of concern deals with
9 | multiple changes, and I think this has already been touched
10 | on. Most often multiple changes are almost necessitated.
11 | You can't make one minor change without causing another one
12 | to also be in place. The guidance specifically states
13 | under the purpose that multiple changes that are concurrent
14 | or that occur over a short period of time requires
15 | consultation with the agency. While that provision exists,
16 | it's not efficient. It's often cumbersome and most often
17 | would result in delays. It requires the agency's time away
18 | from what their other duties and responsibilities are.

19 | The same aspect of multiple changes has already
20 | been captured in one of the other SUPAC documents in draft
21 | form, and it's felt that it should be allowed as a
22 | provision for the immediate release, solid, oral dosage
23 | forms.

24 | The most frequently criticized aspect of the
25 | guidance that individual firms have felt is excessive

1 involves the generation of dissolution data, as has already
2 been touched on, especially in case B and case C situations
3 that are described in the guidance.

4 For immediate release, solid, oral dosage
5 forms, profiles beyond an 85 percent dissolution value
6 seems a little unnecessary, as do the profiles in the
7 multiple medium. In almost all cases, characterization of
8 the drugs' dissolution profiles to this extent exceeds the
9 characterization that was generated in developing the
10 product initially and goes beyond the type of data that was
11 part of the original application as the basis of its
12 approval.

13 Seven of the 13 examples of changes that are
14 described in the guidance require dissolution testing
15 following either case B or case C profiling. So, a fair
16 number of the submissions that would be described by the
17 guidance as it currently exists would seem to necessitate
18 this extensive testing.

19 Finally, I guess one cannot imagine rewriting
20 the guidance to address all post-approval changes, adding
21 the amount of detail, as was done for SUPAC-IR, and being
22 able to do it in one concise document. It's well
23 recognized that SUPAC-IR has spawned a subset of other
24 SUPAC documents that more specifically involve analytical
25 methodology, packaging components, the bulk active

1 ingredient, and the other dosage forms.

2 I started out with a comment in my presentation
3 by stating that with good science the concern of the
4 industry is the speed with which we can accomplish some of
5 our other goals. While there have been some positive
6 experiences in using SUPAC-IR, we eagerly await its
7 revision to reflect some of the changes that have been
8 described this morning and, more importantly, to see some
9 of the other SUPAC-based documents proceed with their
10 issuance and implementation.

11 That's it in a nutshell. My conclusions from
12 what I've heard this morning, it seems that there is a fair
13 amount of consensus on the areas to be revised and we look
14 forward to continuing to work with the agency to see that
15 these are effected. Thank you.

16 DR. SHEININ: Thank you, Roger.

17 Before I turn the mike back to Dr. Taylor, I
18 would like to take the opportunity to introduce someone to
19 the advisory committee. It's very apropos, given Tom
20 White's remarks about needing to define and clarify the
21 role of the field investigator, that we're fortunate today
22 to have with us the District Director from FDA's New Jersey
23 district, Doug Ellsworth, who is also the Chair of the
24 Field Drug Committee. The field, through the Office of
25 Regulatory Affairs, has a number of committees made up of

1 | representatives from the field and various centers. In our
2 | case, it's the Field Drug Committee. We're very fortunate
3 | to have Doug as the head of that committee, as Doug spent a
4 | number of years in the Office of Compliance in CDER. So,
5 | he has the experience and the background of both now the
6 | field and headquarters. He'll be available throughout the
7 | morning if you have any questions. Doug, would you wave or
8 | stand up?

9 | Thank you. Dr. Taylor, it's yours.

10 | DR. TAYLOR: Thank you for your presentation.

11 | According to our agenda, we're scheduled for a
12 | short break, and I'd like to take that because I think that
13 | our discussion will be fairly extensive after we come back.
14 | So, why don't we come back at 10 o'clock. At that time we
15 | will take any open public discussion, followed by the
16 | committee's discussion. 10 o'clock sharp. Thank you.

17 | (Recess.)

18 | DR. TAYLOR: If we can take our seats, we'll
19 | complete the morning session.

20 | At this time our agenda calls for an open
21 | public discussion. We've had no individuals indicate that
22 | they would like to make a formal statement to the committee
23 | at this time. However, the floor is now open for
24 | individuals who would like to make a formal statement. If
25 | you would come to the microphone and identify yourself and

1 | your organization, I would appreciate it. Thank you.

2 | DR. JERUSSI: My name is Robert Jerussi. I'm
3 | with Jerussi Consulting.

4 | I think there's something that fell out of Dr.
5 | Augsburger's remarks this morning which is important and
6 | I'd like to give you some background on it.

7 | The reason a 100,000 batch was selected was
8 | because companies were producing minuscule batches that
9 | basically had no relationship to what they would produce
10 | once production started, and there was a bio question about
11 | that. So, 100,000 was selected as a batch that could be
12 | produced in production equipment it was thought, and that
13 | would give a large enough batch to give good sample
14 | selection, et cetera.

15 | I think the work at the University of Maryland,
16 | particularly with the smaller batches, indicates you don't
17 | need 100,000 tablets. You could do with a lot less. I
18 | think that ought to be part of the consideration of the
19 | revision of SUPAC-IR.

20 | DR. TAYLOR: Thank you.

21 | Are there other individuals who would like to
22 | make a formal statement to the committee on this topic?
23 | Yes, would you come forward please and identify yourself by
24 | name and by your organization?

25 | MR. LUCISANO: Leo Lucisano, Glaxo-Wellcome.

1 I'd just like to make a few comments.

2 One, I work in a regulatory affairs group that
3 supports manufacturing sites. Everything I've heard today
4 is very encouraging.

5 I just want to emphasize the impact that these
6 guidance documents are having. They are literally changing
7 the vocabulary that we use in the manufacturing sites in
8 defining the data and information packages that we have to
9 submit to support post-approval changes. Well-crafted
10 guidance documents are a real plus for pharmaceutical
11 companies that are involved in a fast-changing world.

12 Case C dissolution was discussed today where
13 companies had to develop dissolution in five different
14 dissolution media. That's being challenged. I would
15 encourage that because from a practical standpoint, case C
16 dissolution is required for all level 2 equipment changes.
17 The cost of that precludes us from actually exploring new
18 equipment with different design and operating principles.
19 So, it's an example there where a stipulation in the SUPAC
20 guidance actually discourages exploring new technology.

21 On the positive side, these guidance documents
22 have provided us with a common terminology when I deal not
23 only with the folks in the manufacturing floor, but also
24 with the FDA review chemists. I've had two situations
25 where we've discussed with the FDA supplements that were

1 clearly outside of SUPAC but which included some elements
2 that were covered by SUPAC, such as equipment changes or
3 manufacturing site changes. When we make the statement can
4 we use the principles spoken about in the SUPAC-IR
5 guidance, it provides us a very powerful means for
6 discussing common terminology about equipment and
7 dissolution.

8 We recently submitted a supplement where we had
9 to invoke four different guidance documents.

10 When I go back to my customers in the
11 manufacturing sites, we felt that there was a fair balance
12 between -- I've heard Roger Williams talk about consumer
13 risk versus producer risk. The folks that I work with felt
14 there was a fair balance there between data and information
15 that we had to provide, allowing us to make the changes
16 that we wanted to implement, while also assuring that we
17 weren't affecting product quality.

18 The last comment I'd like to make, and it was
19 alluded to before about the coordination with the field.
20 Several SUPAC changes require that we submit batch records.
21 In dealing with international sites, we often have to
22 supply not only the original version of their batch
23 records, but also the English version. When you look at
24 the amount of paperwork, when we file a SUPAC change that
25 requires a batch record, it may go as long as 100 pages

1 with the vast majority of those pages, over 90 percent,
2 just being the batch records. You might consider
3 coordinating or reducing your requirement to actually
4 include batch records that goes into the submission that
5 goes to the Office of Pharmaceutical Science and that being
6 addressed as an inspection issue.

7 Thank you.

8 DR. TAYLOR: Thank you very much for your
9 comments.

10 Are there other individuals?

11 DR. KUMKUMIAN: Charles Kumkumian. I'm a
12 consultant.

13 I heard a lot of things about the dissolution
14 variations and the absence of an effect on bioequivalence,
15 which sounded very good because the human body is such that
16 it can take care of many factors.

17 I think before anything can really be done,
18 what are the outer limits? Do we have data on failures?
19 When I was with the FDA, we had a few limited failures. I
20 guess the challenge is to industry, do you have examples of
21 failures in your development work and in other areas that
22 you could share with this committee so that we can put some
23 boundaries on the upper limits on these things?

24 DR. TAYLOR: Are there other individuals that
25 would like to make a statement?

1 DR. VUDATHALA: Gopi Vudathala of Procter &
2 Gamble Pharmaceuticals.

3 I think it's really good to see that a number
4 of the changes that are being addressed are questions that
5 were raised originally in the SUPAC-IR training. I think
6 one of the important aspects that was pointed out then was
7 that the f2 dissolution similarity factor -- even though a
8 number of the drugs from that data that Dr. Augsburger
9 showed had very wide differences in vitro, they were still
10 considered to be bioequivalent. So, I think we need to
11 kind of take a look at the conservative measure of f2 that
12 we are looking at for showing similarity in dissolution
13 profiles.

14 DR. TAYLOR: Thank you.

15 Are there other individuals that would like to
16 make a formal comment?

17 MS. MUNDKUR: Hi. My name is Christine Mundkur
18 from Barr Laboratories.

19 I'd just like to say that I'm very encouraged
20 by the revisions. Barr has been using SUPAC-IR since 1995.
21 Right now we're submitting at least one or two supplements
22 a month under it. So, it's a relief to see that we're
23 looking at it again to add additional revisions.

24 One of the examples I just wanted to give,
25 especially on the case C dissolution, is we're looking to

1 make a process improvement, going to a new piece of
2 equipment, going to case C dissolution is just ridiculous,
3 having to do five method validations for it. So, in
4 looking at it, we looked at it and said, well, look, we're
5 doing multiple changes, going to a multiple site. It
6 doesn't fall under SUPAC, so we don't have to do the case C
7 dissolution. I mean, these are things that we're actually
8 looking at to get outside of SUPAC.

9 So, I just wanted to give it as an example,
10 that perhaps we do want to look at the case C dissolution
11 as being a little bit more rigorous than what we've ever
12 seen before. But that is only the down side.

13 For the most part, though, SUPAC-IR has really
14 helped our company a lot. So, I'm happy to at least see
15 the revisions coming.

16 Thanks.

17 DR. TAYLOR: Are there others?

18 I think I'm going to ask -- oh, I'm sorry.

19 Yes. Would you make a comment?

20 DR. AUGSBURGER: I have listened to a number of
21 comments, and I just want to make a couple of follow-up
22 statements. Someone -- I guess it was Tom White -- made a
23 comment, where's the data, the University of Maryland data?
24 As far as I know, all that data is in the public domain and
25 is available under the Freedom of Information, number one.

1 Number two, nearly all that data has been
2 summarized into six core publications and about four
3 collateral publications. Most of these publications are
4 either in print or in press at the present time. So, it is
5 out there and is being reviewed by referees and the like.

6 Leo Lucisano made a comment about case C
7 dissolution, and someone else just recently. Maybe that's
8 an area that I forgot to mention because we did do case C
9 dissolutions on all of our clinical batches, and there's
10 nothing in the Maryland data that would support maintaining
11 a case C dissolution. I think that's probably an area that
12 needs to be examined as well based on their data.

13 DR. TAYLOR: Thank you.

14 I'm going to give Dr. Eric Sheinin an
15 opportunity to make some comments at this time before we
16 begin the committee deliberations.

17 DR. SHEININ: Thank you. I really appreciate
18 all of the comments that people in attendance today have
19 made. A lot of what was said are things that we have been
20 thinking about and directions that we're talking about
21 going, especially one of the things Roger Schwede had to
22 say about going into other areas, taking SUPAC into
23 different dosage forms into the bulk drug substance,
24 analytical methodology, and packaging considerations.
25 Those are all areas that the center is either working on or

1 | has plans to develop guidances in the future. If the
2 | committee has any advice and counsel for us on directions
3 | to go in that area, we certainly welcome them.

4 | I know that Steve Byrn has been heavily
5 | involved with us in the workshop that we put on last year
6 | on BACPAC, which will be a SUPAC-type document for the bulk
7 | active chemical, or as it's now called API, active
8 | pharmaceutical ingredient. So, we are really interested in
9 | developing SUPAC-type guidances for these other areas.

10 | Probably an area that we could go with the
11 | least amount of effort perhaps will be into other dosage
12 | forms. SUPAC was originally developed intentionally to
13 | consider one type of dosage form and then extend it into
14 | other dosage forms. We would be interested in any comments
15 | that you have on how easy or how fast do you think we could
16 | go and what sort of data might we need to extend this into
17 | other dosage forms that are not currently covered.

18 | One area that was not mentioned previously I
19 | guess is we are in the process of developing a SUPAC-type
20 | document for sterile aqueous solutions. We call it PAC-
21 | SAS, post-approval changes for sterile aqueous solutions.
22 | We have a draft that's circulating internally right now on
23 | that that hopefully will be out for public comment -- I
24 | fully expect it to be out sometime this calendar year and
25 | hopefully it will be out sooner than later.

1 So, any other direction that the committee can
2 give us will certainly be welcome.

3 DR. TAYLOR: Thank you.

4 I think we'd like to start now our committee
5 discussion of this topic, and I'm going to ask Steve Byrn
6 to begin that discussion because he has some interesting
7 commentary on some of the things that were said this
8 morning. Steve?

9 DR. BYRN: Thank you very much, Dr. Taylor.

10 I thought we might start by asking mostly Ajaz
11 to define a couple of the terms that he proposed again a
12 little more specifically to cover the areas. I'm just
13 going to ask you in sequence to go over comparability
14 protocols, batch size issues, and case C dissolution. Just
15 define for the committee. Could you just go over
16 comparability protocols and define for the committee how
17 these are envisioned to work and what might happen? Maybe
18 if Eric wants to chime in, it's very fine also.

19 DR. SHEININ: Let me speak to comparability
20 protocols. Ajaz can handle the rest I think.

21 Comparability protocols would be in my mind
22 essentially a mini SUPAC, if you would, or a mini post-
23 approval change document. It would be case by case
24 specific for a particular product for a particular type of
25 change. As an example I can give you, perhaps a company

1 | might want to make certain types of changes in their
2 | packaging material, maybe go from one high density
3 | polyethylene resin to another. Right now, for a solid,
4 | oral dosage form, that's allowed under the regulations to
5 | be an annual report change if -- in the case of HDPE, it is
6 | -- there's a protocol spelled out a pharmacopeia -- in our
7 | case the USP -- or in the application. So, for that type
8 | of change, USP has certain types of testing and criteria
9 | that have to be performed and met when you're making a
10 | change from one HDPE to another. If it meets those
11 | criteria, then that would be an annual report change.

12 | I could envision for other types of plastics,
13 | other components in a container closure system, a company
14 | might want to be able to change from one vendor to another,
15 | and they could have a protocol with the type of testing
16 | that would be performed and what the criteria are for
17 | accepting and comparing the new component to the old
18 | component.

19 | It would be, at least in my mind, something
20 | that could be discussed down the road. The type of testing
21 | that would be performed would be more extensive than the
22 | normal acceptance testing for that component. It would
23 | have to be something that would provide assurance to the
24 | company and to the agency that the change was okay to make
25 | without the agency reviewing the data up front. It could

1 | be applied to most types of changes, but it would have to
2 | be evaluated up front as to what sort of testing is going
3 | to be performed. So, it would really be unique, at least
4 | in my way of thinking right now, to that product and to the
5 | type of change.

6 | DR. BYRN: Could it extend to multiple, say,
7 | equipment and site changes and so on?

8 | DR. SHEININ: Sure, it could, but SUPAC right
9 | now talks about site changes and equipment. I don't, at
10 | least right now, envision that as being a priority for the
11 | industry as opposed to other types of changes that are not
12 | covered, or even it could be a change that's covered under
13 | a SUPAC but a comparability protocol could reduce the
14 | regulatory burden further I guess. We really haven't
15 | gotten that far into the development of these.

16 | I was involved in what, looking back now, a
17 | number of years ago was essentially a comparability
18 | protocol for a company that wanted to be able to do certain
19 | packaging changes. They proposed a certain amount of
20 | testing, and we actually said, well, you're going to have
21 | to do more than this. We agreed on what they would have to
22 | do, and then I moved on to another job. So, I don't know
23 | if they ever used that protocol or not. But it was
24 | something that was negotiated and agreed upon through
25 | discussions with the company and the agency.

1 DR. BYRN: It also was mentioned that it could
2 go in with the NDA.

3 DR. SHEININ: It could be part of the original
4 application for a new product. For a product that's
5 already on the market, it would have to be a prior approval
6 supplement to get this into the application. Then when
7 they wanted to make that type of change, the burden would
8 be considerably less.

9 DR. BYRN: Now, did you want to say something,
10 Ajaz?

11 I just want to say one more thing and then see
12 if the committee has questions on this.

13 This is one of the research areas in PQRI under
14 the Drug Product Committee. That kind of research would be
15 both the type of research we're talking now, which would be
16 evaluate previous data and protocols that have already been
17 done. Was there envisioning that some of that research of
18 PQRI would be laboratory research, or has that been
19 defined? Maybe Ajaz could comment on this further, either
20 Eric or Ajaz.

21 DR. HUSSAIN: I think until the last technical
22 committee meeting, the Drug Product was considering a
23 comparability protocol. We call it "make your own SUPAC"
24 in the sense the company defines what are the criteria.
25 But I think that project has been moved to the Science

1 Management Committee right now. So, we're not planning any
2 lab-based experiments.

3 DR. BYRN: Do you want me to go ahead and ask
4 my questions on the other issues and then have open
5 discussion?

6 DR. TAYLOR: Well, I thought we were going to
7 talk about batch size.

8 DR. BYRN: Yes. Do you want me to go ahead
9 with that?

10 DR. TAYLOR: Yes, and the case C dissolution.

11 DR. BYRN: The second question I had was could
12 you go over the batch size issues, Ajaz, and just clarify
13 again the proposal is to make those multiple equipment and
14 process changes rather than batch size? And would that
15 affect the level of the change, or is that more of a
16 technicality?

17 DR. HUSSAIN: I have some examples that may
18 help clarify.

19 DR. BYRN: Okay, that might be good.

20 DR. HUSSAIN: Let me explain the batch size
21 scale-up situation and how it can be handled in a multiple
22 change category. I'll use the simple example of a direct
23 compression tablet formulation. So, you just look at the
24 blending operation, what is covered under scale-up for
25 blending. I'm using actual data from a published paper.

1 The process involved here is blending of drug
2 and excipients. It's a simple V-blender, and the company
3 wants to blend and scale-up. So, the small batch is a 20-
4 kilogram batch size. It uses a 2 cubic feet V-blender, and
5 they want to scale up to 120-kilogram batch size, which is
6 a 6X scale-up, using a 10 cubic feet V-blender. So, it's a
7 V-blender. It is within the same class, a subclass. It's
8 the same design, same operating principle.

9 The blending profile is simply a plot of the
10 coefficient of variation versus time of mixing. Samples
11 are collected from various different parts of the blender,
12 and here are the locations shown. So, at the end of 5
13 minutes or 10 minutes, the samples will be collected and
14 percent RSD is plotted as a function of time. So, you have
15 a blending profile.

16 Typical blending profiles can be categorized
17 into three classes.

18 One is called a stable blending profile.
19 You'll see variability decreasing, reaching a low, and
20 staying constant.

21 The second type of blending profile is
22 unstable. You'll see a decrease in coefficient of
23 variation in the content uniformity and then it takes off.
24 It goes up. So, you have V-blending process occurring at
25 the same time.

1 And the middle category is you see a steady
2 blending for a long period of time and then it takes off.

3 So, in this scenario, if you use the current
4 SUPAC which allows a 10X scale-up with no other change, so
5 processing parameters cannot change.

6 Now, for example, for the 20-kilogram batch
7 size, the company had chosen 30 minutes as the mixing time,
8 and they went ahead and validated that by making three
9 batches to show that you can do this. So, this is your
10 mixing time fixed. That's your processing parameter.

11 If you want to scale up now, and you find that
12 at the higher batch size you see a blending profile which
13 shows some degree of instability and you would prefer to
14 mix only for 20 minutes in this case, you cannot do that
15 under the current SUPAC because you have to change the
16 processing parameter.

17 What we are suggesting here is -- and look,
18 this was only a 6X scale-up, not even 10X. So, the current
19 proposal is to define a scale-up change would be to say
20 you're using the same design, same operating principle, you
21 can scale-up as long as you validate the scale-up process
22 and adjust your processing parameters to give you the
23 product. So, you have to meet the content uniformity and
24 process blend uniformity. So, that's your specification
25 that you have to do.

1 So, we would like to give flexibility to the
2 company, yes, you can scale up and not worry about 10X or
3 6X and so forth, as long as you validate this. So, that's
4 the example I wanted to present.

5 Obviously if you go to coating and other
6 operations, things get more complicated. I think you have
7 to change processing parameters. Here is a simple
8 blending. V-blender, small size, big size. You have to do
9 it. So, that's the example.

10 I'll stop here, and if you have any questions
11 on this.

12 DR. BYRN: Do you want to go ahead to the next?

13 DR. TAYLOR: Go ahead with this case C.

14 DR. BYRN: Okay. Ajaz, can we go ahead?

15 Several of the audience also made comments on case C
16 dissolution, and could you just go over what the proposal
17 is? And then we also were talking about these early time
18 points or early area under the curve points.

19 DR. HUSSAIN: Just some clarification. I did
20 show you what the current case C dissolution is. It's five
21 media. You have to have an f2 of 50 or above to get
22 approval on that.

23 My question to you is what would help you
24 explain? What we are proposing is instead of those five
25 media, we go down to probably two, use the current

1 application or compendial media, and probably suggest one
2 other pH condition where dissolution is likely to be slower
3 and hence more discriminating. That's the proposal.

4 Although the University of Maryland data
5 suggests that the application and compendial media was
6 sufficient, we didn't need the second medium. That's what
7 the data is telling us, but a question was raised from the
8 audience, have you seen failures? As part of generalizing
9 from six model drugs at the University of Maryland that we
10 did to the rest of the drugs that we have, we have been
11 looking at situations where we wanted to find failures.
12 The problem we run into is we don't have multi-media
13 dissolution profiles on the old products.

14 So, I have examples of failures in one media
15 for changes which are currently classified as level 3. You
16 are changing from wet granulation to direct compression,
17 thereby going from, say, lactose, microcrystalline-based
18 formulation to a dicalcium phosphate based formulation, and
19 you see failures of dissolution under those circumstances.
20 So, that's the reason we suggest or we feel that we would
21 like to see one more pH condition in addition to that.

22 Just to summarize, the current level 2 change
23 for components and composition is fairly stringent. It's
24 very well defined in terms of what percentage you can
25 change. So, under the situation that the second level, a

1 | level 2 change does not include a qualitative change --
2 | that means from lactose to dicalcium phosphate -- you
3 | really shouldn't have a problem.

4 | This is what the University of Maryland data on
5 | naproxen is. What you're looking at here is a ratio of
6 | percent drug dissolved at 10 minutes. The reference is the
7 | reference product, innovator product. On the x axis this
8 | is in vitro dissolution at 10 minutes as a function of Cmax
9 | ratio for the test product to the reference. So, you see,
10 | if you look at the confidence interval for bioequivalence
11 | that we have, 80 to 125 is our current goal post. You
12 | could slow down the dissolution quite significantly. Yet
13 | all the ratios remain, and these are bioequivalent
14 | products.

15 | Naproxen to some extent we feel behaves
16 | differently from other class 2 drugs. One reason is 95
17 | percent of the tablet is the drug. We don't have enough
18 | excipients probably to see such an effect.

19 | To give you an example, here is an example of a
20 | low solubility drug. This is the in vivo profile, blood
21 | level profile, mean estimate of a capsule which is the
22 | reference. It's a weak acid which exhibits very rapid
23 | dissolution. The current specification is simulated
24 | intestinal fluid, 50 rpm. The specification is 70 percent
25 | in 30 minutes. However, these products were all in

1 | solution within 5-10 minutes. So, you really don't see any
2 | difference in dissolution.

3 | Yet, the capsule and the wet granulation tablet
4 | based on starch were bioequivalent, but when you go towards
5 | a direct compression, dicalcium phosphate, the dissolution
6 | in one media did not pick up the difference, and you see
7 | bioinequivalence.

8 | This product was further modified. Now you're
9 | looking at the direct compression. The amount of dicalcium
10 | phosphate was reduced, and you added more microcrystalline
11 | cellulose as a surfactant. Then you're comparing it to wet
12 | granulation. The two products have different
13 | specifications. Yet, these are very rapidly dissolving.
14 | You really don't see much differences.

15 | What you are seeing here is product 1 and
16 | product 2, and the lower and upper 90 percent confidence
17 | interval compared to the original capsule reference. So,
18 | the direct compression, the low bound is 100 and it just
19 | misses the confidence interval for bioequivalence, 130.
20 | So, this was not bioequivalent, but you can see from the
21 | previous example changing to microcrystalline cellulose and
22 | surfactant increased the Cmax, and this is the original wet
23 | granulation product, which is bioequivalent.

24 | Although these changes are level 3 changes
25 | which require a biostudy, at least they give us a hint that

1 | we have to probably look at a medium which is more
2 | discriminating. Small intestinal fluid, pH 7.4, is not
3 | discriminating between these products for weak acids.

4 | Similarly you see a similar trend for weak
5 | bases. If you do dissolution in one medium of .1 normal
6 | HCl, you may not be seeing the differences.

7 | So, that's our proposal. Yes, the University
8 | of Maryland data suggests that current application and
9 | compendial media was sufficient, but when you try to
10 | generalize with the limited data that we have, there is a
11 | need for caution and there is a need for a second pH
12 | condition, at least one, maybe two.

13 | I hope I have clarified some of this.

14 | DR. ZIMMERMAN: Yesterday we had a very
15 | interesting presentation regarding whether or not the use
16 | of Cmax is an appropriate metric for a rate of absorption,
17 | and I think we were pretty well convinced that looking at
18 | early exposure, that is, early area under the curve -- it's
19 | unclear to when that area under the area under the curve
20 | stops, but may be a more appropriate metric for looking at
21 | absorption rate.

22 | I think it would be very interesting to look at
23 | the University of Maryland bioequivalence data using that
24 | metric as opposed to the simple Cmax and the AUC because I
25 | think we're pretty well convinced -- well, anyway, I was --

1 | that the early exposure is a much more sensitive indication
2 | of the absorption and Cmax is very insensitive.

3 | DR. HUSSAIN: I couldn't agree with you more.
4 | In fact, we have looked at Tmax for the University of
5 | Maryland data.

6 | The two model compounds that the University of
7 | Maryland used for class 2 drugs, naproxen and piroxicam,
8 | are long half-life drugs. In a sense I think you would see
9 | more sensitivity towards Cmax and Tmax for short half-life
10 | drugs.

11 | Here is a situation where I think again early
12 | exposure becomes an issue. You're looking at the plasma
13 | concentration profile of a weak acid. Again, dissolution
14 | was so rapid that the first sample was 100 percent. The
15 | first sample was collected at 5 minutes. And you're
16 | looking at three different products: immediate release 1
17 | and 2 -- these are capsules -- and immediate release 3 is a
18 | wet granulation tablet. And here is dissolution data.

19 | Weak acids compared to weak bases and probably
20 | neutral compounds are absorbed to a fair degree to a larger
21 | extent from the stomach itself. What you see is when you
22 | compare a solution versus a tablet blood level profile, if
23 | it's a weak base or neutral compound, the dissolution is
24 | rapid. Then you hardly see any difference between solution
25 | and tablet, but that's not the case for weak acids because

1 weak acid absorption is occurring from the stomach and weak
2 acid would be sensitive to gastric emptying differences.

3 Here is the situation where capsules appear to
4 empty out. This is simply a hypothesis based on this data.
5 Capsules appear to empty out a bit slower than a tablet
6 that disintegrates quickly and particles would come out
7 rather quickly into the small intestines. So, although in
8 vitro the dissolution was so fast that you couldn't
9 distinguish it, in vivo the tablet is getting access to the
10 higher -- going to dissolution quicker and probably
11 emptying out quicker too.

12 So, again, this would not be allowed under
13 SUPAC because we're looking at capsule versus table.
14 That's a major difference, but something to be cautious
15 about.

16 DR. TAYLOR: Dr. Byrn, had you exhausted your
17 questions?

18 DR. BYRN: Yes. I think that I've exhausted
19 the questions I have.

20 I just wanted to say that I think these changes
21 are reasonable. Comparability protocols are reasonable.
22 The batch size issues and the case C changes to two media
23 seem very reasonable to me. I'm sure other people might
24 want to comment, but it seems quite reasonable and I think
25 it was well explained too.

1 DR. TAYLOR: Other members of the committee?
2 Dr. Mayersohn?

3 DR. MAYERSOHN: Ajaz, what was the genesis for
4 the five dissolution media? What was the thinking there?

5 DR. HUSSAIN: I tried to ask the same question.
6 The only thing I could find was, although I was not there
7 at the workshop when that occurred, that was the
8 recommendation of the workshop. I don't have an answer for
9 that. My gut feeling is that it was based on monitoring
10 across the pH ranges available in the GI physiology.

11 DR. MAYERSOHN: Well, I completely agree with
12 your new recommendation. I don't see any reason for five
13 dissolution media. Three at the uppermost I would think.
14 Even that may be somewhat burdensome.

15 What is the concern about surfactants?

16 DR. HUSSAIN: The concern I have with
17 surfactants mainly pertains to soft gelatin capsules which
18 are oil filled. Most of the work we have done at the
19 University of Maryland and our internal research has
20 focused on solid, oral dosage forms which are hard gelatin
21 capsules and tablets. When you look at soft gelatin
22 capsules which are oil filled, it's a very challenging
23 thing to come up with a meaningful dissolution test. We
24 have products on the market which have 5 percent sodium
25 lauryl sulfate just to get some dissolution, and when we

1 recommend a second pH for such a drug, then the amount of
2 surfactant may not work for the second pH condition and
3 there needs to be some thought on what would be the viable
4 approach for addressing such drugs.

5 DR. MAYERSOHN: And this would be in the event
6 that no surfactant is used in a compendial standard
7 procedure?

8 DR. HUSSAIN: Correct. If there is a
9 surfactant used, then the question I have in my mind is the
10 second pH condition that we recommend, should it also
11 include surfactant at the same level or do we have to
12 figure out what the appropriate amount should be? Lack of
13 data is the reason why we are having some difficulty making
14 that decision.

15 DR. MAYERSOHN: Yes. It doesn't seem
16 unreasonable to include a surfactant.

17 DR. HUSSAIN: Yes.

18 DR. MAYERSOHN: There is another issue there
19 which the USP has been concerned about with regard to
20 gelatin and that's pellicle formation which now invokes the
21 need for pancreatin and pepsin. Is this part of your
22 concern at all?

23 DR. HUSSAIN: No. I think we have done
24 extensive research on that issue and we have a separate
25 group which is right now figuring out how to address that.

1 We have solved the problem. We have identified what amount
2 of pancreatin and enzymes would solve that. So, it would
3 be a matter of simply adopting that recommendation that
4 comes out from the other group or referring to it.

5 DR. MAYERSOHN: Finally, the issue, Larry, of
6 this 85 percent release that you criticized. Do you feel
7 that's a burden, that number, in practical terms? It seems
8 to me that holding a company to that rate of dissolution
9 may not be as serious a matter even with the examples that
10 you provided. Of course, you were trying to go out of your
11 way to screw things up. But in a typical situation -- and
12 you did a very good job.

13 (Laughter.)

14 DR. MAYERSOHN: In a typical situation, do you
15 view that as a real burden?

16 DR. AUGSBURGER: It's hard for me to make a
17 definitive statement about that. I only can say
18 anecdotally that some people that I've talked to would view
19 that as a burden, that it is an unnaturally rigorous
20 specification for a drug that has a lot of high solubility
21 and high permeability. Taken together with the biodata
22 that we saw, that doesn't seem to support that either.

23 DR. MAYERSOHN: Were you thinking of a
24 different number?

25 DR. AUGSBURGER: I hadn't thought to suggest a

1 different number, but I think you certainly could, if you
2 look at the data that we have, relax somewhat. Just to
3 throw a number out, maybe 75 percent in 30 minutes or
4 something like that would probably cover it and give you
5 some degree of safety, margin for error, so to speak.

6 DR. MAYERSOHN: Well, obviously, it's clearly a
7 qualitative debatable issue. I assume the 85 percent was
8 more to be conservative and that's why that number was
9 reached.

10 DR. AUGSBURGER: It just seems that for that
11 class of a drug, that's a very conservative number.

12 DR. TAYLOR: Yes, Dr. Brazeau?

13 DR. BRAZEAU: First of all, I'd like to commend
14 those individuals. I think these are very good steps in
15 the right direction. I think the comparability profiles
16 seem like a very reasonable approach in light of that
17 perhaps the sponsor has the data to make or develop
18 appropriate protocols. So, I would encourage the agency to
19 work towards that effort.

20 However, my one caution is, how much detail are
21 you going to require of the sponsors in these protocols? I
22 think that's something that's going to have to be
23 delineated.

24 The second issue is I do agree that the use of
25 buffers in the dissolution could certainly be simplified.

1 I think you can get the same amount of data with fewer
2 buffers that are carefully selected as long as you choose a
3 buffer that won't necessarily impact. You might have to be
4 careful with certain buffers with certain compounds.

5 The third issue that I wanted to raise that I
6 don't think anyone else has raised was this idea of
7 technical grade excipients. My only one concern with that
8 would be is, what about some of the safety issues, some of
9 the impurities that might be in the technical grades? I
10 don't know how those might impact, but we know that, for
11 example, some of the polyethylene glycols might have some
12 impurities. So, I would caution the agency on perhaps
13 looking at that.

14 Finally, I'd like to commend the agency on its
15 efforts in looking at other dosage forms and SUPAC
16 guidances, for example, with sterile aqueous solutions.
17 But I believe probably a more important one would be to
18 look at some of the suspension formulations where there
19 might be more variability and there might be more changes
20 when you talk about different suspending agents, different
21 surfactants that might be involved. To me that might be a
22 more relevant issue, with particularly those that are given
23 by the subQ or intramuscular route.

24 DR. TAYLOR: Other comments? Dr. Goldberg?

25 DR. GOLDBERG: Yes. As a former employee in

1 industry in both innovator and generic companies, I salute
2 the agency on the approach you're taking. I think this
3 morning's session is very relevant and very important.

4 I do want to caution us, though, on putting
5 things together. Yesterday we talked a great deal about
6 early time AUC. It was brought up by Cheryl. We now have
7 a good deal of opportunity to look at the early time data
8 from the University of Maryland, and I think that should be
9 looked at before any decisions are made.

10 The other thing I'd like to talk about is, are
11 the same concepts that are used in SUPAC used during the
12 IND stage where we do make changes to all these steps that
13 we were talking about, batch sizes, equipment changes?
14 When they make changes in their IND, do they follow the
15 same sort of rules as SUPAC does?

16 DR. SHEININ: It's a very interesting question.
17 We have had discussions on how can we apply SUPAC which is
18 more for post-approval changes to the pre-approval arena.
19 At least I think we've been more concerned with changes
20 during maybe the NDA stage than the IND, but certainly it
21 has the same impact.

22 For the most part, though, in the IND right
23 now, companies are making changes like this and merely
24 reporting it in the annual report, or if it's a significant
25 change, perhaps they might do it in an amendment.

1 But we have a guidance on phase I INDs that's
2 out. It has been out for about two years now that talks
3 about what sort of information needs to be in a phase I IND
4 for all disciplines, not just chemistry. The key aspect
5 that we look at during the IND, especially phase I, is, is
6 this a safety issue? Is there something in the application
7 that leads us to believe there might be a problem with
8 administering this product to human beings that there could
9 be a safety issue? As they go through the various IND
10 phases, into phase II and phase III -- and the phases are
11 kind of running together these days, but the emphasis that
12 we're trying to place on material that we get and how we
13 review it again is, is this a safety issue?

14 I think most of these types of changes are not
15 going to be what we would call a safety concern. So, we
16 don't have a formal mechanism as we do post-approval right
17 now in how we go about reviewing what goes on during the
18 IND and what sort of information and how much and how much
19 testing the company has to provide, but it is something
20 that we're interested in.

21 And we are working on a guidance for chemistry,
22 manufacturing, and controls information that should be
23 included or is recommended for inclusion during phase II
24 and phase III. That was the subject of a workshop that we
25 held last December, and we're still in the process of

1 | drafting guidances in those areas.

2 | DR. TAYLOR: Thank you.

3 | Dr. Vestal?

4 | DR. VESTAL: Just briefly I'd like to
5 | underscore the points made by Dr. Zimmerman and Goldberg.
6 | In looking at the data from the University of Maryland,
7 | which I agree are nice data, it's hard to believe that the
8 | very slow dissolution formulations would not influence
9 | early exposure. So, really I agree that I think those data
10 | should be looked at carefully from that perspective and, if
11 | necessary, additional studies be performed with other
12 | compounds.

13 | DR. TAYLOR: Dr. Goldberg?

14 | DR. GOLDBERG: Yes. I would also recommend, as
15 | long as we're going back and looking at the University of
16 | Maryland data, as has been suggested, that we look at not
17 | only early exposure in terms of AUC, but compare ratios of
18 | Tmax's as well.

19 | DR. TAYLOR: I want to emphasize to the agency,
20 | particularly since a lot of the importance is put on the
21 | University of Maryland data, and given the comments of the
22 | sponsors and various individuals in the audience for its
23 | relative lack of availability, it is impressive data and
24 | important, and if regulatory decisions are going to be made
25 | on it, it has to be made freely available. Even though

1 | it's in the literature to some degree, I think there has to
2 | be an opportunity for sponsors to look at it.

3 | Yes.

4 | DR. VESTAL: It seems to me actually that those
5 | data ought to be put together in a single report. That
6 | would make it much more accessible and much more valuable I
7 | think to people, even the data that have been published in
8 | individual articles in the literature.

9 | DR. TAYLOR: I think that's a good
10 | recommendation.

11 | Dr. Byrn?

12 | DR. BYRN: Yes. Just to go on -- and I was
13 | going to mention this, but it's clear how important
14 | research like this is for regulatory decision making, and
15 | it's apparent to me that PQRI offers an opportunity to
16 | continue this kind of work and possibly this could be one
17 | of the first activities under PQRI, to assemble this data
18 | and possibly analyze it in terms of early exposure issues.

19 | I think it shows sort of a spinoff of the type
20 | of regulatory research. I don't think any of this Maryland
21 | work was done to understand early exposure issues, and it
22 | probably wasn't conceived on that basis. Maybe it was,
23 | Larry. But now here we have a body of research that's
24 | available and now can be used to make regulatory decisions,
25 | and I think this supports Roger's concept of science to

1 regulatory decision making in a strong way, and I just want
2 to encourage that this should continue.

3 DR. TAYLOR: Dr. Brazeau?

4 DR. BRAZEAU: I'd like to support Dr. Vestal's
5 idea of compiling because there are a lot of very good
6 minds out there that could also take a different
7 perspective and look at this data, and if this data is
8 available in a single source, I think it could address many
9 of the issues we've talked about over the last two days.

10 DR. TAYLOR: Thank you.

11 Any other comments from the committee?

12 (No response.)

13 DR. TAYLOR: If not, I'm going to ask Dr. Roger
14 Williams to provide some perspective, if you would, at this
15 point.

16 DR. WILLIAMS: If I could speak to the Chair,
17 I'd like to add some comments to this discussion, and then
18 I'd like to make some general comments, if that's all
19 right.

20 DR. TAYLOR: Yes, that's fine.

21 DR. WILLIAMS: I've been listening to this
22 discussion and I didn't say much. That's sort of
23 uncharacteristic for me. But I really wanted to hear what
24 the committee had to say about the presentation. First, I
25 want to make some quick general statements.

1 First of all, I do want to congratulate the
2 University of Maryland and the Industry Liaison Committee
3 that gave oversight to that work and the agency staff who
4 participated in it because it's such a remarkable data set.
5 If you think about it, it goes back to things we discussed
6 six or seven years ago which is the need for publicly
7 available data to support our regulatory policy. I think
8 that whole concept has informed many of our subsequent
9 discussions, but certainly the University of Maryland is to
10 be congratulated for doing this work.

11 The second thing I want to talk about is how
12 complicated all this is. I mean, we're really struggling
13 with a lot of things here. In some ways you've got to go
14 back to those three questions that I alluded to at the very
15 beginning of the talk yesterday.

16 Now, in that context, I'd like to say one of
17 the things you obviously see here is an industry who wants
18 to change. This is an industry who wants to change post-
19 approval, to take advantage of consolidations, people are
20 buying each other. They're moving to a single
21 manufacturing plant in Singapore, et cetera, et cetera.
22 And also a need to upgrade their equipment and come to the
23 most modern and efficient ways in making high quality
24 products. I think in that sense the agency is totally in
25 tune and we want to come to the right set of tests given a

1 certain change, and that's what informs the SUPACs.

2 I might argue there is the consumer argument
3 here, and I feel like turning to Dr. Walkes because she's
4 our consumer representative on this committee. I think she
5 as a practicing physician understands fully the need to
6 have a product, say, 10 years after it enters the
7 marketplace, have a set of quality characteristics that
8 clearly relate to the safety and efficacy database that's
9 in the labeling. And I'll talk more about this in some of
10 my general comments.

11 So, there's a lot of things that we're
12 balancing here.

13 Now, one of the things I see is the second
14 question, what are we willing to rely on? What I see Ajaz
15 asking for in the proposal is we are willing to rely on a
16 lesser set of dissolution testing for case C. Of course,
17 the immediate public health question comes up: If we do
18 that, will we miss some things, and will we especially miss
19 some things in the context of the need for rapidly
20 dissolving products that we talked about early exposure
21 yesterday. So, these are all things that I think we have
22 to balance in the context of the public discussion.

23 The other thing that I think Ajaz proposed was
24 not so much related to the three questions but a different
25 way of defining the type of change, and I think what you're

1 | proposing is that instead of an arbitrary scale-up number
2 | like 10X or 100X, we're going to move away from that
3 | completely and go to a different way of controlling quality
4 | in the presence of batch size.

5 | Now, I would say that's not one of the three
6 | questions. I have to think about it, but I don't think
7 | it's one of the three questions. I think it's a different
8 | way of looking at, given the question of batch size, how do
9 | you control it from a quality standpoint.

10 | The final thing I want to say, as we talk about
11 | the specific thing, is I have to admit I have some disquiet
12 | about the comparability protocol depending on how we think
13 | about it. Let me see if I can explain why I have that
14 | disquiet.

15 | If you think about what this committee has done
16 | over the last several years, it's debate in a public sort
17 | of way the general approaches as embodied in SUPAC, that if
18 | you want to make a change, you do this level of testing and
19 | this level of filing requirement.

20 | Now, what does a comparability do but create an
21 | alternate approach which is sort of a private agreement
22 | between a sponsor applicant and an individual review
23 | chemist. Now, think about that for a minute because I
24 | don't think it's a question for the committee. I actually
25 | think it's an administrative question, first of all, for

1 | the agency. But there are about 100 or more review
2 | chemists in the agency, and what you will have now is kind
3 | of everybody kind of reaching their own conclusions about
4 | the level of testing, the level of change, and the level of
5 | filing requirements.

6 | Now, I guess I'm now going to speak personally
7 | as kind of the obstruct. If I'm willing to tolerate that,
8 | as long as we have some boundaries of what's permissible,
9 | but the more those boundaries get away from the general
10 | approach, as embodied in SUPAC, the more nervous I'm going
11 | to be.

12 | In some ways we've talked about this before in
13 | the committee, and you've heard perhaps Bill Barr talk
14 | about it. He talks about the mapping approach, and I think
15 | in some ways we're talking about mapping, that if you can
16 | create boundaries for your critical manufacturing and
17 | formulation variables and show that across those boundaries
18 | you have two bioequivalent products, that's okay. But that
19 | necessarily involves performance of an in vivo
20 | bioequivalence study.

21 | So, if that's the kind of boundary we're
22 | talking about in the comparability protocol, I could say
23 | yes, but the more we deviate from that, the more concern
24 | I'm going to have about these case-by-case approaches.

25 | That was a very long-winded statement covering

1 a number of topics, but I hope you get a sense of what I'm
2 struggling with.

3 DR. TAYLOR: Thank you.

4 Are there any comments from the committee
5 regarding Dr. Williams' comments just made? Dr. Byrn?

6 DR. BYRN: I just had one idea related to this.
7 I see your point exactly on the comparability protocol. I
8 wonder if -- it's more of an administrative approach would
9 be to have like a study section or a committee that would
10 review the first X number of these to try to establish
11 boundaries, and then once the boundaries were established,
12 then maybe certain SUPACs or new material would come
13 forward based on those boundaries, but some kind of review
14 committee approach might offer an approach while still
15 providing flexibility.

16 DR. BRAZEAU: I would concur with that, but you
17 might even be able to, if you had some real severe issues,
18 take it to a committee like this on some of those things
19 and bring out some of those issues and discuss the proposed
20 protocols based on the data. I think you could do some
21 initial good investigation with the first few protocols
22 that came through.

23 I like the idea, if I'm reading it correctly,
24 of even them being in the ANDA or the NDA. I think that
25 would be useful.

1 DR. BYRN: One other comment that I think Roger
2 made that I really think is important that we have to deal
3 with is -- and I'll just state it in a different way --
4 this idea of a lot of the small incremental changes in a
5 drug product will take it 10 years away from what it was
6 originally unknowingly to anybody. You could imagine a lot
7 of little 10 percent changes pretty soon become 100 percent
8 changes. Of course, I think we know that some of this has
9 happened with old products. Certainly issues have been
10 related to old products.

11 So, we've got to be aware in all of this that
12 we don't allow this to happen. I'm not sure how we're
13 going to put checks and balances in, but I do think we've
14 got to make sure whether every 10 years we go back and
15 compare it to the original blood level data. I'm not sure
16 how we do that, but maybe that's too much trouble. But we
17 need to be aware that this kind of thing can happen.

18 DR. TAYLOR: Dr. Sheinin, would you like to
19 make some comments before we close out?

20 DR. WILLIAMS: I just wanted to add another
21 couple comments. First of all, I think those were very
22 valuable suggestions, and we'll certainly proceed. I think
23 some of the proceeding of things like what Gayle is talking
24 about and you're talking could happen in PQRI in that
25 Science Management Working Group working on the

1 comparability protocol.

2 The other thing I want to say is there is this
3 concept of extrapolation from the University of Maryland
4 database, and I use the word carefully. It's
5 extrapolation, not interpolation. I think there's the
6 concept of extrapolation from these five or six model drugs
7 we used to the 2,500 or so new medical entities that we
8 have in the marketplace. Now, there's a risk there and I
9 think we all have to acknowledge that risk.

10 There's also the concept of extrapolation of
11 relying on dissolution as the canary in the mine, and I
12 think there's the University of Maryland database that
13 gives us great comfort there.

14 But there's also the concept that the
15 University of Maryland database was sort of a mapping
16 concept itself, and if you go outside those boundaries, our
17 willingness to rely on dissolution -- the question
18 associated with that I think increases in the public health
19 concern.

20 DR. TAYLOR: Our consumer representative, Dr.
21 Walkes?

22 DR. WALKES: A couple of people asked questions
23 about the role of the field investigators, and I wonder, do
24 they help police all of these changes that we're worried
25 about, the small incremental changes?

1 DR. ELLSWORTH: I guess, if this is an
2 appropriate place to speak from, the short answer is yes,
3 they do look at those issues, but it is getting more
4 complex as multiple changes are being made and we
5 definitely have to increase communication between the
6 center and the field to assure that the field understands
7 the science behind a lot of these changes and can look into
8 the records to make sure -- look into the manufacturing
9 processes to basically police to make sure that they're
10 following the guidances and the data that firms have
11 support what the firms are doing.

12 DR. WALKES: They also mentioned harmonization
13 between other world systems. I guess that's in a nutshell
14 what they were talking about and also questioned whether or
15 not they were going to be penalized for looking at new
16 equipment and new production systems, and I don't think we
17 talked about that any.

18 DR. TAYLOR: I guess the issue is harmonization
19 and new technologies? Is that basically --

20 DR. WALKES: Yes.

21 DR. TAYLOR: In terms of these changes in
22 SUPAC. Could you comment on that please?

23 DR. WILLIAMS: I could say a few words about
24 it. Maybe I could say those few words in the context of my
25 general comments?

1 DR. TAYLOR: You can.

2 Any further discussion of the SUPAC issue
3 before we go into, I guess, general comments? Is that
4 right, Roger?

5 DR. WILLIAMS: These are more general comments.

6 DR. TAYLOR: Okay. So, we're going to
7 generally close out the discussion of the SUPAC. I think
8 we had an excellent discussion of that, a very robust
9 discussion, and we look forward to some change in the
10 agency in terms of implementing some of these efficiencies
11 in the original SUPAC.

12 So, now we're going to go to some general
13 comments that Dr. Williams would like to present to the
14 committee.

15 DR. WILLIAMS: I'll try to keep these comments
16 to just a few minutes, but I think one of my roles, vis-a-
17 vis the committee, is to step back a little bit every now
18 and then and sort of say what have we all been doing here
19 collectively for the last several years.

20 First of all, I'd like to start out by saying
21 in some ways it's a celebration of the FD&C Act and I think
22 some parts of Hatch-Waxman. I'll try to talk about that in
23 a second. I was just thinking, as I was sitting here
24 talking, we're in our 60th year of the Food, Drug and
25 Cosmetic Act. So, it's really quite a remarkable social

1 | document, and I can't say I've ever read it, but I live
2 | with it daily. It has many aspects of it that are quite,
3 | quite powerful, and I see this in my role in working with
4 | other countries and it relates to what Dr. Walkes talked
5 | about in terms of harmonization.

6 | Now, first of all, it's like you're always
7 | splitting and grouping and splitting and grouping. First
8 | of all, there are drugs and then there are new drugs that
9 | exist within a drug product. Certainly we regulate new
10 | drugs as opposed to the pre-1938 old drugs.

11 | I would say one of the things we struggle with
12 | very deeply in this committee over the years is this
13 | concept of post-approval change. It's going to come up in
14 | the next section of the meeting. I would argue that we
15 | know, as a result of some of our discussions over the last
16 | eight years, have a fairly evolved concept of post-approval
17 | change and how you control it. I would argue that the
18 | motivation for that concept came about as a result of
19 | Hatch-Waxman in a very intensive way because you can think
20 | about an abbreviated application as just a big post-
21 | approval change. Now, I don't want to sound too
22 | threatening about it, but that's sort of what it is.
23 | Sometimes the post-approval changes you see with ANDAs are
24 | less than the post-approval changes you see happening to a
25 | pioneer. So, I think we can also say that that occurs.

1 So, this whole concept of post-approval change
2 came about in a very evolved way, and this committee has
3 worked with it both in the realm of the ANDA, as well as in
4 post-approval change for both the ANDA and the NDA in a
5 very powerful way, resulting in the SUPACs, the BACPACs,
6 the PACPACs, things that we'll talk about in various ways.

7 Now, I think it's all based on a very good
8 discussion of the science relative to the question, and
9 what are you willing to rely on and how confident do you
10 need to be in the answer?

11 It imposes a big burden on industry, as we're
12 all aware. So, I think we're all trying to be sensitive to
13 the need to reduce our burden, at the same time being able
14 to assure the practitioner and the patient that we do have
15 stability in the quality and performance of the product.

16 I will close these brief comments by saying a
17 lot of what happened in this committee -- and Tom White
18 alluded to it -- related to the REGO initiatives that
19 talked about SUPAC in particular and the other SUPACs.
20 Those REGO initiatives were codified in the Food and Drug
21 Administration Modernization Act of 1997 under section 116.
22 So, if this committee likes to think about it, I would
23 argue that as a result of their science and technical
24 deliberations, we have now come to an update of the Food,
25 Drug and Cosmetic Act. So, I congratulate you all. You

1 | may not have realized that was exactly what you were doing,
2 | but I think that is exactly what you were doing.

3 | Now, I want to come to what Dr. Walkes asked
4 | me, which is what about harmonization. In a world of a
5 | globalizing industry, do the SUPACs have international
6 | relevance? And I can tell you they do indeed. I go to
7 | countries all over the world and they're delighted to have
8 | SUPAC. Of course, it's instantly available to them on our
9 | Internet, and it gives them something to use as they work
10 | with their own regulatory authorities sort of in the
11 | context, well, FDA thinks this is okay, you should too,
12 | guys. Now, of course, their regulatory authorities say, I
13 | don't care about what FDA thinks. I'm gong to ask you to
14 | do this.

15 | But that, of course, then leads to your direct
16 | question of what about harmonization. Europe has the
17 | concept of variations and changes, so they use a different
18 | set of words. We use post-approval change. They use
19 | variations and changes which is a more heterogeneous
20 | category of changes than just the PACs that we talk about
21 | here. But certainly a lot of those variations and changes
22 | relate to the PAC concept that we talk about here.

23 | They have something called level 1 and 2, type
24 | 1 and type 2 variations and changes. That's exactly like
25 | our level 1, 2, and 3. We have three levels. They have

1 two.

2 Then you get into the issue of filing
3 requirements. We have three filing requirements: PAS,
4 CBE, and annual report. They actually have a thing which
5 is like a supplement and then a notification. So, their
6 filing requirements are less burdensome. But I could
7 easily imagine that harmonization on some of these things
8 could occur, and it actually has come up in the context of
9 the International Conference on Harmonisation. So, who
10 knows? Maybe 5 or 10 years from now, we'll be dealing with
11 a single global approach as to how you control the quality
12 of a product in the presence of post-approval change.

13 Now, we could talk a lot more about this, and I
14 have a feeling we will come back before this committee and
15 talk about many of these things again and again.

16 Now, something that's kind of fun that I just
17 want to close these comments with is -- and this is
18 intended to drive you crazy. The PAC concept is based on
19 the basic principle that we expect the quality and
20 performance of the approved drug to stay the same in the
21 presence of post-approval change to include the generic.
22 Now, that is a very deep concept that affects here and
23 affects here, and as I say the Hatch-Waxman concept dealt
24 with that in a very clear way. So, innovators and generics
25 are sort of struggling with, well, how do you do this? And

1 I think the PAC approaches are working to tell them how to
2 do this. Some of these concepts perhaps were as startling
3 to innovators as they were to generics, that after approval
4 we expect stability and quality parameters.

5 But I don't know how you can have a generic
6 system if the pioneer reference product is kind of moving
7 around. You know, it just doesn't make sense. So, you've
8 got to fix the pioneer, and that was the essence of Hatch-
9 Waxman. Hatch-Waxman required us to fix the performance of
10 the pioneer just as it required us to fix the generic
11 equivalent to the pioneer. These are things that grew out
12 of Hatch-Waxman whether we wanted them to or not.

13 Now, just a small digression into the routes to
14 the market. The people who constructed Hatch-Waxman I
15 think were some very brilliant social thinkers, and they
16 allowed small differences in an abbreviated application
17 that allowed some differences as long as you don't require
18 clinical trials.

19 This is a route that we lovingly call the j2c
20 petition process. There's a suitability petition where
21 somebody can come in and go from an immediate release, say,
22 to a solution or a suspension. Now, that's a very
23 interesting change in the context of some of the
24 discussions we've had here in early exposure and what are
25 you really doing? Maybe for some drugs you need clinicals.

1 So, we might want to refine our concepts of small
2 differences that don't need clinicals, and I could imagine
3 coming back before this committee and discussing that,
4 perhaps with some safety and efficacy people from the
5 center. It's obviously not just a quality question.

6 Now, there is this world over here of the b1,
7 but we also in Hatch-Waxman allow the concept of b2, which
8 allows some differences for a new drug. This is not a
9 generic concept, but the differences relate to whether
10 you're relying or not on the -- you don't have right of
11 reference to the pioneer product's data, but you're relying
12 on the safety and efficacy judgment of the agency.

13 Now, that is a very powerful concept where I
14 would say the social framers of the Hatch-Waxman said that
15 for all people we will allow improvements in a pioneer
16 product or new indications for a pioneer product even when
17 it's not your molecule. That's sort of the essence of it.
18 Whether we all agree with that or not, this is the law of
19 the land now, and we can certainly allow it.

20 Let me give you a specific example: isolation
21 of an enantiomer from a racemate or going to a controlled
22 release produce from an immediate release product, going to
23 a subset of a mixture from a parent mixture. Now, all
24 these things should strike either terror or excitement in
25 your heart depending on where you're sitting. Sometimes

1 they strike terror in my heart, but it's a very interesting
2 concept there, and I have a feeling we will also come back
3 before the committee sometime and talk about these
4 concepts.

5 Okay, that's all I wanted to say. But it's a
6 very interesting world, and this committee struggles with
7 this world in many different aspects.

8 DR. TAYLOR: Thank you very much. Those are
9 very enlightening and stimulating comments, and I'm sure we
10 will see them again perhaps even in the next meeting.

11 I think we need to wrap up this morning's
12 session. We're way ahead of time, but I think we've had a
13 really detailed and interesting and stimulating discussion.
14 I would allow the committee to make some final comments at
15 this time if you would like to in response to the general
16 comments made by Dr. Williams, if there are any.

17 (No response.)

18 DR. TAYLOR: Okay. There being none, I would
19 like to have our lunch break start early -- it's quite
20 early actually -- and then have us come back early for the
21 afternoon session. We're about 30 minutes ahead of our
22 lunch schedule. So, I would like to come back to begin the
23 afternoon session at about 12:30, unless there is some
24 severe objection to doing so. We were originally scheduled
25 to come back at 1 o'clock. Any problems? The convener of

1 | the afternoon session, are there any problems with starting
2 | at 12:30 instead of 1 o'clock? Okay.

3 | Well, we will come back at 12:30. So, we'll
4 | break for lunch now. We will start at 12:30 sharp. Thank
5 | you.

6 | (Whereupon, at 11:20 a.m., the committee was
7 | recessed, to reconvene at 12:30 p.m., this same day.)

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1 AFTERNOON SESSION

2 (12:30 p.m.)

3 DR. TAYLOR: Good afternoon. If you'll take
4 your seats, we'll begin our afternoon session.

5 The afternoon session is entitled Complex Drug
6 Substances. This is an area I think we discussed two
7 meetings ago, and I think we generated a lot of interest
8 because we feel that a number of the drugs for the new
9 millennium will fit in this category. We applauded the
10 agency for developing a strategy to dealing with them early
11 on.

12 The overview for this topic will be given by
13 Roger Williams.

14 DR. WILLIAMS: Thank you. I'm pleased to go
15 into kind of the last major discussion of this very helpful
16 meeting.

17 I will start out by showing my favorite slide.
18 Again, I'll remind the committee that I think we've moved
19 through a very interesting declension of discussions at
20 this level through the discussion at the level of exposure.
21 This morning we talked about the drug product in the
22 context of change, and now we're going to move inside the
23 drug product to the active moiety. Perhaps the most
24 important part of this slide is the plurality of that word
25 right there because that's the essence of these complex

1 drug substances.

2 Now, the next overhead I'm going to show, first
3 of all, I will emphasize that this is a draft overhead.
4 This is my own attempt to explain perhaps for me, as well
5 as anybody else, what we're sort of dealing with here when
6 we talk about complex drug substances.

7 Now, first of all, I'll start out by saying
8 that this little squiggle here is another manifestation of
9 my natural tremor and it's supposed to represent
10 impurities. There's sort of a boundary line between
11 impurities and things that we care about which I call
12 moieties. If we start over here at the very simplest
13 concepts, we talk about perhaps an enantiomer of a
14 racemate, perhaps the pure expression of a single molecule
15 that creates the safety and efficacy that enters the
16 labeling.

17 I'll move through the declension fairly
18 quickly. Then you get to the racemate. After that, you
19 get into more complicated situations, and a lot of these
20 complicated situations you'll hear about from the
21 discussants, many of whom are quite sophisticated as they
22 talk about these topics because they've been working with
23 them for many, many years both from the Center for
24 Biologics, as well as the Center for Drugs.

25 Some of the terminology that you see that I'm

1 beginning to use here in a draft preliminary way comes from
2 an ICH document that is in step 2, which means it's not
3 final. It was published Gown 9, 1998, so you can see it's
4 a very recent document, for public comment.

5 So, let's move down in that context to some of
6 these other things. Now, here I think you have a non-
7 glycosylated protein, for example, insulin or growth
8 hormone, that has the major molecule here but may have some
9 subsidiary peaks that could be product related substances.
10 I think this is a terminology the Q6b uses, and some of
11 these could be post-translational or manufacturing. But
12 they relate in some way to the major moiety that's creating
13 the safety and efficacy effect, and they shouldn't be
14 considered impurities.

15 Over here you get to a glycosylated protein
16 which may be a mixture of more equivalent types of moieties
17 that create the pharmacologic effect. Over here you get
18 the complex mixtures, and here I think we're talking about
19 things like biologic extracts, for example, conjugated
20 estrogens which this committee has struggled with on many
21 occasions, and botanicals. I might argue that the issue
22 there relates to characterization whether it's fully
23 characterized, partially characterized, or perhaps in the
24 case of a plant extract not characterized at all but simply
25 defined in terms of its chromatographic fingerprint.

1 Now, let's go on because I'm trying to set the
2 stage so that you understand some of these terminologies.
3 But I do want to point that again we're talking about
4 issues that relate to post-approval change, but certainly
5 before we get to post-approval change, there are issues of
6 characterization and setting specifications, so you read
7 that as Q6A and B. These are the ICH documents that deal
8 with those issues. There is the review process where the
9 agency agrees with the applicant/sponsor about those
10 specifications, and then you get into the world of post-
11 approval change.

12 Let me just say one more thing before we get on
13 to the next overhead.

14 Now, when we talk about post-approval change, I
15 think the committee will feel entirely comfortable when we
16 talk about these complex moieties because in some ways
17 they're going to be very similar to the discussions we had
18 for drug products as opposed to drug substances. It will
19 always come to a question of tests, levels of change, tests
20 needed to document sameness, and then filing requirements
21 which, of course, are less of a concern to the committee.

22 I think when we start talking about it, the
23 committee will even see that the tests needed to document
24 sameness in the presence of post-approval change for a drug
25 product are entirely similar to the tests you would apply

1 | to a drug substance, namely physical-chemical tests,
2 | pharmacokinetic/pharmacodynamic tests, comparative clinical
3 | trials.

4 | So, there's a lot of correspondence here, that
5 | as we descend into this discussion with the committee over
6 | the coming meetings, I think there will be a lot of comfort
7 | on the part of the committee in terms of the issues that
8 | we'll talk about and the three basic questions.

9 | Now, let me go on. By way of introducing the
10 | next speaker, I'd like to introduce Dr. Yuan-Yuan Chiu who
11 | will talk about this new coordinating committee -- and I
12 | can tell you it's quite new in the center -- in terms of
13 | its areas of focus and how we're going to start working,
14 | hopefully, with this committee over the coming months and
15 | years in delineating ways to control the quality of these
16 | drug substances in their drug products. Dr. Chiu is a Co-
17 | chair of this committee with me and also a Deputy Director
18 | in the Office of New Drug Chemistry reporting to the Dr.
19 | Sheinin. Yuan-Yuan?

20 | DR. CHIU: Good afternoon.

21 | To follow up what Roger has said, first I'm
22 | going to show you what types of complex substances we're
23 | talking about. The first kind we're talking about is
24 | multiple chemical constituents of small molecules which, as
25 | was alluded earlier, could include conjugated estrogen

1 mixture from the natural source and also botanical products
2 which will remain crude extract. We do not mean drugs
3 purified from plants which is a small molecule and a single
4 component. That will be not considered a complex
5 substance.

6 The second type would be single component of
7 macromolecules. That would include proteins,
8 glycoproteins, polysaccharides, oligonucleotides, peptides.

9 And the third kind would be multiple chemical
10 constituents of macromolecules. That would consider
11 glycosylated proteins which could have many more isoforms.

12 Then the last one would be other types. As an
13 example, it would be like cell metabolites from recombinant
14 DNA technology. As an example, one can have antibiotics or
15 one can have vitamins produced by genetic engineered cells.

16 So, if you divided them into how they're
17 derived, we can separate them into several categories. One
18 is natural products. I have already mentioned conjugated
19 estrogens. One can also have lung surfactants from bovine
20 lungs which is a mixture of lipids, proteins, and the
21 phospholipids, and very much uncharacterized. Then one can
22 have heparin which would be polysaccharides derived from a
23 pig source. Then one can have proteins and glycoproteins
24 derived from animal or human tissues, body fluids, or
25 organs. Then plant chemicals which I mentioned earlier,

1 and then one also can have naturally derived liposomes,
2 phospholipids. They can form monolayer, bilayer vesicles.

3 Then the second source could be based on a
4 recombinant DNA fermentation process. Then one can use the
5 E. coli, genetic engineered mammalian cells, or yeast to
6 produce proteins, glycoproteins, cell metabolites. CDER
7 has the jurisdiction for regulating all the hormones.

8 Then the third category would be hybridomas.
9 The monoclonal antibodies can be used as the reagents in
10 the purification of proteins or other substances. The
11 antibodies itself as a therapeutic agent would be regulated
12 by CBER. However, the antibody and the drug conjugate when
13 the antibodies serve as targeting agents, tissue targeting,
14 they would be regulated as drugs.

15 Then the last one, one can also have the
16 synthetic macromolecules, such as the peptides,
17 oligonucleotides, and the biopolymers.

18 Therefore, when we consider complex substances,
19 we include drug substances which are active ingredients,
20 excipients, and reagents.

21 Why do we need a new coordinating committee to
22 address complex substances? I list the following reasons.

23 First of all, for this type of substances, the
24 chemical identity is often uncertain because if you look at
25 small molecules, you can use very precise methodologies

1 then to determine unequivocally you have the right
2 molecule. However, when you talk about a mixture of
3 macromolecules, the analytical tools often become
4 insufficient to give you the total information on its
5 identity. When you're talking about macromolecules, you
6 not only talk about primary sequence of a protein, you need
7 to address the secondary and tertiary structure and its
8 confirmation. When you talk about mixtures such as
9 conjugated estrogen or botanical extracts, many of the
10 active ingredients are not defined, and many of the
11 constituents, the chemical structures are not known. So,
12 therefore the chemical identity becomes quite uncertain.

13 In the second unique point, unique character is
14 often because the chemical strength means the amount of the
15 substance is not necessarily tells you whether the product
16 would be efficacious. So, you need to consider potency
17 which is determined by the biological assay to determine
18 its activity either in vitro and in vivo. And you would
19 like to have that assay to be clinically relevant, and
20 sometimes it's not that easy to derive a clinically
21 relevant assay.

22 Then the third element is product sometimes
23 defined by process when chemical identity is not easy to
24 determine. When you make manufacturing changes, you may
25 not be able to say you still have the same product.

1 Sometimes you may, sometimes you may not.

2 Also when you have mixtures, when you change
3 the process, then the constituents of the mixture may be
4 different. When you have macromolecules, when you modify
5 the process, then the molecule may be also modified because
6 of the manufacturing step you introduce. If you cannot
7 characterize those product related substances, it's hard to
8 say you still have the same product.

9 Then a special consideration about safety,
10 which is unique to biomolecules, is you will need to
11 consider contaminants. Contaminants may be of viral
12 origin, or if you have an animal or human source, then you
13 may want to consider whether it could be contaminated by
14 TSE. In humans, you will worry about CJV. If it is a
15 bovine source, you may worry about BSE. So, there are
16 special safety concerns.

17 In addition, if you are not sure of the
18 confirmation or the modification of a protein occurred,
19 then you may be facing the immunogenicity issue whether the
20 changes will create different immune responses.

21 So, to characterize a molecule or to
22 demonstrate pharmaceutical equivalence, sometimes you may
23 need consideration beyond just chemistry, CMC. Even though
24 we're not talking about a dosage form change, you may still
25 need to consider PK/PD because there are a lot of data out

1 | there when the chemical data demonstrate you have the same
2 | molecule. However, in vivo the PK/PD may be different.
3 | This is also often true for isoforms like glycoproteins.
4 | When the glycosylation is varied, then the clearance in
5 | vivo will be different. As I alluded to, because of
6 | impurities profile or modification of the active moiety,
7 | then created safety concerns, then sometimes
8 | preclinical/clinical data may also be useful.

9 | In terms of when changes are made during the
10 | IND stage, the agency, CBER/CDER, published a guidance
11 | document called a comparability document which addressed
12 | during the IND stage if changes occurred, and what kind of
13 | procedural framework one can follow.

14 | The last and not the least difficult part of
15 | complex molecules is orphan drug sameness because under our
16 | regulations, when you have a macromolecule -- mono changes
17 | of the molecule under orphan drug, you may still consider
18 | the products still remain the same, which is completely
19 | different from the way we interpret pharmaceutical
20 | equivalence. Therefore, often it's very difficult to
21 | address what is the same, what is different under orphan
22 | drug regulations.

23 | For this reason, -- the previous slide -- the
24 | first item I would like to summarize that one now because
25 | for all those scientific differences, we have realized, we

1 have understood for biological molecules and macromolecules
2 of complex substances, if you look back to all the guidance
3 documents that are published for traditional conventional
4 drugs, you will see it always has an escape clause. The
5 scope would not cover this class of substances, this class
6 of drugs. Therefore, it is important that we will apply
7 different scientific principles to this group of products
8 and then you have consistent oversight of activities for
9 these products.

10 So, for this reason, then we discussed it
11 internally for a long time and then under Roger's
12 leadership, we have formed this coordinating committee.
13 Under this committee there will be technical committees and
14 working groups. The difference between technical
15 committees and the working groups is technical committees
16 tend to stay for a long time to address issues which
17 continuously will occur. Working groups would have a task,
18 and once the task is done, then it would disappear.

19 This chart looks very complicated. It looks to
20 have many groups. Actually many of them are existing
21 groups. They were either under CMC CC before or they were
22 sort of independent within the centers.

23 I will start here, comparability protocol,
24 which was discussed earlier this morning, to address what
25 kind of filing reduction could be done if a firm has a

1 comparability protocol submitted. This concept actually
2 was codified over a year ago when the agency published
3 post-approval changes for biotechnology and the biological
4 products. So, it is already in CFR.

5 Because biological and biotechnology products
6 are very complicated compared with traditional drugs, so
7 the two centers, CBER and CDER, decided we would form a
8 working group to address, to come with a framework for
9 comparability protocols for post-approval changes for
10 biotech products, for biological products, and then we
11 would see whether that kind of framework would be
12 applicable to conventional drugs.

13 Then there's an existing working group between
14 CBER and CDER to work on ICH Q6B for setting specifications
15 for biotechnology drugs. This working group -- the
16 document is already in step 2, published June 9th. The
17 coordinating committee will have oversight from the CDER
18 part of the development of this document.

19 Then under ICH, also there would be a common
20 technical document expert working group. Under that
21 working group there will be two parts, one part for biotech
22 drugs and one part for standard drugs. So, we're hoping to
23 form a working group to address the CTD.

24 This working group has been around for a number
25 of years. They have a guidance document to address

1 recombinant DNA derived cell metabolites because many
2 products in the Center for Veterinary Medicine are common
3 with CDER. So, this working group actually consists of
4 members from both centers.

5 Then we have a working group on botanical
6 products. There's a guidance document that's being
7 developed to include both chemistry, pharmacology,
8 toxicology, and clinical sections, and also address many
9 regulatory and center policies such as combination drug
10 products, whether it's applicable to the mixture of
11 botanicals. The guidance document right now is being
12 reviewed by our GC.

13 Then we have chemistry working group on natural
14 and synthetic conjugated estrogens. This working group
15 includes representatives from our laboratory, Tom Laloff's
16 group, and we're trying to characterize conducting
17 fingerprints of the bulk substance of premarin. Our final
18 goal is to revise the USP monograph for natural conjugated
19 estrogens.

20 We have a document already issued many years
21 ago on synthetic peptides, co-published by CDER and CBER.
22 Right now it is under revision to incorporate the latest
23 scientific information.

24 When you see the boxes with double lines, it
25 means technical committees, and the single lines will be

1 | working groups.

2 | So, under this coordinating committee we intend
3 | to have three other technical committees beyond synthetic
4 | peptides: the Recombinant DNA Reagents Technical
5 | Committee, Protein Products Technical Committee, and the
6 | Complex Excipients Technical Committee.

7 | The reagent committee has two working groups.
8 | One addresses monoclonal antibodies as a reagent. The
9 | draft guidance documents are under internal review and it
10 | is also a collaborative work between CBER and CDER.

11 | Then this technical committee would like next
12 | to address the recombinant enzyme for drug manufacture.
13 | Most of the enzymes actually right now we use are derived
14 | from animal source. However, there is a tremendous
15 | interest to go to a recombinant DNA source because of the
16 | safety especially related to BSE.

17 | The Liposomes Working Group has a draft
18 | guidance document under internal review, and we also have a
19 | group discussing the issues on cyclodextrin as a complexing
20 | agent.

21 | Under the Protein Products Technical Committee,
22 | we intend to have two working groups, one on non-
23 | glycosylated proteins and one on glycosylated proteins.
24 | This working group will try to provide guidance not only on
25 | the general issues related to these two kinds of proteins,

1 also specific products, to establish the criteria for
2 characterization for establishing standards and to address
3 post-approval changes, even to address the issue of
4 pharmaceutical equivalence.

5 There are many other complex substances which
6 could be involved, but at this moment, we're not forming
7 any committee or working group yet. We would address those
8 issues when they come up when there is a need to do so.

9 So, in conclusion, there are the
10 characteristics. The differences between this coordinating
11 committee and the CMC CC are this coordinating committee
12 would have multiple disciplines. It would have chemistry,
13 biopharm, pharm/tox, clinical, and also research chemists
14 and biologists from our laboratories. We may also need
15 legal advise and other things.

16 Then it would include multiple centers as
17 needed. We actually work most closely with CBER. So, many
18 working groups and technical committees and including the
19 coordinating committee would have representation or already
20 have representation from CBER, and we have CVM, as I
21 mentioned earlier, on cell metabolites. For botanicals, we
22 work closely with CFSAN because they have dietary
23 supplements, nutritional supplements, and similar products.
24 Then we work with our Office of Regulatory Affairs for the
25 field investigators, the field offices to address issues as

1 necessary.

2 In conclusion, we would like to have the
3 advisory committee discuss the concept of this coordinating
4 committee, also give us recommendations whether we are on
5 the right track in terms of the structure of this
6 coordinating committee, and also what you see in the future
7 what we need to do.

8 DR. WILLIAMS: Our next speaker is a
9 representative from CBER, Dr. David Finbloom, who we're
10 delighted to have with us today. I think the committee can
11 see how important it is that we stay in tune with CBER on
12 these topics.

13 DR. FINBLOOM: I just want to give some
14 information on the comparability document which was
15 published in April of 1996 and go into some of the issues
16 that have come up with this document and how we use this
17 document when companies who have licensed products or
18 products that are coming near to licensing are going to
19 change that product in one way or another.

20 This just points out there's again a
21 comparability document. I just want to point out that it
22 is for the same product. In other words, it is for the
23 product within one company, and it's a change for that
24 product or within that product.

25 I want to briefly, at the end of the talk, talk

1 about different products, in other words, one product
2 compared to another product, which is sort of the worry
3 that we don't talk about very much over at CBER, which is
4 generic.

5 The reason that the comparability document was
6 important to get out was that this is a process-dependent
7 change. In other words, the change that we're talking
8 about with a product depends upon how that product is made.
9 In other words, the extent to which fermentation, the cell
10 bank, and things like that are formed will depend on how
11 that change is implemented.

12 The other thing that's very important in this
13 document is when the change is made. If it's pre-phase
14 III, this is a very important concept because if it's
15 within a phase I-II type study and if it's before the time
16 that you're implementing a pivotal phase III trial that
17 you're using to base the information that you're going to
18 be using for your licensure, then changes can be made. If
19 it's a post-phase III change, then the changes that are
20 made have to be shown to be similar to the changes made
21 during the pivotal phase III trial, and that's what's
22 critical. The component used during the pivotal phase III
23 trial has to be shown to be equivalent to the marketing
24 product.

25 The changes can be instituted during any part

1 of the manufacturing process, including very early in the
2 molecular biology, in the DNA, in the master cell bank,
3 fermentation, purification, specification, et cetera.

4 Once you initiate any of these changes, then
5 you've got to ask yourselves, are the products comparable?
6 Is the old product comparable to the new product? When
7 you're going to ask yourself that question, then you're
8 going to through a number of tests at certain stages of the
9 whole process. What that means is it's going to depend in
10 part on where those changes are being made. At many of the
11 steps during the process, you may have to go through the
12 whole cycle of tests here to show that these products
13 indeed are comparable. However, there are changes that can
14 be made where you don't have to do many of these tests.

15 Physical-chemical type tests can occur early in
16 the process, such as in molecular biology and the cell
17 bank, fermentation, purification. They may not be needed
18 for changes in formulation. It's just for changes prior to
19 formulation and drug substance. These are a number of
20 tests that would probably be necessary, reverse phase HPLC,
21 size exclusion chromatography, anion exchange
22 chromatography, chromatography zone, electrophoresis, a
23 number of different tests to show that there are no
24 differences between the old substance and the new
25 substance.

1 Viral clearance was already mentioned. I guess
2 you can call it an impurity, but it's going to be very
3 important to show that when you induce changes, especially
4 in column purification and in filtration, that things like
5 viral clearance and MCB validation, there have been no
6 changes between your old product and your new product.

7 Most changes occurring in any process is going
8 to involve some biological assay which shows that there has
9 not been any change, whether it's early in the process or
10 late, including in formulation. These generally occur as a
11 bioassay, as in vivo ones, or in vitro. We have been
12 thinking at CBER about binding assays, including cellular
13 or noncellular, but it's more or less thinking about them.
14 Most of the assays that we have now are based on assays
15 that are cell based or animal based.

16 Toxicology again may occur at any change in the
17 process, even in formulation, such as changes from one
18 product going to another product without the use of albumin
19 as one example, but basically what I think one needs to do
20 here is to talk with a toxicologist and finalize the
21 studies that need to be done to verify comparability.

22 Now we get to sort of the harder aspects or
23 subject in here and that's PK/PD because we can go through
24 the other areas in a comparability study with the
25 pharmacokinetics, with the biologics, with the toxicology

1 studies and may not really show any differences. But the
2 question is could there be differences that we don't see
3 without giving the product to an animal or to a human to
4 pick up something that we're just not able to see on the
5 types of studies that we're doing.

6 So, these studies may not be done if all the
7 physical-chemical, viral, biologic, and toxic studies show
8 comparability between the products before and after the
9 change for drug substance. This statement really has to be
10 worked out with the center in terms of whether a PK study
11 needs to be done. This is almost a one-on-one situation in
12 terms of whether the company needs to go forward because
13 sometimes just to show -- and this is especially for
14 products that are mammalian cell line products that are CHO
15 cell products and recombinant DNA products or monoclonal
16 antibody products, and if we're talking about a scale-up
17 with fermentation, whether there are changes in PK and
18 whether there are changes in glycoprotein and how do
19 glycoprotein changes make a difference in the product
20 itself. So, this may be a subject that may need to be done
21 even though it may not be obvious from the earlier studies
22 that show no change in the comparability.

23 Let me just say one more word on that.
24 Sometimes it may not need to be done in humans. You may be
25 able to pick up changes in animals that may need to be done

1 | in humans, but other times we have had examples where
2 | studies in animals have been negative, whereas studies in
3 | humans have not with basically normal comparability studies
4 | for the studies prior to that, in other words, PK and all
5 | the other ones.

6 | When must the PK/PD studies be performed?
7 | Obviously when there are differences in the physical-
8 | chemical, biologic, viral, and toxic studies, and then it
9 | must be carried out in a way approved by CBER that
10 | obviously will act as a bridging study between the two
11 | products. And this is clear. You don't want a study
12 | that's not going to be done in a way where you can't
13 | adequately judge the study. Generally we prefer a PK study
14 | and not a PD study.

15 | A clinical study is obviously required when the
16 | products are not comparable, and then a study is required
17 | to be done to show efficacy, safety, purity, and potency.
18 | If throughout the comparability study there are things that
19 | are clearly -- especially in a PK/PD study that shows a
20 | difference between the two products.

21 | If there are two different products, then why
22 | can't the comparability guidance be used in this situation?
23 | That sort of has come up frequently. It cannot be used
24 | because the change has to be basically in the same product.
25 | So, we need the change within the same product based upon

1 | the same process with a history regarding the manufacturing
2 | operation of that particular product. It is not comparing
3 | one product with another product with an unknown process
4 | for either one or both of those. Well, obviously, you
5 | won't know one, but for one of the other products.

6 | Basically it comes from regulations. I think
7 | this is from the introduction to the FOIA that there's no
8 | such thing as a me-too biologic. At CBER we are under
9 | regulations that say we have no generic drugs right now,
10 | and if we're going to have generic drugs, then something
11 | will have to be done to get us to that point.

12 | DR. WILLIAMS: David, thank you very much.

13 | Our next speaker is Dr. Bruce Schneider. Bruce
14 | is a physician from the Division of HFD-510, Metabolic and
15 | Endocrine Drug Products. Names change, so I'm not sure
16 | I've got quite the right name. Bruce can correct me. But
17 | Bruce is coming to give a clinical perspective from the
18 | Office of Review Management. Bruce, thanks very much.

19 | DR. SCHNEIDER: Thank you. I was asked to give
20 | a clinical perspective. I'm a clinical endocrinologist,
21 | and the examples that I'm going to be using will come from
22 | endocrinology but they have to do with recombinant and
23 | synthetic proteins. What I'm about to say in the next few
24 | minutes I believe can be and should be generalizable to
25 | other recombinant and synthetic proteins when used as

1 | pharmaceuticals. I guess the bottom line is that I'm going
2 | to make a plea for clinical studies of efficacy and safety
3 | and tell you from the standpoint of a physician why we
4 | believe these studies are required.

5 | Now, recombinant and synthetic proteins are
6 | widely available in endocrinology, and they're used as
7 | hormonally active drugs and probes. Thanks to efforts from
8 | academia and the biotechnology industry and the
9 | pharmaceutical industry, we clinicians have been blessed
10 | with many, many drugs which are used, artificial proteins,
11 | peptides, which can be used for diagnosis and therapy.
12 | Here is just a brief list of some of the agents that are
13 | used for diagnosis in endocrinology. There are hormone-
14 | releasing factors. These are GnRH, TRH, GHRH. That's
15 | gonadotropin-releasing hormone and thyrotropin-releasing
16 | hormone, growth hormone-releasing hormone. CRH is
17 | corticotropin-releasing hormone. All of these are
18 | available synthetically. They're generally small molecules
19 | and are most often produced by solid-phase synthesis and
20 | there aren't major problems that have to do with tertiary
21 | structure for most of them.

22 | These compounds are used for imaging. They can
23 | be radiolabeled with I-123 or with indium-111. For
24 | example, indium-111 labeled somatostatin analog called
25 | octreotide is a marvelous instrument that we use for

1 scanning for neuroendocrine tumors which express
2 somatostatin receptors.

3 Also these compounds have afforded us many
4 materials for development of radioimmunoassays and other
5 hormone assays.

6 They're also used for therapy, and here some of
7 the molecules that we use now get a little bit bigger and
8 bigger in the molecular weights and in their complexity.
9 Here is where some of the issues will arise, issues which
10 will require clinical testing. They're used for
11 replacement and for therapy. They can be used in a
12 continuous manner. For example, insulin given to a type 1
13 diabetic must be given several times a day. DDAVP, which
14 is an analog of arginine vasopressin for diabetes
15 insipidus, GnRH for precocious puberty, and these are given
16 as pulsatile or constant levels of drugs, and the
17 pharmacokinetics of these agents are critical for their
18 action.

19 They may be given intermittently. By
20 intermittently, I mean perhaps once or twice or three times
21 a week, for example, growth hormone perhaps parathyroid
22 hormone for osteoporosis, leptin, which is a very exciting
23 new molecule, which definitely does regulate feeding
24 behavior and body weight and obesity and is now currently
25 under development and analysis for treatment of obesity.

1 Leptin is a 16.7 kilodalton peptide which is non-
2 glycosylated, but which has a single internal disulfide
3 bond which is required for its biological activity.

4 Or finally, under C, these recombinant hormones
5 -- now we're getting to the size, for example, TSH, which
6 I'm going to speak about at greater length, which have to
7 be produced by recombinant technology, and these may be
8 given yearly to patients for diagnosis and treatment of
9 recurrent thyroid cancer. More about this in a bit.

10 Here's just an example of somatostatin, which
11 is a 14 amino acid peptide. It comes in an interminably
12 extended form of 28 amino acids, and octreotide which
13 superficially looks a little bit like somatostatin. It has
14 a number of unnatural or artificial amino acids placed in
15 it to resist proteolytic degradation. It has a beta turn.
16 The PHE, D TRP, LYS, and 3-anine over on the right side of
17 the molecule which is important for receptor binding.

18 I put this up as an example for the future to
19 make the point that a derived or synthetic molecule can be
20 artificially or designer or tailor-made to suit a purpose
21 and not look a heck of a lot like the parent compound. It
22 turns out that octreotide beats somatostatin
23 pharmacologically in many ways; that is, it has a much
24 higher affinity for the receptor on somatotrophic cells
25 than native somatostatin does. Unlike native somatostatin,

1 | it binds very little to pancreatic receptors and so it
2 | doesn't cause diabetes. So, it's much more useful than the
3 | native material. This model or paradigm may be important
4 | for future drug development, but let's go on to larger
5 | compounds.

6 | In endocrinology, the size range of peptides
7 | and proteins that we're talking about now for diagnosis and
8 | therapy ranges from 3 amino acids to 40 kilodaltons or more
9 | and in other areas, such as clotting factor development,
10 | vaccine development, and so on and so forth, monoclonal
11 | antibodies, of course, we're talking about even larger
12 | molecules.

13 | There's a hierarchy in levels of complexity of
14 | polypeptides from small peptide chains to very complex
15 | molecules which are normally extensively post-
16 | translationally modified in order to yield biologically
17 | active forms, modified by enzymatic cleavage, disulfide
18 | bonding, subunit association, glycosylation in many cases,
19 | and other.

20 | And the prediction is -- and the prediction is
21 | coming true -- that increases in size and complexity of
22 | protein molecules reduces the ability of simple chemical
23 | analysis to ensure pharmaceutical and biological
24 | equivalence to the native protein. I put quotation marks
25 | around the word "native" for a reason, which I'll show you

1 | in a moment.

2 | The post-translational modifications, including
3 | the disulfide bonding which correct inter- and intrachain
4 | folding are often absolutely required for bioactivity.
5 | Multiple subunits need to be associated in many cases. For
6 | example, the alpha and beta subunits of LH, FSH, TSH, and
7 | HCG.

8 | Glycosylation is a very, very complex issue.
9 | It turns out a biological method causing subtle and not-so-
10 | subtle alterations in glycosylated molecules. LH, FSH,
11 | TSH, and HCG, by the way, are heavily glycosylated. The
12 | reason for glycosylation is that the process favors the
13 | intracellular combination of subunits which are synthesized
14 | from separate RNAs. For example, in the case of TSH, the
15 | alpha and beta subunits are synthesized separately. As a
16 | matter of fact, the genes are encoded on two entirely
17 | different chromosomes, and so the glycosylation is needed
18 | to effect proper chain association. The pattern of
19 | intracellular glycosylation changes from predominantly
20 | mannose to oligosaccharides during the processing of the
21 | mature form.

22 | Glycosylation also stabilizes hormones in the
23 | circulation. That means, for example, if you desialate a
24 | molecule, you can drastically reduce its half-life, for
25 | example, with LH from 20 or 30 minutes in plasma to 2

1 minutes. And there are many other examples of that so that
2 the PK characteristics of a glycosylated peptide or hormone
3 depend on its degree of glycosylation and how proper the
4 glycosylation is.

5 Glycosylation also affects receptor binding.

6 Now, it must be also understood that there is
7 considerable microheterogeneity of glycosylated hormones --
8 FSH, LH, TSH, for example -- present normally in the
9 pituitary and circulation. That means that, for example,
10 the glycosylated forms of FSH change normally in women
11 during the menstrual cycle. TSH glycosylated forms can
12 change depending on how much TRH there is around and the
13 thyroid status of the patient. So, there is no such thing
14 as an absolutely perfect molecule, even the molecules that
15 are synthesized in vivo in situ in a normal human being.

16 Of course, there are other post-translational
17 modifications such as sulfation, amidation,
18 phosphorylation, acetylation, which are all important for
19 stability and action.

20 I'd just like to say a word about the
21 measurement of these hormones normally and also the
22 measurement techniques that are used for PK studies.
23 Circulating levels of peptide hormones, most of them
24 circulate free. Some circulate like the insulin-like
25 growth factors bound to larger proteins. Most circulate

1 free in low concentrations, about 10^{-7} to 10^{-10}
2 to the 10^{-11} molar concentrations. Therefore, PK
3 studies or studies of endogenous levels generally employ or
4 need to employ radioimmunoassays or other antibody-based
5 detection systems, such as immunoradiometric assays or
6 ELISA assays.

7 However, it must be emphasized that
8 radioimmunoassay is an immunochemical assay in which the
9 potency of an unknown sample is compared to that of a
10 standard. Radioimmunoassay is not a bioassay.
11 Fortuitously, most of the time when we measure a hormone
12 level by radioimmunoassay, the bio and immunopotencies are
13 roughly equivalent. But the biologic to immunologic
14 potency ratio of a substance can vary from 0 to even
15 greater than 1, and I'll show you an example of that in a
16 moment.

17 With complex protein molecules that are made by
18 recombinant technology or just normally, the heterogeneity
19 of the circulating hormonal forms can result from the
20 production process itself, from degradation during storage,
21 and by in vivo proteolysis. Now, the in vivo proteolysis
22 can take place during transit through the skin. It can
23 take place during passage through the liver, and of course,
24 there are proteases all over the body, including the kidney
25 and the lung especially, which are responsible for clearing

1 peptide hormones. This may lead to the formation of
2 derived fragments of hormones which may be immunologically
3 potent but biologically inactive.

4 Now, let me give you a semi-hypothetical
5 example, the case of thyroid stimulating hormone. This is
6 a problem under development now and a problem that our
7 division has been working with extensively.

8 Thyroid stimulating hormone, of course, is made
9 by the pituitary and it normally stimulates the function of
10 thyroid cells. It causes the increase of iodine, of I
11 minus, but of course of radioactive iodine, I-131, into
12 thyroid cells and it, fortunately for patients and for
13 clinical medicine, is useful for stimulating the uptake of
14 I-131 into metastatic or recurrent differentiated thyroid
15 cancer cells.

16 Normally patients with thyroid cancer are
17 operated on. They're rendered hypothyroid and they be
18 ablated with I-131, and they're carried for, let's say, six
19 months or a year post surgery on thyroid hormone
20 replacement to suppress their TSH levels because TSH also
21 stimulates the growth of these cells.

22 Now, if you want to determine whether there is
23 a recurrence of thyroid cancer, a standard technique is to
24 withdraw the patient from thyroid hormone and allow the
25 endogenous TSH to rise. That will then stimulate the

1 uptake of I-131 into the malignant tumor cells. This is
2 sort of a long and somewhat unpleasant procedure which we
3 have to put our patients through periodically.

4 In order to circumvent this, at least one
5 company has been trying to develop a recombinant TSH, human
6 TSH, which will be used in the following manner. The
7 patients can be kept on thyroid hormone. They'll be given
8 one or two injections of this material, and hopefully the
9 material will do what native TSH does and stimulate the
10 uptake of I-131 into cancer cells. So, the goal is
11 production of recombinant human TSH, which will replace
12 thyroid hormone withdrawal protocols used for the detection
13 and treatment of recurrent thyroid cancer.

14 TSH is a 28 kd, alpha-beta heterodimer. It's
15 about 15 percent glycosylated, first with mannose and then
16 with complex oligosaccharides.

17 The methods of production are standard. The
18 cells, which are generally COS cells, are capable of
19 glycosylation and extensive post-translational
20 modifications of nascent proteins. These cells are
21 transfected with expression vectors containing full-length
22 cDNAs encoding alpha and beta subunits of human TSH.

23 The result is that the resulting recombinant
24 human TSH is chemically indistinguishable from human
25 pituitary TSH within the limits of current methodology.

1 | Now, remember, this means that the primary sequence can be
2 | determined. The details about inter-chain association can
3 | determined the degree of glycosylation. But you really
4 | can't determine every residue that's glycosylated and
5 | exactly what sugar is on that residue and how highly
6 | branched that sugar is.

7 | Let's just say that the product also reacts
8 | fully in a TSH radioimmunoassay and also exhibits full
9 | activity in an in vitro bioassay; that is, you give it to
10 | FRTL cells or other thyroid cultured cells and it
11 | stimulates the cells to take up I-131.

12 | The question is, will it work in patients?
13 | Will it work in this population of patients, and also is it
14 | safe to use? And the answer that I would give as a
15 | clinician is that we can't tell without doing the clinical
16 | trial.

17 | Why not? Because even subtle alterations in
18 | the glycosylation patterns can drastically affect the
19 | biological activity in vivo.

20 | Now, even if a molecule passes the chemistry
21 | tests, it may not be fully active biologically, of course.
22 | But even if it passes the chemistry tests and is bioactive
23 | in vitro, it may not work in vivo. Then you go into a
24 | hypothyroid animal and you show that it may even work in
25 | vivo in an animal system, but it still may not be effective

1 | clinically for several reasons, including PK in humans.
2 | And even, finally, if the molecule has acceptable PK
3 | characteristics, the clinical activity is not guaranteed
4 | because the PK data are determined generally by RIA and not
5 | by bioassay.

6 | Let me just insert here that there really is a
7 | critical need to develop good bioassays which would be
8 | sensitive enough to detect circulating molecular forms of
9 | peptide and protein hormones which are present in the
10 | concentrations that you find them during PK studies and
11 | also endogenously.

12 | Let me give you a brief example to support this
13 | from clinical medicine. There's a disorder called
14 | hypothalamic or tertiary hypothyroidism in which there's
15 | impairment of hypothalamic TRH which results in the
16 | production of ample pituitary TSH but with aberrant
17 | glycosylation patterns. The abnormal TSH is biologically
18 | inactive, but fully active immunologically. It's not only
19 | active in radioimmunoassays, but also in immunoradiometric
20 | assays, which were supposed to be better but still these
21 | molecules are active in IRMA assays as well. Thus, the
22 | blood TSH levels, as determined by RIA, are misleadingly
23 | normal or even elevated in the presence of hypothyroidism.

24 | The numbers that I've give in example are taken
25 | from a patient of mine who was clinically hypothyroid, who

1 had a total T4 of 2, with the normals of 4 to 8, a low
2 total T4, low free T4 of .3, normal of 1 to 3, and a
3 slightly elevated TSH of 4.2 microinternational units per
4 ml. This TSH is biologically inactive. The TSH can be
5 fixed, if you will, by giving injections of TRH. You can
6 actually show that there's stimulation of pituitary TSH and
7 that with repeated administrations you can alter the
8 glycosylation patterns.

9 So, here's a marvelous example of how you can
10 have a molecule which is immunologically fully active which
11 chemically sort of looks pretty much like regular TSH which
12 has high levels in blood which has delayed clearance, so
13 you would think it would have better PK values, PD
14 activity, and it doesn't. It's completely devoid of
15 biological activity.

16 So, again, this would be true not only for TSH,
17 but for any complex molecule, subtle biochemical
18 alterations can abolish TSH bioactivity. In this
19 particular case, aside from clinical trials, no presently
20 available method can determine whether this recombinant
21 human TSH is capable of stimulating I-131 uptake into human
22 metastatic thyroid cancer cells in vivo, and no method can
23 determine, aside from clinical trials, whether this
24 pharmaceutically equivalent TSH can match the ability of
25 endogenous TSH to aid in the detection of recurrent thyroid

1 cancer.

2 There are also safety issues with complex
3 molecules. By that I mean whether or not the recombinant
4 human TSH is completely normal or abnormal, antibody
5 formation in patients cannot be predicted with certainty
6 prior to clinical trials. You can take a completely normal
7 sequence and pass it through the skin and develop
8 antibodies. We see this with human insulin, and those of
9 us who have developed radioimmunoassays know that you can
10 develop an assay in antibody to a homologous amino acid
11 sequence.

12 The above safety and efficacy considerations
13 apply to polypeptide hormones and proteins with complex
14 structures generally with molecular weight greater than a
15 few kilodaltons. Here are some examples from endocrinology
16 and general medicine in which this would be true:
17 insulins, IGFs, leptin, LH, FSH, TSH, HCG, growth hormone,
18 certain growth factors, cytokines, soluble cytokine
19 receptors, and many others.

20 There's one more issue that I'd like to bring
21 up about immunological reactions. This hasn't come up in
22 recent trials, but it's a possibility, and that is the
23 formation not only of antibodies but idiotypic antibodies
24 which can be induced, for example, in insulin treated
25 diabetics occasionally. These are antibodies which look in

1 three space like the FAB fragment and therefore can bind to
2 -- rather, they recognize the FAB fragment and they look
3 like the antigen itself and are capable therefore of
4 binding to the normal receptor for the hormone and either
5 blocking or stimulating. If such an idiotypic antibody
6 appeared following repeated injections of recombinant human
7 TSH, the result would be a clinical nightmare because if
8 the antibody were agonistic to cancer cells, it would
9 stimulate their growth and there would be no way to turn it
10 off.

11 Thank you.

12 DR. WILLIAMS: Thanks very much, Bruce.

13 Our last speaker for this session is Dr. Ken
14 Seamon. Ken is going to give an industry perspective and
15 comes from Immunex in Seattle. Many of you also know that
16 Ken used to work at CBER prior to his transition to
17 industry. Ken?

18 DR. SEAMON: Thank you, Roger, Mr. Chairman,
19 and committee.

20 If I could have the first overhead, please. I
21 think it's particularly appropriate that this committee
22 start addressing the issues related to equivalence of these
23 types of molecules, in particular with respect to some of
24 the trends over the past few years. It's quite clear that
25 there are a lot of issues that are related to the quality

1 of these molecules that are going to be necessary to try
2 and provide newer therapeutics to the public.

3 For example, there's clinical trial
4 compression. More and more trials are being looked at
5 using fast track or accelerated approval, and there is use
6 of phase II/III data for accelerated filing. What this
7 means is that there is a greater number of studies that are
8 being carried out using safe and effective, but early
9 development batches of drug for these trials, such as pilot
10 scale batches, and therefore, there's a need to be able to
11 qualify these and validate these clinical trials for
12 filing.

13 In addition, there's greater number of protein
14 pharmaceuticals that are actually achieving commercial
15 potential. I think we're starting to see a large increase
16 in products that are really showing tremendous potential
17 for public health. There is, as we've heard, pressure for
18 generic versions.

19 I think the issue related to equivalence of
20 products is becoming more and more an issue, particularly
21 as people are talking about generic competition. I believe
22 Dr. Finbloom addressed that.

23 What is the impact of these trends? Well,
24 clearly pivotal trials are being carried out earlier in
25 development, using pilot material. Again, there's an

1 increased emphasis on comparability and I think Dr.
2 Finbloom addressed that very adequately.

3 Also guidance for product development is needed
4 earlier in the clinical development process so that people
5 can develop high quality materials early in these trials
6 that are suitable for pivotal trials and commercialization.

7 Clearly, there's the issue of harmonization of
8 global standards as companies are looking more and more
9 toward global development of molecules. ICH has clearly
10 had an impact in this area in developing a number of
11 harmonized quality guidelines for biotech products.

12 I think we've heard very adequately about the
13 protein based pharmaceuticals. There are multiple sources.
14 There are recombinant, synthetic, and naturally derived
15 based pharmaceuticals. We have heard that these are
16 heterogeneous, and I think what's important to point out is
17 that the heterogeneity of these recombinant molecules is
18 frequently less than the actual naturally occurring
19 molecule. In many cases the naturally occurring protein,
20 when it's isolated, actually shows a greater distribution
21 or microheterogeneity than the recombinant protein,
22 although when we're giving the recombinant protein, we're
23 giving it in large pharmacologically active doses.

24 However, there is also the issue that the
25 methods for analysis of these proteins are not well

1 | standardized for some parameters. This is particularly
2 | relevant for bioactivity, for some types of contaminants,
3 | and some types of impurities. This again becomes a very
4 | important issue when one considers the ability to actually
5 | compare two products from two different manufacturers.

6 | Using the ICH nomenclature of some of the
7 | parameters for the drug substance, if one looks at
8 | impurities such as process-related impurities, which could
9 | be host cell DNA, host cell protein, these types of
10 | impurities are very dependent on the process of
11 | manufacturing and they're also very dependent on the method
12 | of analysis and on the standard which is being used in the
13 | analysis. It's very difficult to compare this type of
14 | parameter from one product or one process to another,
15 | particularly when you're looking at two different
16 | companies.

17 | Therefore, the overall assessment of
18 | equivalence, when one is comparing products between two
19 | different companies, can be very difficult. However, when
20 | one is looking at a process change within a single company
21 | or a single process, and you're using the same
22 | methodologies and the same standards, it's more
23 | straightforward to be able to actually compare these
24 | products.

25 | In terms of some of the tests for identity and

1 the overall quality of the product, such as product related
2 substances, oxidized or aggregated species that may be
3 present at very low levels, looking at glycoforms or N-
4 terminal heterogeneity, for example, the methodologies for
5 these types of analyses are actually getting very good and
6 one can do very good profiling and comparison between
7 products using very sophisticated techniques such as LC
8 mass spec, various other chromatographic techniques for
9 glycoanalysis.

10 There are some very unique issues related to
11 the evaluation of these types of protein molecules that I
12 just want to touch on briefly.

13 First of all, it's clear that in any evaluation
14 of the product, whether it's for comparability or
15 equivalence, there has to be clear clearance and no
16 evidence of any type of contaminations using the ICH
17 definition for viral, bacterial, mycoplasma, and as Dr.
18 Chiu pointed out, TSEs. This all relates to the source
19 material in the process of validating the removal of any of
20 these during the manufacturing process.

21 Most of the adverse events or adverse activity
22 which has been associated with many of these molecules has
23 really not been associated with impurities or small
24 degradation products. It's really has been mostly observed
25 due to the exaggerated biological activity of the product.

1 So, again, these are critical characteristics of these
2 types of molecules and by understanding the biology, you
3 are better able to predict some of the adverse events that
4 may occur as you administer large quantities.

5 A very unique aspect of these types of drugs is
6 the potential for immunogenic responses, and this is very
7 unique. Antibody formation is frequently observed, and
8 it's very difficult, as pointed out by Dr. Schneider, to
9 predict. If one looks at the package insert for many
10 approved biological or protein-based drugs, you'll see
11 percentages anywhere from 0 percent to 40 percent antibody
12 production. However, what's important to point out here
13 is, again as pointed out by Dr. Schneider, this is not
14 unique to recombinant proteins, but is also observed when
15 just the naturally occurring protein is administered.
16 Frequently there will be antibody production.

17 I think again it's important that we focus on
18 what are the real critical safety and efficacy issues that
19 are related to this antibody formation. The major impact
20 from an efficacy perspective is really not the presence of
21 the antibodies, it's the presence of neutralizing
22 antibodies that can affect the pharmacokinetic clearance of
23 the molecule or its ability to have biological activity.

24 Severe allergic responses really have not been
25 observed for most of these molecules that have been

1 administered, and this really hasn't been a problem. So, I
2 think again presence of antibodies itself should not
3 preclude the ability to move these molecules into
4 benefiting the public health. The real concern is the
5 potential neutralization of biological activity.

6 As I alluded to, impurities are very difficult
7 to quantitate with these proteins, and they're not so much
8 difficult to quantitate with respect to a given product and
9 process. It's very difficult to compare these across two
10 different processes or two different companies just due to
11 the inconsistency in the methodologies, the lack of any
12 good standards, and really the lack of really good
13 quantitative methodologies for these impurities.

14 On the other hand, I think it's important to
15 point out that for both impurity levels of host cell
16 proteins and even for very low impurity levels of host cell
17 DNA, there really is no specific risk which has been
18 attributed to these, although it has been suggested that
19 host cell proteins, to a certain extent, can act as an
20 adjuvant in eliciting or exacerbating an immune response.

21 I want to just briefly touch on a couple issues
22 related to comparability. Can I have the first slide
23 please?

24 This just illustrates again some of the points
25 that have been previously made. This is an isoelectric

1 focusing gel of a recombinant product that has been
2 approved for many years and has been administered safely to
3 literally hundreds of thousands of patients. One sees a
4 banding pattern with four major bands and two minor bands.

5 The important point I want to point out here
6 is, yes, this is heterogeneous, but if you look at the
7 isoelectric focusing pattern of the natural hormone, you
8 will find that it's even a greater heterogeneous
9 population.

10 Now, as pointed out earlier, each of these
11 bands has a slightly different ratio of in vivo to in vitro
12 activity due to the sialic acid content. However, it was
13 important to be able to demonstrate that this could be
14 produced very consistently between batches, and that was an
15 important controlling point.

16 In terms of analytical methodologies being
17 applied to these proteins, it's important not to believe
18 that we know that there are only five species here, but
19 each of these bands also probably consists of a
20 heterogeneous population of glycosylation.

21 This just again shows three different bands on
22 an SDS gel. Again, they differ in their overall
23 glycosylation. Again, in this particular case, these three
24 different bands or forms of the molecule did not show any
25 differences in pharmacokinetic behavior.

1 This just shows again an SDS gel that again
2 shows the heterogeneity which is associated with a
3 recombinant molecule, again which was licensed many years
4 ago and has shown very good safety and efficacy in hundreds
5 of thousands of patients, and again just demonstrates the
6 heterogeneity that is frequently observed with these types
7 of molecules.

8 Now, what I want to indicate is that for each
9 of those products that were licensed many years ago, the
10 issues about pharmacokinetic bioequivalence came up during
11 their manufacturing process. During the actual licensing
12 or approval of these, questions were raised about, when
13 there was a scale-up for commercial production, were there
14 any differences in the molecule. What was required at that
15 time to demonstrate comparability consisted of the
16 analytical methodologies, pharmacokinetic comparisons, as
17 well as clinical trials to actually establish comparable
18 dosing.

19 However, over the past few years -- this was
20 looking at these molecules as historical biologics where
21 the product equals the process. Over the past few years,
22 clearly what has happened is, as the technologies have
23 developed and as our understanding of these molecules has
24 developed, we've been able to look at these types of
25 products in a context which is maybe a little bit closer to

1 | the small molecule drugs and is a little bit different from
2 | the biologics. This has resulted in the comparability
3 | protocols as one instance of the ability which has been
4 | facilitated by the ability to actually be able to analyze
5 | these molecules.

6 | So, again, previously demonstrating
7 | equivalence, or in this context comparability, required in
8 | vitro studies, some preclinical studies, and clinical
9 | studies for bioavailability and dosing efficacy that led to
10 | assurance of identity, purity, safety, and potency.

11 | As I said, previously, comparability required
12 | analytical data, real time stability and clinical data, a
13 | bridging study for safety and/or efficacy. Now, based on
14 | the comparability talk that Dave Finbloom gave, clearly
15 | there are opportunities for demonstrating comparability
16 | using analytical data and other data may not be required
17 | depending on the data, real time stability, pharmacokinetic
18 | data, and potentially clinical data when the data is not
19 | consistent with the product being the same.

20 | So, for the purposes of comparability, I think
21 | it's a very important concept that has helped facilitate
22 | development in a number of different areas. The same
23 | methods, when one is looking at comparability in the same
24 | product and the same process, the same methods can be used
25 | for assessing impurities and for comparison with the

1 reference standard. The data can be compared to the
2 database that the innovator or the manufacturer has
3 developed all through the development process. So, there's
4 a very good database to actually compare this data to. And
5 the conditions for manufacturing have been validated based
6 on this development data.

7 In the case of therapeutic equivalence between
8 two different products where you don't have a history of
9 one of the products, it's more difficult to actually
10 compare the two different products. For example, with
11 impurities there really is no standard, as I mentioned, for
12 some impurities, and the methods are very process-
13 dependent. So, it makes the actual comparison much more
14 difficult.

15 So, therefore, with respect to determinations
16 of equivalence, clearly from a CMC perspective the process
17 needs to be very carefully evaluated. There has to be
18 safety from any level of contamination. This is a critical
19 parameter and is assured through the process validation and
20 GMPs. There need to be comparable specs for both drug
21 substance and drug product. There need to be comparable
22 methods used for the evaluation and a comparable impurity
23 profile.

24 So, therefore, in evaluating two different
25 products, it's very important that the company A, if one is

1 | now looking at an issue of therapeutic equivalence, that
2 | the actual process be evaluated between company A and
3 | company B, that the specs, method of validation, stability
4 | be compared very carefully both for drug substance and for
5 | drug product. Therefore, any reviewer doing evaluation of
6 | one product needs to have the history, understanding, and
7 | context of the innovator product.

8 | I want to talk very briefly about some of the
9 | limits of bioequivalence studies, and I think again Dr.
10 | Schneider illustrated these very well.

11 | For some protein drugs, there may not be a very
12 | good correlation between biological activity and plasma
13 | levels. Parenteral administration does not always assure
14 | bioequivalence. With many of these products, if you
15 | deliver them subQ, IM, or even IV, they have half-lives
16 | that range from a few hours to some of a few weeks. What
17 | this does is this also makes the determination of
18 | pharmacokinetic equivalence much more difficult due to the
19 | long half-lives.

20 | Therefore, clinical studies for comparability
21 | may need to be carried out in some situations, particularly
22 | where you don't have a history of the drug as developed in
23 | an overall development pathway such as for a second product
24 | coming on. There might be a need to establish
25 | comparability through the use of pharmacodynamic or

1 surrogate endpoints. There might be a need for limited
2 studies to confirm optimal dosing and efficacy, and there
3 might even been a need for limited studies to establish
4 antigenicity.

5 Again, as was alluded to earlier by Dr.
6 Schneider, the assays for pharmacokinetic comparability can
7 be quite complicated. They are ELISA, RIA. In some cases
8 they're bioassays. One is concerned about assay
9 specificity, accuracy, and precision. Again, one has to
10 ask the question, what is the sensitivity of the assay to
11 the active species, the parent drug metabolites, any
12 degradation products, and also endogenous levels of the
13 drug may also be present that can confound it. One also
14 has to address the potential influence of antibodies that
15 may be present or other endogenous binding proteins on the
16 assay.

17 In terms of clinical issues in looking at
18 comparability or equivalence, the issues may be very
19 different for chronic versus acute administration. Many
20 biological molecules, monoclonal antibodies, cytokines are
21 being used in acute, life-threatening situations and are
22 usually being used more for an acute. Now, I believe that
23 we are getting many more very, very promising therapies
24 that are going to be used chronically for long periods of
25 time, so these issues may become much more important to

1 really assess any types of issues for the long-term chronic
2 administration.

3 It might be necessary for some types of
4 immunological assessment to be carried out in naive
5 patients or potentially in patients that were previously
6 exposed to another molecule.

7 Again, this is an area that is in clear need of
8 standardization. Determination of antibody levels is an
9 extremely imprecise science. It's dependent on a reference
10 antibody, no really good standard proteins, no good
11 standards or methods of quantitation. Again, although
12 there are a number of values out in the literature, it's
13 very difficult to compare antibody levels between different
14 laboratories or between two different preparations.

15 Again, I just want to emphasize that the
16 presence of antibodies itself is not necessarily the
17 significant factor. It's really related to the
18 neutralization of activity. There really have been no
19 severe allergic reactions that have yet been observed.

20 Then again if there are clinical studies that
21 need to be carried out for demonstration of equivalence, I
22 think the issue of numbers for safety and numbers for
23 equivalence is something that needs to be addressed and
24 needs to be addressed very openly. If one is looking for
25 equivalence, formal equivalence, between two different

1 products, then you're actually requesting a clinical study
2 that might be even greater than just establishing its own
3 efficacy. In addition, establishing through safety through
4 any type of small trial may really be inadequate and might
5 even be slightly misleading.

6 So, what are the overall recommendations?

7 I think there need to be consistent standards
8 for drug products regardless of origin or characteristic.
9 I was pleased to see that in the coordinating committees
10 that there is a single committee that has oversight on all
11 of the protein molecules because I believe that the issues
12 related to heterogeneity are basically the same. It's just
13 the origin of heterogeneity.

14 Clearly the issue related to whether it's a
15 naturally derived protein or a recombinant protein or a
16 synthetic protein really relate more to the source material
17 with regard to safety and really the lack of any type of
18 adventitious virus, bacteria, or contaminant. That needs
19 to be made sure that that's carefully excluded.

20 It's very important to start harmonizing
21 standards and guidelines. We were very pleased to see that
22 any committees have both representatives from CBER, as well
23 as CDER. It's important to have harmonized between the two
24 centers for these products. Again, I think one has to look
25 back at the progress that was made in ICH for developing

1 | harmonized standards for these products for both stability,
2 | viral safety, for specifications, and also for cell
3 | substrates. I think that's a model where there was very
4 | good international harmonization of guidelines and I think
5 | it's a model that we might look at in terms of bringing the
6 | available science to bear on these issues, using academic,
7 | industry, and the other international regulatory
8 | authorities.

9 | It's very important that if there is any
10 | evaluation of bioequivalence of molecules from different
11 | manufacturers, to maintain the continuity of review between
12 | reviewers for an innovator molecule, as well as any other
13 | versions of the molecule. There's a lot of data in
14 | industry and academics. It's important to utilize that
15 | database and bring that to bear on these issues.

16 | And I think it's also important to recognize
17 | that as the technologies develop and are developing, we
18 | will continue to see small differences in molecules. I
19 | think it is very important that we don't jump to an ultra-
20 | conservative approach where any small difference is viewed
21 | as a major difference. It's important to view the
22 | difference in the context of what we know about the
23 | molecule and also with respect to the clinical setting and
24 | the impact of that parameter on the clinical setting.

25 | I think this committee, as well as the agency,

1 is going to be faced with a number of future issues.
2 Again, it's very important to understand what are really
3 the specific issues related to the assessment of safety for
4 therapeutic substitution. We need to focus on what those
5 safety issues are and not just focus on what the analytical
6 parameters are.

7 Can the safety concerns be addressed through
8 analytical and bioequivalence? Clearly I think one company
9 making changes, the comparability protocol addresses that
10 very well. I think when one is comparing different
11 companies, it becomes more complicated.

12 But again, one has to then address what are the
13 specific concerns related not only to a generic
14 substitution, but also related to immunogenic activity that
15 might be elicited as a result of a second product. Is it
16 pharmacokinetic, allergic reactions that aren't really
17 observed, neutralization activity, or as pointed out again
18 by Dr. Schneider, antibodies against endogenous activity?

19 Ultimately what is the role of pharmacodynamic
20 studies in determining clinical equivalence?

21 I apologize for going over my time, Mr.
22 Chairman, but thank you for your attention.

23 DR. TAYLOR: Thank you very much.

24 We're scheduled for a brief break before the
25 committee discussion of this. I think we'll take that

1 break and then when we come back, we'll have an opportunity
2 for some open discussion, public discussion, as well as
3 committee discussion. Let's take about 10 minutes so that
4 we can remain on track. So, return at 2:10.

5 (Recess.)

6 DR. TAYLOR: I'd like to restart the session.
7 Our 2:10 time has come.

8 We did not have any individuals indicate that
9 they had formal presentations for this phase of the
10 meeting. However, I'm taking the liberty to open the floor
11 for any such brief presentations at this time. If you do
12 have a brief statement to make to the committee, you may
13 come to the microphone and identify yourself.

14 (No response.)

15 DR. TAYLOR: If not, then we'll go forward into
16 the committee discussion of the issues that were presented
17 regarding complex drug substances. Dr. Mayersohn.

18 DR. MAYERSOHN: Roger, this is a terrific plan.
19 I think this is exactly what we want to see developed when
20 Pharmaceutical Science was formed. It's proactive. You're
21 anticipating difficulties. These are obviously very
22 complicated issues, but I congratulate you. It's really
23 great.

24 DR. TAYLOR: Dr. Branch?

25 DR. BRANCH: I'm intrigued by two different

1 | senses of perception. One is the complexity of the
2 | molecules that you're leading into, and the other is a
3 | sense that I get from the research community where we're
4 | doing phase I and II studies that I've been involved
5 | peripherally with in a clinical research unit where the
6 | clinical investigators are getting a sense that -- well, my
7 | sense is that the research in this arena is actually much
8 | simpler than that with small drugs. The adverse reaction
9 | profile has, on average, been much less. The unexpected
10 | effects which are so prevalent for small drugs don't appear
11 | to be occurring with anything like the frequency. The
12 | ability to use a common methodology to measure your
13 | endpoint drug in terms of radioimmunoassays makes for a
14 | fairly uniform ability to track your new entity, maybe not
15 | from the point of view of the multiple complexes, but as a
16 | single numerical value that that particular assay measures.

17 | I'd be interested as to whether, being out in
18 | the sticks, I and co-investigators around are being lulled
19 | into a false sense of security, or are we maybe overdoing
20 | the level of complexity? So, that was the first question I
21 | had.

22 | The second was there was one slide that really
23 | intrigued me and sort of seemed to be internally
24 | inconsistent, and it was a comment that comparability tests
25 | between entities before phase III and after phase III are

1 different. That seems to me illogical. It would mean that
2 you'd have the real potential of developing a whole group
3 of phase II studies, designing a phase III study, but
4 changing your production line and all that data giving you
5 erroneous information. Is it really true that there is
6 this breakpoint between pre phase III and post phase III
7 when you talk about comparability?

8 DR. FINBLOOM: Maybe I probably phrased it a
9 little too specific in terming it pre phase III and post
10 phase II. Maybe I should have phrased it as pivotal and
11 non-pivotal. As you said, you're doing a lot of phase I/II
12 studies, and I think it has been said in these discussions
13 that those types of studies are going to be done more
14 frequently using pilot type facilities, using drug in a
15 condition where it may not have had many of the
16 specifications that we would like to see when we would go
17 on certainly toward a marketing type of evaluation.

18 Then you go on to a phase III study. Many of
19 the properties of the drug should be characterized or a
20 pivotal type study. Let me just rephrase it. We like to
21 have most of the specifications of the drug in place when a
22 pivotal study is about to be performed, and we would not
23 like the company to be changing specifications during that
24 type of study.

25 DR. BRANCH: But you do have a real issue in

1 terms of a lot of the compounds are being developed by
2 biotechs, smaller companies rather than big companies.
3 There is this compression of phase II to phase III, the
4 fast track approval, et cetera that we were hearing about.
5 So, in the pressure to get an idea to a usable drug, it
6 would seem to me that you should use the same set of rules
7 all the way through.

8 I agree with the full characterization, but
9 your implication was that you could actually be changing
10 the characterization between what you're using in the early
11 phase II studies and what comes out of a phase III. That
12 seemed to be inconsistent with the approach that's taken
13 with small molecules.

14 DR. FINBLOOM: I think if you're going to
15 change it or if a company goes ahead and makes the decision
16 to change the drug in what you would be calling a pivotal
17 trial, then they have to show prior to marketing that the
18 product that they used is basically the same product used
19 in the pivotal trial. And if it is not, then that product
20 cannot be marketed. I think that that pretty much states
21 where we are, at least certainly within our division.

22 CBER consists of a number of different
23 divisions and things like that, and some of the products
24 are more -- I don't want to say inconsistent -- but there
25 are vaccines that are made out of several different

1 products and there are other products that are 95, 98
2 percent pure such as enzymes used for some enzyme
3 deficiencies.

4 If you have a study where you're doing in a
5 phase I/II of 20 patients and then you're going to go into
6 a so-called pivotal study of 80 patients or things like
7 that or 100 patients or 200 patients or things like that,
8 then there are a number of things that have to be done with
9 that product before you enter that study. If you make
10 changes in that product, then we would expect to see that
11 the changes be made during the pivotal trial are basically
12 the same as after the pivotal trial.

13 DR. CHIU: I would like to add to what David
14 said. During IND stages, the main concern is safety. So,
15 when you move from a phase II to phase III and you do some
16 changes, the agency is most concerned with whether it will
17 harm the patients. During phase III, you continue to
18 collect safety and efficacy data. So, if the change does
19 not impinge on safety, the firm can continue to phase III
20 and collect safety and efficacy data.

21 But once the pivotal trial and the phase III
22 study is completed, then the safety and efficacy is
23 established. Then you make further changes. You will have
24 to have a higher standard to show pharmaceutical
25 equivalence. Therefore, the safety and efficacy data can

1 | be transferred. So, that's the difference in my mind.

2 | DR. BRANCH: No. I understand the differences.
3 | In most small drugs you make your drug to start with and
4 | then you go with it. This one here you're making a
5 | biological system to make your drug and it has a much
6 | greater level of complexity and much greater potential for
7 | change over time, a much bigger potential for change. I
8 | understand the problem behind it.

9 | But I think the underlying logic is that you
10 | don't accept phase II studies with a different chemical
11 | entity. The acceptance of the information that was
12 | obtained as you're doing your early study. Then if you
13 | change your product, you should be just reviewing the data
14 | that's obtained with that particular product that you're
15 | actually hoping to take to market. The implication was
16 | that you were actually incorporating some of your phase I
17 | and phase II studies that may be a different formulation
18 | into the overall final decision making because it's based
19 | on that pivotal phase III, but the information you have in
20 | the phase I and II is used in the product label. Am I
21 | being confused?

22 | DR. TAYLOR: Yes, Dr. Williams?

23 | DR. WILLIAMS: I think it's a good discussion
24 | but I think it's an example where people are sort of
25 | talking about different things. Yuan-Yuan gave you an

1 answer that focuses on the CMC aspects of the development
2 process. Bob, I think what you're talking about very
3 properly is like a clinical pharmacology study in phase I
4 and phase II, drug-drug interaction, and if a change is
5 going phase II to phase III, what does that data mean? So,
6 I think everybody has got a good point. It's just that
7 it's not the same point.

8 DR. TAYLOR: Dr. Vestal?

9 DR. VESTAL: Roger, I wonder if we could have
10 maybe a little more clarification of what you see the role
11 of this committee being? For example, I think we heard
12 from Dr. Chiu that in the situation where there's a
13 monoclonal antibody drug targeting complex, that then
14 involves CDER. It wouldn't necessarily involve this
15 committee I guess, but I suppose it might surrounding
16 pharmaceutical science type issues. These discussions we
17 are having are very, very interesting, very exciting, but
18 the question I'm having is, where does this committee fit
19 in, do you think?

20 DR. WILLIAMS: Well, I might ask the Chair. As
21 you can imagine, I was going to ask for some time at the
22 end to answer that question, but I didn't want to cut off
23 the discussion. But I could certainly respond now.

24 DR. TAYLOR: I think now is the time.

25 DR. WILLIAMS: Okay.

1 When I listened to this discussion, I'm
2 thinking of Indiana Jones frankly. Are you willing to
3 descend into the jungle and deal with it? I think of it in
4 a very positive way, so I wouldn't want that initial
5 comment to be construed in any way as negative.

6 I do think this committee has a very strong
7 role, and I might also draw attention -- and David, please
8 correct me if I'm wrong, but I understand there's a
9 corresponding committee in CBER called the Biologic
10 Response Modifier Committee. Did I get the name right?
11 It's close enough.

12 In one of my dreams, I could even imagine the
13 two committees having a joint meeting, and I think that
14 might be a very powerful thing to take all their incredible
15 expertise in the realm of molecular biology, coupled with
16 your incredible expertise in sort of dealing with these
17 issues over a multi-year period and from sort of a small
18 molecule drug product standpoint. So, I think there are
19 many places we could go together in the future if we're all
20 willing.

21 The other thing I'd like to say is I think this
22 is the time when those three questions that I keep coming
23 back to are so critical to help us sort through the issues
24 as we move down the path. Now, I'll move through them one
25 at a time.

1 What's the question? That has come up several
2 times in the prior discussion, and sometimes we're talking
3 pharmaceutical equivalence and sometimes we're talking
4 bioequivalence.

5 Now, I would argue for the most part I think
6 the debate hinges on pharmaceutical equivalence. Why do I
7 say that? For the most part these are solutions, they're
8 not suspensions, and for the most part the inactive
9 ingredient, certainly when it comes to a j application,
10 have to be qualitatively and quantitatively the same.

11 So, I would be very willing to say -- I'm
12 getting into the second question -- that I don't think of
13 this primarily as a release of the drug substance from the
14 drug product question, but I certainly want to explore that
15 further in light of Dr. Seamon's comments that when you
16 give these things parenterally, the question of
17 bioequivalence comes up, and I think that's a question we
18 might discuss in front of this committee.

19 Going to the second question, what are we
20 willing to rely on, I think you heard from many of the
21 prior speakers that frequently they are not willing to rely
22 on anything lesser, if you will, than a comparative
23 clinical trial. Now, I think that's a very interesting
24 position which I think would merit some discussion in front
25 of this committee. What I'd like to imagine -- and I'm

1 | just being hypothetical here -- is the unwillingness to
2 | rely presumably relates on when a prior approach failed to
3 | signal a problem that then was discovered in a clinical
4 | trial. It's when the canary in the mine failed to signal
5 | the problem that was subsequently detected in the clinical
6 | trial.

7 | Now, I could imagine a very interesting
8 | advisory committee, which might have to be a closed
9 | committee meeting so that we could adequately look at the
10 | data, where we would look at those subsidiary failures of
11 | the canary, both in terms of either CMC, PK/PD, and then
12 | say, why did the comparative clinical trial answer the
13 | question finally? Now, I think that would be a great
14 | debating point and discussion point. It goes back to was
15 | there a true failure in our prior understanding.

16 | I have to admit my intellectual bias here is
17 | that the subsidiary measures, PD/PK, CMC, are always more
18 | precise and in a way sensitive to what we care about than a
19 | comparative clinical trial, which I tend to think of as
20 | fairly noisy. So, I'd be very interested in this
21 | discussion in front of the committee.

22 | Let me go on to the next question. The third
23 | question, of course, is how certain do we need to be, and
24 | that relates to the issue of sameness. You've heard a lot
25 | of words here used in front of the committee: "identical,"

1 "equivalent," "comparable," "same."

2 Now, necessarily when you get into those kinds
3 of statements, we get into issues of comparisons. As I
4 said at the very beginning, to make a comparison,
5 particularly when you get into the realm of PK and PD and
6 comparative clinical, you need a criterion. I want the
7 committee to brace themselves. I think the issue of
8 population and individual bioequivalence is going to come
9 up and replicate designs and the whole story, and I think
10 there's enough under our belt here that we know the issues,
11 and my main question for the committee is, can you imagine
12 a molecule-by-subject interaction? It's not the
13 formulation-by-subject interaction. It's the complex
14 mixture-by-subject interaction. If you're willing to say
15 no, it can't occur, then we can drop that out of the
16 equation.

17 So, I'm just alluding to the three questions in
18 the context of everything we've heard in a previous set of
19 discussions that I think the committee can help us in a
20 very important way.

21 DR. TAYLOR: Dr. Brazeau?

22 DR. BRAZEAU: Roger, I think this committee
23 that you proposed is almost at a point where it's too late.
24 I think you're going to have to do a lot of running to
25 catch up because some of these complex biological products

1 are coming at us with full force. There are going to be
2 more and more, and I would hate to see the agency be behind
3 the 8-ball with a lot of these questions that were raised
4 today by the various presenters.

5 These are really fascinating molecules and
6 their interactions with tissues and their interactions,
7 their PK/PD are going to, I think, literally surprise us at
8 every turn.

9 So, I would encourage that this group really
10 start to work a fairly good rate or I think you're going to
11 be behind the 8-ball. I think you need to work with CBER
12 and you need to really start thinking about these,
13 otherwise you're going to take time to catch up.

14 DR. TAYLOR: Yes, Dr. Byrn.

15 DR. BYRN: Yes. I was really happy to see the
16 complex of excipients on the list because I think that's an
17 important issue and also the synthetic peptides is
18 obviously important and the botanicals are going to be
19 extremely important over the next few years.

20 My sort of bias -- maybe Jim wants to comment
21 on this -- is that this is a giant analytical problem
22 initially. We can't go very much further until we delve
23 into the analytical chemistry of these substances and do
24 everything possible with high end analytical capability to
25 understand the components and the proportions of them.

1 Then the question will come up, what's the
2 same? We need to get some powerful analytical methods
3 applied to some of these. Let's take a peptide or an
4 excipient. If all of the components are the same within a
5 certain range, we have to address the question, will they
6 then be equivalent? Will they be clinically equivalent?

7 It seems to me like we're just turning the
8 clock back on small molecule drugs. First we had to do
9 analytical to get that part under control. Then we have to
10 do dissolution and product behavior.

11 DR. TAYLOR: Roger, let me just make a comment
12 before you because it builds on what he's saying. I'm
13 reminded from my days of being involved in toxicology, when
14 you start talking about complex mixtures 10, 15 years ago,
15 as you know, most toxic exposures are not to a single
16 compound but to a variety of compounds. The question that
17 always comes up is, is it compound A plus B plus C behaving
18 in their normal way when they're together at some PD site
19 or is it compound A plus B plus C equals compound Z that's
20 doing something at that PD site? I think we're going to be
21 in the same dilemma.

22 So, using our usual reductionist approach by
23 measuring discrete things may not serve us well if we don't
24 move into looking at it from a different perspective, that
25 is, some perspective where these things interact with each

1 other, interact with their PD counterpart, and they may do
2 different things than we might predict, and we have to look
3 at that.

4 DR. WILLIAMS: Well, a quick comment to Steve.
5 I couldn't agree with Steve more because, in a sense, when
6 we have to go to PK/PD or comparative clinical, it sort of
7 signals that the analytical method failed, that we're not
8 willing to rely on the analytical method. The better and
9 better we get, in terms of characterizing these proteins
10 and mixtures, the more we'll be willing to rely on them
11 alone.

12 Bob, I couldn't agree with you more, and
13 particularly when you get to complex mixtures and
14 botanicals, what is happening at the level of the receptor.
15 It would be very difficult, and we certainly dealt with
16 that particular issue in the matter of conjugated
17 estrogens.

18 DR. TAYLOR: Any further discussion?

19 I'm sure this isn't the last time we'll do
20 this. I remember actually two meetings ago we had a fairly
21 extensive discussion that sort of whetted my thirst for
22 this, and I agree with Gayle that I would have hoped that
23 we would have a bit further along on this. I think today's
24 discussion was very much more organized and actually laid
25 out the pitfalls for us to an even greater degree. So, our

1 work is really cut out and the agency's work is really cut
2 out in this area. So, good luck.

3 Any other comments before we move ahead?

4 (No response.)

5 DR. TAYLOR: Now, the remainder of the meeting
6 is going to be carried on by Dr. Williams. He's going to
7 bring us up to date on many issues that involve topics for
8 the Office of Pharmaceutical Science.

9 DR. WILLIAMS: Thank you very much. I might
10 ask the Chair -- I'm going to cover four topics very
11 quickly -- would you like me to pause for questions and
12 comments after each one or just roll through?

13 DR. TAYLOR: Why don't we stop after each one.

14 DR. WILLIAMS: Okay, good.

15 DR. TAYLOR: I think they're very
16 heterogeneous.

17 DR. WILLIAMS: They're very heterogeneous, yes.
18 Macroheterogeneity.

19 These are the four topics I'd like to talk on
20 before the committee. The first one is the Product Quality
21 Research Initiative, and I have a series of about three
22 overheads that will tell the story. I might turn to Dr.
23 Hussain, who is still in the audience, who can help me
24 respond to the questions of the committee, if there are
25 any.

1 Now, basically what's happening in a very broad
2 overview way is that the agency has been talking about two
3 collaborations with academia and industry to generate
4 information that then can be used by the agency in forming
5 its policies that are developed in guidances in the
6 coordinating committees. There's a very broad set of
7 aspects to this picture, but I won't dwell on it because
8 I'm sure the committee sees it quite clearly.

9 Somebody talked a little bit about this being a
10 semi-permeable membrane where the information from the
11 collaborations can flow into the agency, but that's an
12 important concept because I think it's important for the
13 agency to always generate the guidance. I think the agency
14 does not see us building the guidances with industry for
15 the most part, recognizing that there may be some
16 occasional exceptions.

17 Now, this is a manifestation of Ajaz' technical
18 skills at the word processor. He's much more skilled than
19 I am. But essentially this is the way the collaboration
20 has been formed, and it has a steering committee composed
21 of representatives from the involved trade associations.
22 Those trade associations are PhRMA; three generic
23 associations, GPIA, NAPM, and NPA; an OTC organization,
24 NDMA; and then two more professional scientific societies,
25 AAPS and PDA. Now, the fact that I can even say all those

1 | acronyms -- I know somebody complained about acronyms, and
2 | I hope those names are all quite clear to you, but I can
3 | explain if the committee has any questions.

4 | Sometimes it's important to say who's not in
5 | the picture and who's not in the picture is BIO. BIO is
6 | the Biotechnology Industry Organization, and I think they
7 | have held back from participation here perhaps for some of
8 | the reasons we talked about in the prior session. It's a
9 | little unclear now about how this is all building and where
10 | we're all going, and I think for that reason, they're going
11 | to stick with their center CBER in terms of solving some of
12 | these issues that we talked about in the prior session.
13 | But that's not to say that we wouldn't always welcome BIO
14 | if they wanted to join.

15 | Now, I'll tell the committee that we've been
16 | talking about the collaboration for over two and a half
17 | years. So, it's had a fairly long gestation period. I
18 | actually think that was a necessary gestation period, as I
19 | look back at all the issues that we've been struggling
20 | with. Some of the issues we've been struggling with have
21 | been brought to our attention by this committee, as the
22 | committee recalls.

23 | The general thesis now, as it's being built, is
24 | that AAPS will establish a foundation which will have a
25 | board of directors, but it will also have oversight from

1 the steering committee membership for what it does in a
2 science and technical way. Now, you know me. I like to
3 draw pictures and boxes. I think I could draw this as a
4 picture much more easily than I can say the words, but I
5 think you need to see AAPS as having an umbrella oversight
6 for the foundation with a board of directors that has a lot
7 of responsibilities delineated in a set of bylaws,
8 responsibilities that are fiduciary in character, as well
9 as perhaps legal, a lot of other things that relate to
10 setting up a foundation and receiving and disbursing funds.

11 But the oversight for the true science and
12 technical activity for the collaboration, PQRI, will be
13 given by the steering committee, and that will all be
14 sorted out in the next several months hopefully by a series
15 of documents, bylaws and operating principles that we can
16 all certainly look at and make public and get public
17 comments in an appropriate way, if that's what we choose to
18 do.

19 Now, the agency will work with the foundation
20 via a cooperative research and development agreement, and
21 that will establish how this public agency, which has many
22 conflict and other rules governing its actions, can work
23 appropriately and in the public eye with the foundation.

24 Now, it took us a long time to get here, but I
25 can tell you that at a recent meeting of the steering

1 | committee, they did endorse this approach. I have to admit
2 | I'm delighted with it myself. I think it's a good solution
3 | to a number of very complicated problems.

4 | I might mention that the academic
5 | representation that we've all been concerned about will
6 | come from AAPS, and I think how that evolves we can watch
7 | in the future. But I think the way this is settling down
8 | creates an opportunity for good, fair, equitable academic
9 | representation via the professional society.

10 | Now, last month all the technical committees
11 | met, and these are the technical committees. They will be
12 | entirely familiar to this committee because they cover
13 | topics that we talk about time and again. They've actually
14 | created now a set of working groups that have chosen their
15 | topics, and I think the next step now is to form the
16 | working groups, write the protocols, write the game plans,
17 | get working. In parallel with that, hopefully there will
18 | be resources come available to let the work get
19 | accomplished in a, as we say, timely manner.

20 | I was delighted with this meeting. It really
21 | got down to some very skilled expert science and technical
22 | people talking to one another in a nice environment, and it
23 | was just a pleasure to watch the way they kind of all saw
24 | what each other was doing and how the interactions and
25 | linkages should be built. I don't have to point out for

1 | you that Dr. Byrn, who's a member of this committee, is
2 | also a Chair of one of the technical committees.

3 | I think that's my last one on this topic. I'll
4 | pause and see if there are questions, comments.

5 | DR. TAYLOR: Gayle?

6 | DR. BRAZEAU: Roger, as I was looking at this,
7 | we sort of have a modified flow chart of the last one that
8 | you showed us. An area that I thought of -- where is the
9 | area of excipients covered in this?

10 | DR. WILLIAMS: Kimberly, maybe you could turn
11 | that back on.

12 | Well, I'll give my answer. Ajaz, do you want
13 | to speak? But I think it's somewhere in there, the drug
14 | product. Ajaz?

15 | DR. BRAZEAU: I think that is an area that
16 | really requires some serious looking because we really are
17 | limited in some of the excipients we can use, and I think
18 | to provide some collaboration between industry, the agency,
19 | and academia would be a useful point. I would suggest that
20 | perhaps you do need to think about a working group that
21 | might deal with some of these issues of excipients.

22 | DR. TAYLOR: Ajaz?

23 | DR. HUSSAIN: There is a working group.
24 | Actually for the sake of clarity, I have combined the
25 | excipient working group under SUPAC-IR. So, there are

1 | three groups under working group number 2 under drug
2 | product. One will deal with stability, one deals with
3 | specifically excipients and other issues.

4 | DR. BRAZEAU: Will this cover some potential
5 | safety issues of some excipients or probably more product
6 | quality?

7 | DR. HUSSAIN: They deal with bio issues,
8 | bioequivalence issues. So, that's the limit.

9 | DR. WILLIAMS: I might mention I think Gayle is
10 | talking about a very important point which may talk
11 | specifically to how do you qualify a new excipient in terms
12 | of its safety and efficacy. Now, that obviously all goes
13 | beyond quality and gets into the realm of pharm/tox and the
14 | clinicians, but there's no reason why we couldn't start a
15 | group discussion there and draw in the appropriate experts
16 | from clinical and pharm/tox.

17 | I might mention that this is a very flexible
18 | structure that allows participation of other trade
19 | associations and interested parties. Example: When we
20 | talk about excipients, there's the International
21 | Pharmaceutical Excipients Council that has branches in this
22 | country and Japan and Europe. We intend to draw them into
23 | this effort in this particular technical committee.

24 | Also in terms of manufacturing equipment,
25 | there's the International Society of Pharmaceutical

1 Engineers, and I think they have a role here to play too,
2 and we've made an invitation to them to participate.

3 DR. TAYLOR: If there are no other comments,
4 we'll go to the next topic. Oh, I'm sorry. Dr. Byrn.

5 DR. BYRN: I just wanted to comment and say
6 that I think that this organization will allow -- doing it
7 by AAPS, it's now a good organization and it's an open
8 organization. There's a mechanism to get input from
9 everybody, and I'm really pleased with it because it is
10 open.

11 The other thing on Gayle's comment. A lot of
12 these projects at the meeting were what Dave Savello called
13 low-hanging fruit. The hope is that we can get some
14 projects going where we can get some big successes early
15 and then maybe take on some more complex issues like
16 approving excipients or doing research that will form the
17 basis for understanding excipients better which was
18 considered a more complex issue. So, some of these
19 projects are just aimed at getting some work done in a
20 reasonable period of time so we can show success.

21 DR. BRAZEAU: Could I ask an additional
22 question?

23 DR. TAYLOR: Sure.

24 DR. BRAZEAU: I guess I don't really
25 understand. Tell me how CRADA will work. I don't even

1 remember what the acronym CRADA stands for.

2 DR. WILLIAMS: I'm turning to Ajaz. He
3 probably knows a lot more about CRADAs than I do.

4 DR. HUSSAIN: CRADA stands for collaborative
5 research and development agreement. It allows the agency
6 to participate in research projects and even exchange
7 resources for that. It also has legal language associated
8 and everything else. So, it is an agreement to collaborate
9 on a given project.

10 DR. BRAZEAU: So, this is for the agency to
11 collaborate on research projects.

12 DR. HUSSAIN: Correct. The agency will not be
13 part of the foundation, so the agency has to step away from
14 being a member of the board of directors and so forth. So,
15 the CRADA will allow us in the agency to participate in the
16 working groups, technical committees, and so forth.

17 DR. BRAZEAU: Will this foundation then have a
18 competitive grant process?

19 DR. HUSSAIN: That's what we hope.

20 DR. BRAZEAU: And those details are being
21 worked out now?

22 DR. HUSSAIN: Yes.

23 DR. TAYLOR: Gayle, I think the CRADA is just a
24 generic. Correct me if --

25 DR. HUSSAIN: Yes, it is a generic.

1 DR. TAYLOR: It's a generic form of doing
2 business for the entire agency. For some of these
3 projects, for example, with Pittsburgh, I'm sure you have
4 CRADA documents you work with to do your project. So, it's
5 sort of like a memorandum of understanding. It just has an
6 acronym for it.

7 DR. STEWART: Does the foundation allow money
8 to come in from industry also?

9 DR. WILLIAMS: Yes.

10 Just to amplify, I think what the committee is
11 asking -- each one of these working groups may have some
12 projects that need to be done. Work needs to get done, and
13 I think the hope is that we'll have an open process so that
14 people, when there's a need, can compete and have access to
15 the opportunity to work with the collaboration.

16 DR. TAYLOR: Well, I think we need to move on.
17 Thank you. We can move on to the next topic.

18 DR. WILLIAMS: Now, the next thing I wanted to
19 talk about was this locally acting dermatologic products
20 bioavailability/bioequivalence guidance. That guidance, as
21 you know, is out as a level 1 for comment, and the comment
22 period ends in August of this year.

23 This is the status of where it is right now,
24 and we have discussed many of the aspects of this
25 particular guidance before the committee as well as before

1 the corresponding ORM advisory committee, DODAC, Division
2 of Ophthalmologic and Dermatologic Drug Products.

3 As we move to the fall then, what we're
4 imagining -- and I think we're in the process of discussing
5 just exactly how this will work -- we would like to bring
6 ACPS and DODAC back together again to talk about this
7 guidance and look at it from several standpoints, first of
8 all, to look at the public comments that came into it and
9 also consider the various issues.

10 Now, many of this committee participated in a
11 meeting in March with the DODAC advisory committee and are
12 aware that there are some very critical issues connected
13 with this particular guidance. I would say the key issue
14 relates to question 2, what are you willing to rely on, and
15 the key question there probably is the approach called
16 dermatopharmacokinetics as a means of assessing
17 bioavailability and bioequivalence. Members of this
18 committee were there and many of you know that the DODAC
19 members were not willing to rely on
20 dermatopharmacokinetics.

21 Now, I think what we want to do is come back to
22 the joint committee and say perhaps let's revisit the
23 issue. Would we be willing to rely as a society on
24 dermatopharmacokinetics as a means of assessing
25 bioavailability/bioequivalence? I think in that context we

1 | would like to imagine as part of the discussion additional
2 | research in PQRI that might amplify our willingness to
3 | rely. So, I think what we can talk about at that
4 | particular committee meeting is not only the public health
5 | decision, are we willing to rely on
6 | dermatopharmacokinetics, but also additional research that
7 | might increase that willingness. Research protocols are
8 | now in development in PQRI that will start to address these
9 | issues, and I would like very much to bring them before
10 | this committee and DODAC as well to see if they're
11 | satisfactory to achieve the intended purpose.

12 | Pause.

13 | DR. TAYLOR: Okay, this section is open. Dr.
14 | Brazeau?

15 | DR. BRAZEAU: Roger, having the privilege of
16 | attending that meeting in March, I think the reluctance of
17 | the DODAC committee to look at this was because it was a
18 | very rushed meeting. I believe that their real reluctance
19 | was that they didn't understand what was going on. For
20 | those of us who were there who had heard this before, it
21 | made good scientific sense, but for the majority of that
22 | particular committee, I'm not sure how much they had heard
23 | about it.

24 | So, I would encourage, if you're going to bring
25 | the two committees back together, that it's got to be very

1 educational. It might have to be taken at a level that's
2 not as fast paced because I think you might have done
3 yourself a disservice by having to do it in such a short
4 time frame. I think it's going to be critical that that
5 committee has a chance to really reflect on the material
6 and really understand the process because I don't think
7 they understood the process, and that's why I think they
8 were reluctant.

9 DR. TAYLOR: Yes, Dr. Lamborn.

10 DR. LAMBORN: I just concur. I had the same
11 sense, that having heard it in the two different
12 environments, it was so much more clear when it was
13 presented to this group than it was when it was presented
14 to them. I don't think it was just because we heard it the
15 second time.

16 DR. WILLIAMS: Well, you said very nicely what
17 I also heard perhaps more bluntly at the committee meeting,
18 and I couldn't agree with you more. I appreciate those
19 comments, and we will work very hard to get a good package
20 out to the two advisory committees next time. I take the
21 responsibility myself for not kind of thinking it through.

22 The reality is we're speaking to a very
23 important constituency, namely the clinicians who use these
24 drugs, and we have to build a solid case to say why they
25 should be willing to rely.

1 Now, I don't have to tell you it directly
2 relates to the prior discussion about complex molecules.
3 So, pretty soon we're going to be seasoned veterans of
4 these debates and we'll know just what to do in every
5 particular instance.

6 DR. BRAZEAU: I think it's going to be
7 critical, if you have this joint meeting, that you have to
8 show data that demonstrate the usefulness of these
9 techniques and it has to be clinical data, that clinicians
10 can understand. The theory they probably can understand
11 but it only really hits home when they actually see the
12 numbers and see how you do a comparison. I would carefully
13 choose your compounds such that they would have relevance
14 to the type of practice that some of these clinicians are
15 involved with.

16 DR. TAYLOR: Okay, the next topic.

17 DR. WILLIAMS: A hotly contested topic this
18 committee certainly is aware of is population and
19 individual -- I always like to add population, but it was a
20 critical component of the discussion.

21 There's a long history back here that I won't
22 go into. The last time we discussed this in depth before
23 the Advisory Committee for Pharmaceutical Science was in
24 August of 1996. It's a little hard to believe we're coming
25 on two years from that discussion.

1 The subsequent events were there was a meeting
2 in Boston last fall where I think the industry pointed out
3 to me that they needed a very clear, deliberate, public
4 discussion process before they themselves would be willing
5 to support the approach to the extent that that might ever
6 happen. I think the agency, me and others in particular,
7 took their concerns very seriously, and we have engaged now
8 in a process where we want to allow ample opportunity for
9 this possible change in our approach which I think all of
10 us realize has certainly revolutionary aspects.

11 Now, what is that deliberative process? One is
12 we shared all our data publicly. You can go on the
13 Internet and find that data if anybody wants to look at it
14 and massage it and subject it to any kind of analysis you
15 want.

16 We had a March workshop this year which
17 discussed individual bioequivalence, and there will be a
18 conference report. That workshop was sponsored by AAPS and
19 it proceeded along the usual path where we've been very
20 pleased to work with AAPS to kind of generate a consensus
21 about the issues and topics to be considered.

22 Then in conjunction with that workshop, we had
23 the first meeting of something we're calling an expert
24 panel. The panel is chaired by Dr. Les Bennett from the
25 University of California at San Francisco. It has

1 representation from a broad array of interested parties,
2 including this committee, and Dr. Lamborn is your
3 representative to that expert panel, so that she's aware of
4 what's going on.

5 Now, there were two meetings of the expert
6 panel in conjunction with this workshop. The notes of
7 those two meetings have been finalized and we'll make them
8 available to this committee at the right time so you can
9 see what was discussed. There was nothing concluded.

10 I think the next step after this is we will
11 pull together a packet of information for the expert panel
12 that will take into account the public comments to the
13 guidance plus some other further additional information and
14 evaluations and present it to the expert panel and see if
15 they can come to a conclusion, a recommendation to perhaps
16 this committee as well as the agency on how to move forward
17 on the general approach.

18 I could imagine perhaps some discussion of this
19 at the fall meeting of this committee if we're ready to do
20 that, and I can't quite commit to it now because some of it
21 depends on the availability of the expert panel.

22 Now, with that process statement I just made,
23 let me focus on the substance. The substance of the issue
24 I think in a core sort of way relates to that innocuous
25 looking little term, sigma D. Sigma D has always been the

1 challenge associated with individual bioequivalence.

2 I will congratulate this advisory committee
3 because I think the core discussion in August of 1996
4 focused on the public health need associated with whether
5 subject-by-formulation interactions were of concern or not.
6 So, I think at that advisory committee meeting -- and I
7 think we know we've had some difficult times discussing
8 this in front of the advisory committee -- the advisory
9 committee did hit on the core issue, and we've been
10 struggling with that issue in one way or another ever
11 since.

12 Let me postulate a game plan down here, and I'm
13 not announcing anything and I'm certainly not signaling a
14 decision from the expert panel because it wouldn't be my
15 decision. But they did talk in March about this
16 possibility, perhaps going through a multi-year public
17 health experiment where in our bioequivalence studies we
18 would ask for replicate designs but use average
19 equivalence.

20 Now, what that would do would be to not
21 increase significantly the burden to industry. You might
22 enter, say, half the number of subjects in a bioequivalence
23 study but study each person twice. Then at the end of that
24 multi-year period, you would have evidence that could be
25 used to specifically ask this question: Are subject-by-

1 formulation interactions likely or not? At the end of that
2 period, the agency and perhaps this advisory committee as
3 well would sift through the data and come to a conclusion
4 as to whether we will recommend individual bioequivalence
5 as an approach.

6 Now, at that point in time, which I'm trying to
7 figure out the numbers -- it might be 2003 or something
8 like that -- we might bifurcate and say if there is strong
9 evidence that subject-by-formulation interactions occur, we
10 will put it in the guidance and put the guidance out as a
11 recommendation so that if a firm wanted to not use
12 replicate study designs and look at individual
13 bioequivalence, they'd have to justify why they think
14 that's the case.

15 If it turns out we think subject-by-formulation
16 interactions are not likely, then we might allow individual
17 bioequivalence as an option for industry where the value to
18 them would be scaling and reduced variability, in other
19 words, these aspects of the equation. But you can see that
20 would be a more optional opportunity for industry that
21 would be to their benefit if they wish to choose the
22 benefit.

23 Now, I am not saying that is the path. I think
24 it's a possible path that was discussed in March.

25 I'll stop.

1 DR. TAYLOR: This topic is open for discussion.
2 I think the topic has received a lot of press
3 and I'm sure you a lot of heat because of it. Our initial
4 foray into it back in August of 1996 I think was a good
5 one, and I still stick by our recommendations at that time.
6 I do like the deliberative process that you are using to
7 come up with some consensus as to whether this is a
8 reasonable approach to this problem. So, the use of the
9 expert panel I think is quite good. I'd like to see that
10 data come back to this committee for review, and then we
11 can make further recommendations.

12 Dr. Vestal?

13 DR. VESTAL: Also I'd just like to add that, as
14 I recall, the issue we brought up before was the absence of
15 compelling data, and I think the proposal that data be
16 acquired is a very good one. I guess that depends a lot on
17 sponsor willingness to participate.

18 DR. TAYLOR: Dr. Branch?

19 DR. BRANCH: Given the level of discussion and
20 heat that has gone about this, does the agency actually
21 have enough information to be able to have enough replicate
22 studies already in hand to be able to at least look at this
23 in time for the next discussion meeting? In other words, a
24 few well-designed studies could really provide some useful
25 insights.

1 DR. WILLIAMS: I think the answer to that is
2 generally no. We have about 12 data sets of our own that
3 are replicate, and interestingly we heard from a sponsor at
4 the March meeting who had about another 13 or 14 replicate
5 study data sets. We're trying to obtain those data, and we
6 want to do it in a confidential way so that we protect the
7 sponsor. And then there have been a few other data sets
8 that sort of appear. So, we might end up with something
9 like 30 data sets that address the issue.

10 I think, however, there will always be the
11 suspicion that there was some bias in why those studies
12 were done originally as replicates. So, I think no matter
13 how many data sets we show in a retrospective way, it may
14 never get to the core issue that we would address in the
15 prospective way that I talked about.

16 DR. TAYLOR: Dr. Brazeau, did you have a
17 question or comment?

18 DR. BRAZEAU: No.

19 DR. TAYLOR: Any other comments about this last
20 issue, individual bioequivalence?

21 (No response.)

22 DR. TAYLOR: Then I think we've concluded the
23 business portion of the meeting. Dr. Williams, if you'd
24 like to make some concluding remarks.

25 DR. WILLIAMS: No. Did I cover all four

1 | topics? No.

2 | DR. TAYLOR: You skipped one, if you'd like to
3 | cover it. You did, you skipped it.

4 | DR. WILLIAMS: I'm sorry. I didn't mention
5 | BCS. I apologize.

6 | Biopharmaceutical Classification System is also a
7 | very new approach, and we are working right now on a draft
8 | guidance that embodies many of the principles and issues
9 | that were discussed before this advisory committee. We
10 | want to put that out over the summer as a level 1 document
11 | for public comment.

12 | I think the committee knows the science and
13 | technical aspects of the approach. What we're working on
14 | right now is the regulatory applications, and the
15 | regulatory applications are three in number: how the BCS
16 | approach could be used in the pre-approval period; in the
17 | post-approval period, how does it work for an ANDA, an
18 | abbreviated application; and then finally, for both a
19 | pioneer NDA and an ANDA, how does it work in the presence
20 | of post-approval change. Some of that third application
21 | the committee already heard about in the context of SUPAC-
22 | IR.

23 | Now, again I think like exposure, like
24 | individual bioequivalence, BCS is revolutionary in
25 | character as opposed to some of the other things that we

1 | talk about. I think its motivation is to reduce the number
2 | of in vivo studies that are needed to show bioavailability
3 | and bioequivalence. I guess I'm pleased to say whereas the
4 | other two revolutions have a tendency perhaps to increase
5 | the regulatory burden under certain circumstances, BCS
6 | tends to reduce the regulatory burden. So, I see it as a
7 | balancing approach among the three.

8 | I'll also emphasize that there's a strong
9 | interrelationship between individual bioequivalence, for
10 | example, and BCS because individual bioequivalence
11 | postulates a subject-by-formulation interaction that BCS
12 | assumes doesn't occur because if it did, you would want to
13 | see a replicate in vivo study. So, I don't have to
14 | emphasize for the committee that it's a very complex
15 | interrelationship of policies and science and technical
16 | issues here that we're struggling with, but I think the
17 | struggle will ultimately be successful, and at the right
18 | moment, we will bring BCS and the public comments to it
19 | back before the committee for a review.

20 | DR. TAYLOR: Thank you.

21 | Well, that concludes the business portion of
22 | the meeting. If there are any comments, Dr. Williams,
23 | would you like to make any last comments?

24 | DR. WILLIAMS: Except to say thanks to the
25 | agency staff who obviously put a tremendous amount of work

1 | into bringing this discussion to the committee and also
2 | thanks to the committee and the public for the opportunity
3 | to have the discussion.

4 | DR. TAYLOR: Thank you.

5 | I'd like to thank the committee for their hard
6 | work and perseverance. It has been a long two days. I
7 | know it has for me just coming off another trip.

8 | I'd like to thank the agency for organizing a
9 | tightly controlled presentation schedule. That made it
10 | easy for us to understand some of the principles that were
11 | being enumerated.

12 | And I'd like to thank Kimberly Topper for
13 | providing us the administrative overview so that we had no
14 | snafus.

15 | Any comment about the next meeting date or do
16 | we need to address that at this time? I'm told that we
17 | will probably have a meeting in October. The dates will be
18 | communicated to you by either e-mail or snail mail or some
19 | other mechanism.

20 | At any rate, if there are no other comments,
21 | I'd like to adjourn the meeting and thank you very much for
22 | your participation.

23 | (Whereupon, at 3:10 p.m., the committee was
24 | adjourned.)

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