FOOD AND DRUG ADMINISTRATION

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

8:34 a.m.

Thursday, July 19, 2001

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

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

2 (8:34 a.m.)

3 DR. BYRN: Good morning, everyone. I'd like to
4 welcome you to the Advisory Committee for Pharmaceutical
5 Science meeting on July 19th.

6 First I'd like to ask Nancy Chamberlin to read
7 the conflict of interest statement.

8 MS. CHAMBERLIN: Good morning.

9 The following announcement addresses conflict
10 of interest with regard to this meeting and is made part of
11 the record to preclude even the appearance of such at this
12 meeting.

13 Since the issues to be discussed by the
14 committee at this meeting will not have a unique impact on
15 any particular firm or product, but rather may have
16 widespread implications with respect to entire classes of
17 products, in accordance with 18 U.S.C. 208(b), all required
18 committee participants have been granted a general matters
19 waiver which permits them to participate in today's
20 discussions.

21 A copy of these waiver statements may be
22 obtained by submitting a written request to the agency's
23 Freedom of Information Office, room 12A-30 Parklawn
24 Building.

25 With respect to FDA's invited guests, Dr.

1 Robert G. Hollenbeck, Dr. Jeanne Moldenhauer, Dr. G.K.
2 Raju, Dr. William Kerns, Dr. Gordon Holt, Dr. Leon Shargel,
3 Dr. Roger Dabbah, and Dr. Leon Lachman have reported
4 interests which we believe should be made public to allow
5 the participants to objectively evaluate their comments.
6 Dr. Hollenbeck would like to disclose ownership
7 of stock in Aerogen, Inc. and University Pharmaceuticals of
8 Maryland, Inc. He is also Vice President and serves as a
9 scientific advisor to University Pharmaceuticals of
10 Maryland, which is a contract research and clinical studies
11 manufacturer. Additionally, he consults with various
12 companies in the pharmaceutical industry.
13 Dr. Moldenhauer would like to disclose that she
14 is employed by Vectech Pharmaceutical Consultants.
15 Currently, she has a paper being prepared for publication
16 with David Jones regarding feasibility of Scan RDI
17 Technology for biological indicators, based upon original
18 research performed at Jordan Pharmaceuticals. She also is
19 editing a book on lab validations which includes some
20 chapters on rapid microbiology methods. However, she has
21 no financial interest in the chapters of the book.
22 Additionally, Dr. Moldenhauer receives honoraria from
23 Parenteral Drug Association for teaching a college course
24 on aseptic processing.
25 Dr. Raju would like to disclose that some of

1 his past research has been funded by Purdue University as
2 part of a project funded by the Camp Consortium, a non-
3 profit consortium of Pharma Companies. Currently, he is
4 serving as the principal investigator on a project funded
5 by the Camp Consortium. He consults for a number of other
6 pharmaceutical companies. Additionally, he has other
7 fiduciary relationships with Light Pharma, a consulting
8 company.
9 Dr. Kerns would like to disclose that he is a
10 scientific advisor to Canfite Biopharma, Elsai Co., Ltd.,
11 Biocentra, and Omniviral Therapeutics.
12 Dr. Holt would like to disclose his employment
13 with Oxford GlycoSciences, a toxicology biomarker company.
14 Dr. Shargel would like to disclose that he is
15 employed by Eon Labs Manufacturing Company.
16 Dr. Dabbah would like to disclose that he is
17 employed by U.S. Pharmacopeia.
18 We would also like to disclose that Dr. Leon
19 Lachman is President of Lachman Consultant Services, Inc.,
20 a firm that performs consulting services to the
21 pharmaceutical and allied industries.
22 In the event that the discussions involve any
23 other products or firms not already on the agenda for which
24 an FDA participant has a financial interest, the
25 participants are aware of the need to exclude themselves

1 from such involvement and their exclusion will be noted for
2 the record.
3 With respect to all other participants, we ask
4 in the interest of fairness that they address any current
5 or previous financial involvement with any firm whose
6 products they may wish to comment upon.
7 DR. BYRN: Thank you very much.
8 Now let's go around and introduce some members
9 that are seated at the panel, and also we'll test the
10 microphones, and we can start over here to the left. What
11 you do is press the talk button. It should light, and then
12 you can introduce yourself.
13 DR. KERNS: Good morning. My name is Bill
14 Kerns. I'm representing the expert working group on
15 vasculitis in a presentation later this morning.
16 DR. HOLT: I'm Gordon Holt. I represent the
17 cardiotoxicity expert working group this morning.
18 DR. SHARGEL: I'm Leon Shargel. I'm Vice
19 President, Eon Laboratories, a generic pharmaceutical
20 manufacturer.
21 DR. MEYER: I'm Marvin Meyer. Two weeks ago I
22 retired from the University of Tennessee. At that time I
23 was chair, professor, and associate dean for research in
24 the College of Pharmacy.
25 DR. LEE: I'm Vincent Lee, professor and chair

1 at the University of Southern California.
2 DR. BLOOM: Joseph Bloom, from the University
3 of Puerto Rico.
4 DR. BOEHLERT: Judy Boehlert, and I have my own
5 pharmaceutical consulting business.
6 DR. JUSKO: William Jusko, professor at the
7 University of Buffalo.
8 DR. RODRIGUEZ-HORNEDO: Nair Rodriguez,
9 associate professor of pharmaceutical sciences, University
10 of Michigan.
11 MS. CHAMBERLIN: Nancy Chamberlin, Exec. Sec.
12 DR. BYRN: Steve Byrn, chair and professor at
13 Purdue and chair of the committee.
14 DR. ANDERSON: Gloria Anderson, Callaway
15 Professor of Chemistry and chair at Morris Brown College in
16 Atlanta.
17 DR. VENITZ: Jurgen Venitz, associate
18 professor, Department of Pharmaceutics, Virginia
19 Commonwealth University.
20 DR. DOULL: John Doull, clinical toxicologist,
21 University of Kansas Medical Center.
22 DR. BARR: William Barr. I'm professor and
23 director of the Center for Drug Studies at Medical College
24 of Virginia, Virginia Commonwealth University.
25 DR. CHOWDHURY: I'm Badrul Chowdhury. I am a

1 medical team leader, the Center for Drugs, U.S. Food and
2 Drug Administration, Division of Pulmonary and Allergy
3 Drugs.
4 DR. ADAMS: Good morning. I'm Wallace Adams,
5 Office of Pharmaceutical Science in CDER, and involved with
6 the nasal BA/BE guidance that we'll be discussing this
7 morning.
8 DR. BYRN: I'd like to introduce Helen Winkle,
9 who will give an introduction to the meeting. Helen is
10 acting director of the Office of Pharmaceutical Science.
11 MS. WINKLE: Well, first of all, I want to say
12 good morning to the committee. They spent a long day with
13 us yesterday. We went through some different training
14 sessions on what we actually do in the Office of
15 Pharmaceutical Science. They already had a long day
16 yesterday, so hopefully today we can really get into the
17 science and talk more about the things that they probably
18 have a real interest in. So, I want to, first of all,
19 welcome them. I appreciate their time and effort in
20 participating with us on this advisory committee.
21 I also want to welcome the prospective new
22 members. We're still processing the paperwork for these
23 members, but this is Dr. Meyer, who's already introduced
24 himself. And also Art Kibbe, who will be joining us at the
25 next advisory committee meeting.

1 Also for the first time at this advisory
2 committee meeting we have some industry members on the
3 advisory committee. They will not be voting members, but
4 they will represent the industry in discussions that we
5 have. Dr. Shargel has joined us for this purpose, and also
6 Dr. Shek will join us in the future. Dr. Shargel
7 represents the generic side of the industry, and Dr. Shek
8 represents the innovator side.
9 I also want to welcome our distinguished guests
10 who are here to participate with us today in discussions on
11 various issues that we're bringing before the committee, as
12 well as the audience.
13 Before I start, I want to go quickly through
14 the agenda so everyone will understand what we're going to
15 talk about today, the issues we're going to address. But
16 before I do that, I sort of want to make three points about
17 the importance of this advisory committee. We talked
18 yesterday at the training session some about this
19 importance, but I want to emphasize that today again.
20 Basically the three points I want to bring out
21 is the importance of this committee in enhancing the
22 science base in CDER. Secondly, I want to talk a little
23 bit about how this advisory committee fits into developing
24 our standards and regulations and guidances, and also the
25 fact that this advisory committee is very important to us

1 in CDER and in the Office of Pharmaceutical Science in
2 fostering communication.
3 First of all, enhancing the science base. We
4 talked about this yesterday as well, but I want to make
5 this point again. This is a very unique committee. Most
6 of the advisory committees in FDA and in CDER especially
7 are looking at product-specific areas. They will discuss
8 products that are before us for approval and get into the
9 various aspects of the process and science that affect
10 those products.
11 However, this committee, again as I said, is
12 unique. It really is dealing with all types of issues that
13 affect us in the Office of Pharmaceutical Science, issues
14 that cross the borders. I already mentioned we have
15 generic and innovator representatives here. We also look
16 at a variety of disciplines and support those disciplines
17 through some of the recommendations that come from this
18 committee. So, it's very unique. It's dealing with a
19 variety of issues. These issues are very important to us
20 in the Office of Pharmaceutical Science in making
21 regulatory decisions. Without their scientific expertise,
22 we really cannot make the decisions that are necessary to
23 help us in developing standards and guidelines, et cetera.
24 The development of these standards and
25 guidelines are important in how we do business in CDER.

1 The standards are used externally by companies. They're
2 very important to go out to companies and let them know how
3 we expect business to be done in order to enhance the
4 regulatory process. But they are also very important to us
5 internally within FDA. We use these guidances and these
6 policies to help our own reviewers in doing their day-to-
7 day processing so that we can ensure appropriate and
8 consistent decisionmaking. So, it's very important, the
9 decisions we make here will have an effect, again, not only
10 on industry but us here as well.
11 Fostering communication. This is difficult, I
12 think, from the committee's standpoint to understand this
13 concept, but these are public meetings and the public is
14 available to hear what we have to say and the types of
15 issues that we're grappling with and the information and
16 recommendations that we get from outside organizations,
17 from outside scientists and get to hear their expertise and
18 how that expertise helps influence what we do. So, it's
19 very important to us at the FDA to have this process go on.
20 We're very appreciative of the people who give
21 up their time to come in here. Each one of you has, I'm
22 sure, other things that you're very busily involved with
23 and we appreciate the time that you take to come in here
24 and spend with us to help us in these really important
25 aspects of the regulatory process.

1 As I said, I want to go through the agenda.
2 I'll try to do that quickly, but I want to give you a feel
3 for the next two days. I'm hoping that on all of these
4 topics we can have a lively discussion. Some of the topics
5 are more heads up than actual topics to obtain
6 recommendations, but others are important issues where we
7 really want the input of the members of the advisory
8 committee.
9 You all have the agenda in front of you. The
10 first two agenda items are focused on updates from the two
11 subcommittees of the advisory committee. The first
12 subcommittee, the Orally Inhaled and Nasal Drug Products
13 Subcommittee actually met this week on Tuesday to address
14 the issue of dose response for nasal sprays. This
15 subcommittee is chaired by Dr. Lee, and the discussion on
16 the dose response was generated by a need to address the
17 issues on the current draft guidance on BA and BE. The
18 subcommittee representatives, who have already introduced
19 themselves, will provide you with background on the issues
20 and will provide you also with the recommendations of the
21 subcommittee.
22 It was a very interesting subcommittee meeting.
23 I think that we feel that this is an issue now, as far as
24 the guidance, that we can move forward with, after we are
25 able to address these recommendations to you and get your

1 concurrence on it.

2 The second subcommittee that will present today

3 is the Nonclinical Studies Subcommittee, which is chaired

4 by Dr. Doull. This subcommittee met in May, and at the

5 subcommittee meeting the two working groups that are under

6 this subcommittee met to determine future direction, and

7 Dr. Holt and Dr. Kerns are here today to talk about the

8 issues that were discussed at these two expert working

9 groups, and to talk about the process of these working

10 groups. Later on in that presentation I will also talk a

11 little bit about the future of this subcommittee. We are

12 looking at other alternatives on how we will handle this

13 subcommittee in the future.

14 The next item on the agenda is an update to the

15 committee on what we are doing on our initiative on risk-

16 based CMC reviews. If you all remember, we had an

17 introduction to this particular topic at the November

18 advisory committee last year, and today we're going to talk

19 a little bit about the outcome of our workshop, which was

20 held on this topic in June, and to update you on the

21 direction that we're going as far as this particular

22 initiative is headed.

23 After lunch we'll have an open public hearing,

24 and then when we will discuss the topic of optimal

25 application of at-line process controls for pharmaceutical

1 products. This is a new initiative that we're undertaking,
2 and Dr. Hussain will introduce the initiative to the
3 advisory committee, along with a case study that will be
4 presented by Dr. Raju.
5 As science and technology change and are
6 further advanced, we in FDA need to be sure that we're on
7 top of these changes and that we can explore the ways that
8 these changes are going to affect our regulatory process.
9 Today we're going to look for the committee's thoughts on
10 this initiative and to explore with you any ideas that you
11 may have on our best way to pursue this initiative in the
12 future. This is an area that I can assure you that we'll
13 be talking more about in the next few years with this
14 advisory committee.
15 The next item on the agenda is a similar item.
16 It's also a new topic. And it's to solicit the
17 committee's input on establishing acceptance limits for
18 microbiological tests that use newly developed
19 technologies. I think this is one of the things we have to
20 grapple with day to day in the FDA, the changing
21 technologies. And as we look at those changes, we have to
22 look at how we're going to change our regulatory processes,
23 or what we need to do differently in our regulatory process
24 to adapt to these changes.
25 Tomorrow the first thing on the agenda is to

1 discuss clinical pharmacology issue on drug transfer into
2 breast milk and to get some input from you as to how best
3 to interpret data that we will be gathering. We're in the
4 process of developing a guidance on lactation studies and
5 would like your recommendations on moving forward with that
6 guidance.
7 The second item on the agenda, after the public
8 hearing, is to discuss some of the issues and concerns we
9 have as we move forward regulating liposome drug products.
10 Obviously, this form of drug delivery is expanding, and we
11 need to make sure that we are correctly addressing all the
12 issues. This too is a technology that we need a lot of
13 assistance on in deciding how we will move forward in the
14 regulatory process.
15 Tomorrow we will mainly present to the
16 committee where we are in regards to this area of
17 regulation and what issues we've identified that we still
18 need to address. We also had a workshop on this subject in
19 the spring, and FDA has some issues that came out of that
20 workshop that we would like to address with you.
21 One of the topics you may find that I didn't
22 mention today is dermatopharmacokinetics. This is an issue
23 that's come up several times in this committee. We at OPS
24 are reconsidering the direction that we want to take with
25 this methodology for determining bioequivalence for

1 dermatological products, and we're really not ready at this
2 time to discuss what direction we're going. However, I
3 want stress the fact that we are definitely interested in
4 the importance of alternative methods for doing
5 bioequivalence, and we're really trying to commit to
6 eliminating or reducing the testing requirements for these
7 products, where possible. We are looking at exploring new
8 alternative methods besides just DPK. So, in November of
9 this year, when the next advisory committee meets, we will
10 bring that topic up again.
11 I know this is a full agenda. I look forward
12 to the committee's discussion and input. I think all of
13 these topics are very important to us in the Office of
14 Pharmaceutical Science, and I know that your input will
15 help us in setting our regulatory direction.
16 Before I end this morning, I do want to
17 recognize that this is Dr. Byrn's last meeting as chairman
18 of this committee. I want to publicly acknowledge how much
19 we in CDER appreciate Dr. Byrn's support and dedication to
20 this committee. He's worked very hard. We've worked with
21 Dr. Byrn in various different settings. He's very
22 dedicated to the whole idea of product quality research and
23 product quality regulation, and we really appreciate all
24 his help. So, I want to publicly announce that FDA really
25 will miss you, Steve. We appreciate everything, and thank

1 you.

2 So, unless there are any questions, I'm going

3 to hand it back to Dr. Byrn. Thank you.

4 DR. BYRN: Thanks very much, Helen. I enjoyed

5 my participation on this committee, even the site-specific

6 stability work.

7 (Laughter.)

8 DR. BYRN: Some of you realize what was

9 involved in that. It was very enjoyable.

10 We're going to move ahead with the

11 subcommittee, and as Helen said, we have two reports of

12 subcommittees. The first one is the Oally Inhaled and

13 Nasal Drug Products Subcommittee, and Dr. Vince Lee will

14 introduce the issues, and then we'll proceed. Thanks very

15 much, Vince.

16 DR. LEE: Thank you, Steve. I didn't realize

17 that this is your last meeting. It could be a long

18 meeting.

19 In any event, I'm here to report to you to set

20 the stage for the presentation to follow. We met about two

21 days ago in this very room to talk about issues concerning

22 the nasal aerosols and nasal sprays. Before I begin, I

23 would like to say that I'm so impressed with how quickly

24 the government got this documentation printed. This was

25 done last evening. Thanks to e-mail, we had the visual

1 material sent here, and then I was impressed to find that
2 it got printed by the government Kinko for us.
3 (Laughter.)
4 DR. LEE: So, the meeting was very interactive.
5 It was meant to last until 5:30 in the afternoon. I'm
6 pleased to report that we finished our business before 4
7 o'clock.
8 The specific issue that we were asked to
9 address was suspension formulations. Helen already talked
10 about that we were there to talk about dose response for
11 these formulations. And the main issue is to see whether
12 or not we can use it as a way to determine the comparable
13 in vivo performance for local delivery. Those of you
14 following the guidance must be aware of the four points
15 above it. You have it and Wally might reiterate it in his
16 presentation.
17 So, by the time we come to this point, we
18 already know the comparability in the actives and
19 inactives, the device, the in vitro performance, and the in
20 vivo performance in regards to systemic exposure.
21 The subcommittee was asked to address two
22 questions, and I highlighted the main points we were asked
23 to consider. The first point was whether or not the
24 placebo-controlled traditional 2-week rhinitis study
25 conducted at the lowest active level would be sufficient to

1 confirm equivalent local delivery of the suspension
2 formulation for allergic rhinitis. So, that was the first
3 question.
4 The second question was similar, except that
5 the test would be different. There we were asked to look
6 at the placebo-controlled park study or the EEU study
7 conducted at the lowest active level. In order to address
8 these two questions, a special panel was constituted, and
9 this is the subcommittee of 10 individuals -- actually 11.
10 Dr. Shek was not able to join us. Dr. Leon Shargel
11 attended. I was there, and Gloria Anderson was there.
12 Both of us were in red because we were members of this
13 committee.
14 The individuals in blue were really the
15 experts. They were the practitioners in the clinic
16 settings and they were useful in the discussion. Dr. Hauck
17 many of you might know.
18 The individuals in green are the industrial
19 representatives.
20 The individuals in purple -- and this by the
21 way is the Lakers' color --
22 (Laughter.)
23 DR. LEE: -- were the representatives from the
24 agency. In fact, Dr. Chowdhury and Dr. Meyer will be
25 giving us the background leading to the recommendations of

1 the subcommittee.

2 So, this is a very busy slide. It was work of

3 Wally Adams. He asked me to put it up there so that you

4 can all read it to understand the issues. So, the point

5 that we were asked to address that the draft guidance

6 recommends the conduct of a clinical study for allergic

7 rhinitis to confirm equivalent local delivery, and I would

8 like to emphasize that point.

9 So, this is the background for the report this

10 morning, and understand that we have Dr. Meyer and Dr.

11 Chowdhury to teach us so that we can all understand the

12 recommendations of the subcommittee. Wally is going to

13 come up after those two presentations to tell us what the

14 recommendations of the subcommittee were.

15 Thank you.

16 DR. BYRN: Thanks very much, Vince.

17 The next speaker will be Dr. Chowdhury, who

18 will talk about difficulties with showing a dose response

19 with locally acting nasal sprays and aerosols.

20 DR. CHOWDHURY: Good morning.

21 I'll be talking about the point that it is very

22 difficult to show a dose response for locally acting drugs

23 for allergic rhinitis. We had the same discussions in the

24 presentations two days ago. I'll go through the same

25 points again and make the point that for locally acting

1 drugs, which is used for treating allergic rhinitis, it is
2 indeed very difficult if not impossible to show a dose
3 response. As you remember, dose response is one of the
4 points that is typically asked for for showing
5 bioequivalence.
6 I will use three drugs and five clinical trials
7 as examples to make my point. Before I go into that, I
8 would like to briefly introduce a topic about nasal sprays
9 and aerosols, and talk a bit about allergic rhinitis, the
10 disease that we're talking about, and the clinical trials
11 that are done for drugs which are to be approved for
12 allergic rhinitis, to kind of introduce the topic, the
13 background, and then I'll go to the clinical trials itself.
14 I think that will make the clinical trials more easy to
15 follow.
16 Now, we are talking about nasal sprays, which
17 can be either solutions or suspensions, or nasal aerosols,
18 which means that these have some propellant in them. The
19 point for discussion today are really the suspensions.
20 These are some examples of drugs which are currently
21 available for treating allergic rhinitis, which falls in
22 these categories. Examples of solutions are an
23 antihistamine, anticholinergic drug, which is Atrovent,
24 sodium cromoglycate, and some steroids. The suspension
25 nasal sprays and the suspension nasal aerosols are all

1 steroids, and the focus of discussion today is actually on
2 the suspensions.
3 Allergic rhinitis is a pretty common disease.
4 The patients who have allergic rhinitis are sensitized to
5 something in the environment that are called allergens, and
6 when they get exposed to it, they have disease which is
7 typically manifested by a constellation of symptoms, which
8 I'll go through in my second slide as I talk about clinical
9 studies.
10 The clinical studies that are used for looking
11 at these drugs in terms of efficacy for the purpose of
12 approval are of three general types, and they're named as
13 natural exposure study, day-in-the-park study,
14 environmental exposure unit study, or EEU study. I'll go
15 through them one by one.
16 Natural exposure studies are typically done in
17 a season when the patients are exposed to the allergens and
18 are symptomatic. For example, a person who is ragweed
19 sensitive would be studied in ragweed season, which around
20 here is late fall. And the patients for these studies are
21 recruited. They're usually symptomatic, and once
22 recruited, they're taken through a couple of days when they
23 are either given placebo or nothing, to establish the
24 symptoms, and this period is the baseline period.
25 After that, they are put on the drug in

1 question. They are treated for a couple of days, typically
2 for seasonal allergic rhinitis, about 2 weeks. For
3 perennial rhinitis it's about 4 weeks in a double-blinded
4 fashion.
5 Again, the patients score their symptoms and
6 they get some measure of the drug's effect. The difference
7 between the baseline, which is the run-in, and the
8 treatment is taken into consideration to find if the drug
9 is better than placebo or not. They're typically parallel-
10 group studies, double-blinded.
11 A day-in-the-park study is pretty similar.
12 However, the study is done over a very short time period,
13 typically 1, 2, or 3 days. The patients are taken in a
14 park where there is a lot of exposure to allergens, and
15 then they're given the drug and the symptoms are scored
16 again. These again are typically parallel group studies.
17 The EEU study is really an artificial
18 situation. The patients are put in a room -- for example,
19 a room like this -- and are exposed to allergens in a very
20 controlled setting. This out of season. The patients are
21 not asymptomatic. They are given this exposure for a
22 couple of days to make them symptomatic, and then they're
23 brought back in and they're given the drug or the placebo
24 to have an efficacy assessment.
25 So, let's go over these. A natural exposure

1 study is more natural, typical outpatient, and as you move
2 down they become more pharmacodynamic in nature. For dose
3 response which we're talking about today, typically the
4 natural exposure study and day-in-the-park study are used
5 and we have more experience with. The EEU study is used
6 mostly for questions like pharmacodynamic issues like onset
7 of action, offset of action, and things like that.
8 When I go through my examples, I'll have an
9 example from one day-in-the-park study and the rest will be
10 natural exposure studies.
11 For assessing efficacy, we typically depend on
12 patients' rating of symptoms. They are listed here. The
13 nasal symptoms like itching, sneezing, rhinorrhea, or
14 congestion. Or they can be non-nasal symptoms. As I go
15 through the examples, this will become more clear.
16 The symptoms are more typically scored by the
17 patient and there are various scales used. The one that we
18 use now are typically 0, 1, 2 and 3 scales. However, other
19 scales can be used, as my examples will show.
20 Now, in addition, there are often other
21 measures which potentially may be used. I say potentially
22 because these are more experimental and they are used
23 mainly to study disease pathology or pathogenesis. For
24 example, objective measure like nasal passage patency are
25 markers of inflammation. The point I want to make is,

1 these are very interesting tools. However, they are not
2 yet to the point where they can be used for assessing the
3 drugs in a clinical setting because they are not clinically
4 validated, and perhaps may or may not relate to the
5 disease's activity.
6 Let me go through the examples one by one. The
7 examples that I will be using, some of them are actually in
8 the public domain, others are not. Just to be fair, I'll
9 not name the drugs. I'll call them drug A, B and C. I'll
10 have an example of a solution nasal spray. I realize this
11 is not the question for today. However, I want to put up
12 an example to show that the difficulty in dose response is
13 not unique for suspensions. Then I'll have suspension
14 nasal sprays and aerosols.
15 A total of five clinical trials I'll be using
16 to make the point. For the solution it will be a day-in-
17 the-park study. For the others they will be a natural
18 exposure study, dose-ranging, and then there will be two
19 comparative studies in which the aerosol and the aqueous
20 spray were used in the same study.
21 Let's go with one example at a time. The first
22 one is a day-in-the-park study, using a solution nasal
23 spray I'll call drug A. This was a two-center U.S. study
24 conducted about 11 years ago. It was conducted in seasonal
25 allergic rhinitis patients, ages 12 and above, and the

1 patients were in the park for 2 days. Three dose levels
2 were used, which will become clear in the next
3 transparency. Drugs were given on a b.i.d. schedule.
4 Since the patients were in the park for 2 days, on the
5 first day they got a drug in the morning, in the afternoon,
6 and the next day they got it again in the morning.
7 Efficacy was instantaneous scoring.
8 Instantaneous means the patients scored the symptoms at the
9 time they were scoring. For example, how do I feel right
10 now? And the six symptoms which were scored are listed
11 here, some nasal symptoms, some eye symptoms. And the
12 scale here was 0 to 5. On the days when the patients were
13 in the park, which was day 1 and day 2, early in the
14 morning, they scored the symptoms very frequently, and then
15 in the evening less frequently. All the scores were summed
16 up and the result that I am going to show will be as major
17 symptoms complex, which is a summation of all the scores.
18 Now, this is the baseline. Throughout my trial
19 presentation, the same format of graphs will be used, the
20 bar graphs, and the bars from left to right will match with
21 the legend from top to bottom. Placebo will be on the left
22 all the time and blue in color.
23 In this study, the three dose levels were one
24 spray b.i.d., two sprays q.d., and two sprays b.i.d. It's
25 a pretty large study with about 50 patients. And the

1 baseline is here, which is pretty close but not exactly the
2 same.
3 Now, this is the result of the study, and I'm
4 expressing the result as mean percentage change from
5 baseline to take care of the baseline differences. We note
6 here the placebo response was about 10 percent. The study
7 had an active control, which is an antihistamine,
8 chlorpheniramine, and the effect size here was about 40
9 percent. So, the difference was about 30 percent here in
10 this study. And if you look at the result, this is the
11 lowest dose, one spray b.i.d., and this is two sprays
12 b.i.d., so this is two-fold higher. This is one spray
13 b.i.d., and this is two-fold higher.
14 If you look at it, perhaps there is a trend of
15 dose response. However, if you look between these two,
16 this is two sprays q.d., and this is two sprays b.i.d..
17 This is higher than this, and the effect goes in the
18 opposite direction. So, the point here is, you don't
19 really see a dose response. It's almost like a random
20 phenomenon. This will become more clear as I go through my
21 other examples.
22 A second example will be the suspension nasal
23 spray, and the first one will be a natural exposure study.
24 This study was conducted in the U.S. a couple of years
25 ago. It was again a natural exposure study, the first one

1 which I talked about. It was conducted in ragweed
2 sensitive seasonal allergic rhinitis patients, ages 6 and
3 above. The study had a 1-week baseline where no drug was
4 given, followed by 4 weeks of treatment in which the
5 experimental drug was given. The treatment was q.d. dosing
6 of four dose levels, and note here the doses were over an
7 eight-fold range. The previous example was just a two-fold
8 range.
9 The efficacy assessment here was 12-hour
10 reflective. The reflective is different than the
11 instantaneous which I said earlier. Reflective means the
12 patients scored their symptoms noting how they feel over
13 the previous 12 hours or so. The symptoms scored here were
14 three nasal symptoms: runny nose, congestion, sneezing.
15 The scale was the typical 0 to 3 scale. The sum of the
16 three scores was used, and we just called it a nasal index
17 score.
18 This is the result. Nasal index score. This
19 is the baseline, treatment, and this is the change, which
20 means the difference between this and this. The baseline
21 here is very similar, so I'm using the raw score. And if
22 you look at the change here, this is the placebo, and the
23 placebo actually had some response, quite a bit of
24 response. And this will come back later on also that for
25 allergic rhinitis, placebo indeed is almost a drug, has

1 some good response.

2 And the dose levels used here were between 32

3 and 256. There's an eight-fold difference, and these are

4 the four bars showing the four dose ranges. The point here

5 is virtually flat. The lowest, 32, and the highest, 256,

6 were very close. So, essentially it cannot really make a

7 difference in the clinical study with this example over an

8 eight-fold range.

9 This study had three symptoms. Just to look at

10 it a bit further, I looked through if these three symptoms

11 looked individually would make any difference or not. And

12 if you look through it, it really did not. Perhaps for

13 congestion there was some trend. However, they were almost

14 flat, and the changes were really, really very small.

15 The next example, in the same study a spray and

16 aerosol was used. The drug substance, drug B, was the

17 same. It was a natural exposure study. It was a Canadian

18 study done in seven centers in 1994. Patients were

19 ragweed-sensitive, seasonal allergic rhinitis patients,

20 ages 12 and above. The design was very similar: 1 week

21 baseline, 3 weeks of treatment, and the dosing was q.d. of

22 three dose levels.

23 Efficacy assessment was the same again:

24 12-hour reflective of three nasal symptoms. And these are

25 the results here. This is the primary efficacy endpoint in

1 this study, which was the nasal symptoms. This is a
2 summation of the scores of rhinorrhea, sneezing, and
3 congestion. Eye symptoms are also here. The point really
4 can be made with the total symptoms here, and if you look
5 at it, this is a spray, spray, 256, 400. These two powers.
6 And this is a lower dose, this is a higher dose. However,
7 on efficacy it goes in the opposite direction.
8 This is the aerosol, 200 b.i.d., same as this
9 as a nominal dose. It really does not fall on top of each
10 other. Essentially the theme is recurrent here that these
11 differences that we see are essentially fluctuation over a
12 baseline efficacy.
13 Now, the last example is drug C. It is again a
14 suspension nasal spray. Now, when I was preparing for this
15 talk, I went through almost all the clinical studies which
16 were done for getting these drugs approved, and I picked up
17 drug B as a classic example. This is what we typically
18 see. Drug A is a solution example, and drug C is perhaps
19 the best-case scenario for a dose response that we have,
20 and I'll show even for this drug we don't really see a
21 typical dose response.
22 This study was a 15-center U.S. study conducted
23 in 1992, a pretty large study. This was done on SAR
24 patients, ages 18 and above. The study had a 1-week
25 baseline period followed by 4 weeks of treatment. And in

1 this study q.d. dosing was used over a 16-fold range, very
2 large 16-fold range. Efficacy was very similar to the
3 studies before, 12-hour reflective. And eight symptoms
4 were measured here, some nasal and some eye symptoms. They
5 were scored on a 0 to 6 scale.
6 In this particular study, the primary endpoint
7 was on physician-rated symptoms, so that's what I'm showing
8 first. And I'm showing the results over the whole study
9 time period, day 3, day 7, 14, 21, and 28. All the times
10 can be used. I'll just use day 21 to make my point here.
11 The placebo response here as a change from
12 baseline percentage was close to 30 percent. The drug
13 response was 50 to 60 percent, so the separation between
14 drug and placebo was not that large. If you look at it,
15 there was perhaps a dose response, at least numerically
16 trending. However, the separation here between the lowest
17 and the highest, a 16-fold difference, is really less than
18 10 percentage points. Very tiny area to work with.
19 If we look at other times, like day 14, day 28,
20 it really doesn't hold true. Indeed, on day 28 the lowest
21 and the highest dose, 16-fold apart, you really could not
22 pick up a difference between these two.
23 Now, typically we use a patient-rated score in
24 this study which was also done, so we looked at that to see
25 if that would be different. The result is here, and the

1 answer is really no. On day 21, the symptoms that the
2 patients rated were very similar to what the physicians
3 rated.
4 The last example is again the same drug
5 substance. It was one study where aerosol and spray
6 suspensions were used. The study was conducted in 32
7 centers in the U.S. two years ago. It was conducted on
8 seasonal allergic rhinitis patients, ages 12 and above.
9 There was 1-week baseline period followed by 2 weeks of
10 treatment, and the dosing was three dose levels from two
11 devices and over 8-fold range. Again, a pretty large
12 separation.
13 Efficacy was 12-hour reflective of four nasal
14 symptoms, scored on a 0 to 3 scale, and the sum was nasal
15 symptom score.
16 The result is here. The first bar here is the
17 placebo, and the second, third, and fourth bar are with
18 aerosol, and the last three are with the spray. This is
19 mean percentage change from baseline. First week, second
20 week, total, which is week 1 and 2.
21 If you look at it here, again for this drug
22 there is some trend of a dose response at least
23 numerically, but again, we are within 5 percentage points
24 or less. So, a very small difference between the lowest
25 and the highest dose, quite a bit of separation within the

1 two doses.

2 So, again, the same point here. Even with a

3 very good example here perhaps, the lowest and the highest,

4 you cannot really pick up a difference. If you look at

5 week 2, they're almost flat.

6 So, the point that I made here with all the

7 seasonal allergic rhinitis studies, because typically those

8 were studies that are used for showing dose response, if

9 you look at patients who had perennial allergic rhinitis,

10 the same would hold true.

11 The question comes up, we do not really see a

12 dose response, which is very clear based on the examples,

13 and why we did not see a dose response. Perhaps the

14 clinical studies that we used for looking at efficacy,

15 which is the typical outpatient kind of study, are

16 sensitive enough to pick up a separation from drug and

17 placebo, however, are not discriminative enough perhaps to

18 pick up a dose response, if it existed. They are pretty

19 crude measures. Unfortunately, that's what we have.

20 The second point may be that perhaps for some

21 of these drugs which are already approved, they may already

22 be at the high end of the dose-response curve, so a large

23 separation of dose would not really mean any differences as

24 far as efficacy is concerned.

25 So, that's all I have. If there are any

1 questions.

2 DR. BYRN: Questions for Dr. Chowdhury? Yes,

3 Bill?

4 DR. JUSKO: William Jusko. I think another

5 reason for the lack of showing efficacy is the fact that

6 the patients being studied in many of these studies,

7 particularly the first one, did not present with very

8 serious scores. For example, the baseline scores were 10

9 on a scale that could go up to 30. So, a major problem, if

10 this persists for the other studies, is the fact that the

11 patients being studied only have very modest disease

12 symptoms.

13 DR. CHOWDHURY: That is true for the first

14 study. However, not always because in some of the studies

15 patients who are more symptomatic were recruited, and some

16 of the studies are designed like that. In the placebo run-

17 in period, those who respond to placebo or those who do not

18 have the cut-off symptom scores are excluded. So, they

19 start off being symptomatic.

20 However, again we're talking about a large

21 study with 100 patients in one treatment arm. Some may be

22 more symptomatic than the others, and when you average out,

23 it's almost impossible to get the extreme high level of

24 symptoms which you would ideally want to get, but that

25 doesn't really happen.

1 DR. BYRN: Yes, Marvin?
2 DR. MARVIN MEYER: You didn't really mention
3 anything about the variability in the results. Are there
4 differences in the variability between the three types of
5 studies? I'm particularly interested in the EEU. Is that
6 less variable in the measurements?
7 DR. CHOWDHURY: As you go down, you are moving
8 from a natural exposure to a controlled setting, and that
9 would be the case. The variability would be less, and
10 again in the EEU setting, you're taking in patients, making
11 them symptomatic, so they'll be higher on the dose
12 response. Not on the dose response. I take it back.
13 Higher on the symptom scores and perhaps closer to each
14 other.
15 DR. MARVIN MEYER: But I take it that's not an
16 acceptable way to normally study these drugs because it's
17 not actually clinical?
18 DR. CHOWDHURY: They're good study designs for
19 answering pharmacodynamic questions, but again, we are
20 moving away very much from the real life of the patients
21 who are exposed to the pollens in a real-life environment.
22 So, they're not very good study designs for looking at
23 drug efficacy. For the dose response questions, it again
24 is not perhaps a very good tool, and also we do not have a
25 lot of experience in the EEU study for dose response

1 questions.

2 DR. MARVIN MEYER: Could you argue, though,

3 that the typical clinical trial is somewhat constrained as

4 well, a little artificial in that the selection process and

5 the monitoring, et cetera, as opposed to the real world

6 person?

7 DR. CHOWDHURY: The clinical trials try to

8 mimic the real world as much as possible, but again, the

9 study itself is an artificial setting, but as close to the

10 real world, which is a natural exposure study, is better we

11 have a handle of the drug itself and the disease itself.

12 DR. BARR: Did you do repeated measures that

13 would give you an estimate of the intra-subject variability

14 that you're dealing with? Do you have some estimate of

15 that?

16 DR. CHOWDHURY: Not in these presentations, but

17 again, the intra-subject variability is indeed high. I

18 cannot really give numbers right here, but again, the

19 patients who are symptomatic to begin with may change over

20 the time, yes.

21 DR. BARR: What was also surprising is that you

22 are at the top of the dose response curve, that platform

23 for compounds that have different modes of action, which is

24 kind of surprising that you were successful in getting to

25 that upper level in all cases, and it may indicate perhaps

1 more a lack of methodology rather than the drug effect
2 itself.
3 DR. CHOWDHURY: Perhaps true because these are
4 really pretty crude study designs, which I pointed out,
5 based on how the patients are feeling, and that's what
6 really we have for assessing drugs for the purpose of
7 approval.
8 DR. BYRN: Do we know whether during
9 development any of the firms were able to get dose-response
10 curves?
11 DR. CHOWDHURY: The ones that I showed towards
12 my last two slides, that's what really what we see. There
13 is a numerical dose response, but again, we are in a very
14 flat portion of the curve.
15 DR. BYRN: Right. Was anybody able to get down
16 on the curve that you know of?
17 DR. CHOWDHURY: No. The answer is no. If you
18 look at that particular slide, which was the second to last
19 slide, the placebo is very close to almost where the flat
20 portion is. So, I don't think based on the examples I'm
21 showing that we are on a steep dose-response curve to begin
22 with. The curve itself is pretty flat. Between the lower
23 drug and the placebo, the separation is not that much. The
24 placebo response in this study is about 30, 35 percent, and
25 the drug response is about 50 to 60 percent. So, we do not

1 really have much of room to work with.
2 DR. BYRN: One more question. Marvin.
3 DR. MARVIN MEYER: If you have no dose response
4 curve, and these are typical results for what people would
5 see, why would you even want to market the higher
6 strengths, or approve the higher strengths?
7 DR. CHOWDHURY: Typically one would like to
8 approve as low a strength as possible. However, it becomes
9 an issue. We can almost go to a placebo and still show a
10 separation depending on sample size.
11 Another factor that comes in is the safety.
12 These drugs are relatively pretty safe. So, the equation
13 brings in both efficacy and safety. So, if a drug is
14 better than placebo, and with all available tests that drug
15 is safe, that drug is safe and effective for marketing.
16 But your question is well taken. The lower dose, which is
17 safe and effective, the better it is.
18 DR. DOULL: I think the point is, you can't say
19 that there is no dose response. What you can say is you
20 haven't shown a dose response. But clearly there is a dose
21 response there. If you were to use lower doses, you
22 probably could in fact show that.
23 DR. CHOWDHURY: The answer is yes and no. I
24 mean, perhaps there is a dose response, but the method that
25 we have didn't show it.

1 DR. BYRN: Thanks very much, Dr. Chowdhury.
2 Our next speaker is Robert Meyer, who is going
3 to address clinical study options for locally acting nasal
4 suspension products.
5 DR. ROBERT MEYER: Thank you very much. Just
6 let me follow up on that last point because I think the
7 belief that we've had, and I think to some degree continue
8 to have, is that although it may be very difficult to show
9 dose response in these studies, clinically there has been a
10 practice and a rationale for having a range of doses
11 available and titrating patients up who would fail to
12 respond to lower doses, as long as the safety profile
13 assures us that those doses are safe. Whether that's been
14 scientifically established or not, that's the rationale.
15 What I'd like to do actually then today is take
16 you through a bit of the presentation that I gave the
17 subcommittee, but I do want to pause on the first slide
18 here to really just recap how we came to have this
19 subcommittee discussion, and how we actually came to have
20 what we had in the draft guidance, which was a
21 recommendation for any one of three potential study
22 designs, with a requirement to show a dose response within
23 those study designs.
24 Back in about 1995, the Division of Pulmonary
25 Drug Products at the time -- the "allergy" has been added

1 since I became director two years ago, but the Division of
2 Pulmonary Drug Products had advised the Office of Generic
3 Drugs that we felt that clinical study really wouldn't be
4 needed for locally acting nasal spray on the basis of the
5 fact that we thought that the in vitro characteristics and
6 perhaps the added assurance of some pharmacokinetic
7 assessment would fully assure us of bioequivalence.
8 However, a letter to the center from one of the
9 corporate sponsors raised the issue that one could not in
10 these products fully assess the particle size in the actual
11 drug formulation, for the suspension products, anyway. For
12 the suspension products, the excipients of these products
13 are such that there was no accurate and validated way to
14 actually assess the particle sizing of the drug substance.
15 And furthermore, the generic manufacturers wouldn't have
16 access to the particle sizing or the micronization
17 characteristics of the drug substance. This sponsor
18 pointed out that perhaps particle sizing would matter quite
19 a bit in terms of local bioavailability, which would be
20 definitely tied in to efficacy.
21 While they present no data to substantiate that
22 concern, I think it was a concern we took seriously and
23 actually led to us in the draft guidance for nasal
24 suspension products intended for local activity, asking for
25 a clinical study -- not just any clinical study, but one

1 that establishes a dose response. And the reason for this
2 is to really assess or to show within that clinical study
3 the sensitivity of the study to reflect differences in
4 local bioavailability or dose, should one exist between the
5 test and reference product.
6 So, in talking today -- and again, this is a
7 recap of what I said to the subcommittee -- I want to focus
8 on the options for a clinical study, many of which Dr.
9 Chowdhury has already gone through, but I'll spend a little
10 time talking about those and then turn to really what is
11 the question that's being put to any clinical study that
12 might be required as a part of a bioequivalence package for
13 a locally acting nasal suspension product. Once we focus a
14 little bit on what the question is that's taken to that
15 study, I think then we can get to what is the best answer
16 and the subcommittee's advice on that. And I'll close with
17 some observations and recommendations that we had on
18 Tuesday for the subcommittee.
19 Again, as Dr. Chowdhury has pointed out, the
20 disease in question here is allergic rhinitis, which is
21 primarily experienced and historically assessed
22 subjectively. The basis for approval for our drugs has
23 come from subjective symptom scoring, such as the total
24 nasal symptom score that Dr. Chowdhury took us through.
25 More, if you will, pharmacodynamic type questions in terms

1 of onset of action, appropriate dose interval and so on,
2 are frequently addressed through differing study designs,
3 but still most often approached through clinical symptom
4 scoring.
5 So, in the draft guidance, we had proposed
6 three potential study designs. There was, if you will, the
7 natural clinical study, and this is essentially a 2- to 6-
8 week study. Seasonal allergic rhinitis studies tend to be
9 shorter, in the range of 2 weeks, and the perennial
10 allergic rhinitis, as one advertisement likes to say, the
11 outdoor versus indoor allergens, but these are more like
12 cats and dogs and indoor, if you will, allergens. The
13 perennial allergic rhinitis allergen studies tend to be
14 somewhat longer. They're parallel-group studies looking at
15 comparative changes in total nasal symptom score over the
16 treatment period.
17 As Dr. Chowdhury pointed out, the patients are
18 enrolled prior to or at the start of their season, and
19 randomized when they are sufficiently symptomatic, albeit
20 not always terrifically symptomatic, and this allows for
21 the assessment of efficacy, but also because it is a 2-week
22 study and it's used more typically how a patient might use
23 it in a general real-world setting, it allows for
24 assessment of safety and tolerability over a reasonable
25 period of use.

1 The EEU study takes a patient out of season and
2 exposes him to a high level of a specific pollen to which
3 they are allergic. It really takes cohort of patients at
4 the same time and it assesses the symptoms over a short
5 period of time, commonly over a period of hours. These, at
6 least in new drug applications, are often used for
7 assessing such parameters as onset of effect or perhaps in
8 dose-finding, but I'll have more of a comment about that in
9 a minute.
10 A day-in-the-park study is somewhat
11 intermediary between these two. This is again a cohort of
12 patients with a known allergy sensitivity, but typically a
13 fairly low level of symptoms at the start of the day, and
14 they're taken to an outdoor setting, a park if you will, in
15 a cohort for natural exposure to an allergen. Days where
16 the allergen exposure is high are targeted, although you
17 won't know that necessarily prospectively. These typically
18 are fairly short-term studies, so we get short-term
19 efficacy and safety assessed those data. Again, in the
20 NDA, new drug application, setting we don't consider these
21 necessarily the best of pivotal trials because they don't
22 so much generalize as far as all the findings that come out
23 of them, but they are used and typically used in trying to
24 assess dose effects, duration of effect, and so on.
25 From the approval purpose then, as I've tried

1 to emphasize, the Division of Pulmonary and Allergy Drug
2 Products regards the natural clinical study to be the most
3 informative, and we regard the EEU and the day-in-the-park
4 studies as useful, but typically used for more
5 pharmacodynamic-type assessments.
6 Other objective endpoints in any of the study
7 designs really, if you will, more true pharmacodynamic
8 endpoints, such as nasal patency through acoustic
9 rhinometry or other measures of air flow or specific
10 markers of inflammation in the nasal mucosa or nasal
11 secretions are regarded as interesting, but they are not
12 clinically validated. I would also point out that they're
13 not really validated as a reliable detector of dose
14 response.
15 Let me just take a slide that Dr. Conner showed
16 the other day, just to remind us why we're focusing on this
17 issue of the clinical study at all for talking about the
18 question that we're taking to it. It really stems from the
19 fact that for a topically acting drug, a nasal suspension
20 or a nasal spray, the therapeutic effect is coming from
21 local delivery and local activity and is not predicted
22 through assessment of pharmacokinetics, although there
23 could be a small contribution of any drug that gets to the
24 blood, either through local absorption or through systemic
25 absorption from the GI tract or any that might come through

1 the lung. There may be contribution to the therapeutic
2 effect, right over here, but in general most of the
3 therapeutic effect comes from the local delivery.
4 On the other hand, the assessment of what gets
5 into the blood, only some of this is coming through nasal
6 absorption, and even for drugs of fairly low
7 bioavailability through the GI tract, if they have low
8 bioavailability through the nasal mucosa, a substantial
9 portion of what does get into the blood will be coming
10 through these other routes, primarily the GI tract.
11 So, to fully get a handle on the therapeutic
12 effect and for bioequivalence, if one really places a lot
13 of concern over any differences in local delivery, one
14 needs to assess more than just the pharmacokinetics. One
15 needs to get some kind of handle on the clinical or
16 pharmacodynamic measurements to accurately reflect the
17 local bioavailability.
18 So, the question as I framed this the other day
19 for the subcommittee is what are we really asking the
20 clinical study to do in the bioequivalence package for a
21 nasal suspension spray. I need to emphasize that I don't
22 want to use these in the regulatory term sense, but just
23 using these in a more casual sense. Are we regarding the
24 clinical study as necessary, but playing a confirmatory
25 role, or are we really looking for it to primarily

1 establish the bioequivalence? That really depends on your
2 interpretation of the unknowns left after you've done a
3 full in vitro assessment and, again, you have Q1 and Q2
4 sameness for the two products and, in fact, your
5 pharmacokinetic assessments as well.
6 For a more confirmatory role, the study would
7 then be necessary to really confirm that given the unknowns
8 that might remain after you've shown sameness in a fairly
9 rigorous in vitro package in pharmacokinetics and Q1 and Q2
10 sameness, that the unknowns left there just require the
11 clinical study to confirm a lack of important clinical
12 differences as a part of this larger bioequivalence
13 package. In a more pivotal sense, then, if you're asking
14 the study to establish the bioequivalence in and of itself,
15 the clinical study would really need to be able to discern
16 differences in dose in quite a sensitive manner, and then
17 to show that no differences exist between the test and
18 reference product.
19 So, again, in a more confirmatory, necessary
20 but confirmatory role, the design would be to broadly
21 assure that no important clinical differences exist. A
22 rigorous showing of dose response and strict equivalence
23 over the dose response between test and reference is not
24 required. The comparison therefore could be on one dose
25 level, such as the lowest dose level, to assure that you're

1 not on any kind of downslope of a curve, for each of the
2 test and reference to show comparable efficacy, safety, and
3 tolerability.
4 If you really look to the study to fully
5 establish bioequivalence almost as a stand-alone question,
6 the design must show sensitivity of the assay. That is, it
7 must show the study could have detected a dose response if
8 any difference in dosing local bioavailability were to
9 exist, and then you must show a rigorous equivalence
10 between the test and reference product. Of course, even in
11 this role you could look at the comparability of safety and
12 tolerability.
13 As Dr. Chowdhury has pointed out, our
14 experience is that certainly the standard clinical study,
15 the 2-week to 6-week standard natural, if you will,
16 clinical study does not typically show sensitivity to dose,
17 and in fact in our experience that it's even very difficult
18 to show for EEU or day-in-the-park studies. So, we feel
19 that the clinical study could be very good in terms of
20 assuring that there is not an important clinical difference
21 left in a bioequivalence determination when all other
22 points show comparability, but it would be very difficult
23 to use the standard clinical study despite our draft
24 guidance of 1999. It's a herculean task to show dose
25 response and therefore to rigorously establish

1 bioequivalence through the clinical study.
2 While the more pharmacodynamic studies, if you
3 will, the EEU and day-in-the-park studies might be a better
4 approach because of less variability, it's not really been
5 established that they firmly can establish sensitivity to
6 dose effects either.
7 As I pointed out when I discussed these briefly
8 earlier, using more true pharmacodynamic endpoints such as
9 markers of inflammation or measures of nasal patency are
10 both unproven in sensitivity to dose response as far as
11 data to which we have access. Nor are they clinically
12 validated, as representing important features of predicting
13 the response to allergic rhinitis drugs.
14 Other endpoints that might be potentially used
15 in standard trials -- and these have been suggested in
16 comments to the docket about our guidance -- are unproven
17 as being superior in sensitivity to dose response. I
18 include things like well validated, health-related quality
19 of life instruments.
20 So, where we came to is in the guidance we're
21 assuming that to get to the clinical study you would need
22 to show, or a sponsor of a new product would have to show,
23 equivalence in vitro by a fairly substantial package of
24 attributes. They would have to have, even before that, the
25 same qualitative and quantitative makeup of the product,

1 and if not the same actuator spray device, at least one
2 that is very similar in attributes. And after establishing
3 all that they would have to show equivalence to systemic
4 exposure, or if measurement of systemic levels is
5 impossible, through pharmacodynamic equivalence to things
6 like HPA axis assessment for corticosteroids, for instance.
7 So, the main uncertainty left at the point for
8 nasal suspension products that we're talking about is what
9 contribution any differences in particle sizing in the
10 formulation itself might present in terms of clinical
11 efficacy, given everything else being the same. Clearly
12 that's an issue, as I hope I've already conveyed, for the
13 aqueous suspension sprays, and it's more difficult in fact
14 for these sprays than the aerosols perhaps, but even for
15 the aerosols, the MDIs, we don't have a proven, validated
16 way to particle size in the way we do for the orally
17 inhaled, for instance.
18 Given all the difficulties of establishing dose
19 response, but also given a real rethinking of what
20 questions are left at the point that we're discussing or
21 coming to a clinical trial, the FDA presented to the
22 subcommittee that fact that we're now contemplating
23 shifting the question that we're asking of that study in
24 the bioequivalence package. I must emphasize no matter
25 what, however, the clinical study would not trump a lack of

1 equivalence from the prior data set. So, it would have to
2 be Q1/Q2 the same, they would have to be equivalent in the
3 in vitro characteristics, and all the attributes tested, as
4 well as systemic bioavailability.
5 If you have all that, if you have that
6 equivalence established, then we're really seeing perhaps
7 the clinical study as a necessary part to establish
8 bioequivalence, but that it's doing so in a more
9 confirmatory sense, that establishing at the lowest level
10 dose that there is not really an important clinical
11 difference between the test and the reference product.
12 Under this paradigm, then, we put to the
13 subcommittee the question of what would be the best study
14 design if you took this question to the clinical study.
15 Should it be the traditional 2-week clinical study and SAR,
16 seasonal allergic rhinitis? Should it be an EEU study, an
17 environmental exposure unit study, or should it be a day-
18 in-the-park study?
19 I'll stop there and see if there are any
20 questions.
21 DR. BYRN: Questions?
22 DR. BOEHLERT: Question. Judy Boehlert. I
23 have a question with regard to the particle size. I assume
24 that the agency would always require a meaningful test for
25 particle size on the active ingredient, so that you know

1 what's going into the product. The challenge, then, in a
2 suspension where you have active ingredient and perhaps
3 other suspending agents is determining whether there's any
4 growth in that particle over the shelf life of the product.
5 Is that correct?
6 DR. ROBERT MEYER: Well, we certainly want the
7 particle sizing of the micronized drug substance
8 characterized and expect that to be done. There is the
9 question that you have, but also the challenge for a
10 generic drug manufacturer, be it that no matter how well
11 they characterize their micronization process, they don't
12 have access to the data of the innovator or the reference
13 product to match that.
14 DR. BOEHLERT: I would agree that that's the
15 case, but the agency, when they review those submissions,
16 would be able to evaluate whether or not they have a
17 meaningful test for particle size.
18 DR. ROBERT MEYER: Oh, absolutely. Absolutely.
19 But I think within certain bounds we also have some
20 uncertainty to what small differences in the micronization
21 in the drug substance might mean in the drug product, so
22 it's both that uncertainty for the innovator and, to some
23 degree, for us, but then any change in the attributes of
24 the particle sizing within the drug formulation would also
25 come into play.

1 DR. BARR: It seems to me that the basic
2 problem is just the inadequate bioassay that we have
3 available to us. The global assessment is extremely
4 insensitive to the point where we can't measure any changes
5 between doses, except an all-or-none effect. So, in trying
6 to go back to something that's more sensitive, for example,
7 a pulmonary patency or the measures of inflammation, you
8 indicated they had no clinical relevance. I'm not sure how
9 you're going to be able to show clinical relevance if, in
10 fact, the measure of clinical relevance that you have is so
11 insensitive itself, and it's very difficult to show that.
12 But it would seem to me that that would be some approach to
13 get to something that is more reproducible, more sensitive.
14 I wonder if there's an approach to that.
15 DR. ROBERT MEYER: Yes, when I say that they're
16 not well clinically validated, I'm not putting that to a
17 very, very high standard. We don't have a lot of data
18 relating then to how they perform in clinical studies
19 compared to standard assessments, so we don't even know
20 that a change in any specific biomarker would in any way
21 predict clinical response. So, you have both the question
22 of the predictive value of it, but also whether any
23 differences seen are meaningful.
24 So, I think the upshot is that for nasal
25 solutions we're really talking about getting away from even

1 having a clinical study at all because we're assuming that
2 the in vitro characteristics can really characterize
3 sufficiently how a test product and a reference product
4 relate.
5 Here we're talking about suspension products,
6 which are a bit more complex and we have the main issue
7 being the particle size that is in the drug formulation.
8 So, given that, given the pharmacokinetic assessments that
9 would be a part of this package, how much are we worried
10 about a difference in an individual patient, or in a mean
11 population between a test and a reference, and how do we
12 best examine that?
13 So, I think it remains unclear, even if we had
14 more experience with some of the biomarkers and acoustic
15 rhinometry and so on, what role that might play, given the
16 question that we're really asking this study to answer in a
17 BE package.
18 DR. BARR: Right, but in a way it's a little
19 bit like our use of blood levels as a surrogate. We don't
20 always have a very clear relationship between those, but we
21 can measure them and there is some measurement that we have
22 that's intermediate between an overall global assessment
23 and something that does show differences in onset,
24 differences in duration, difference in intensity, that
25 gives us some measure that there may be some differences

1 between the product. It just seems to me that some
2 compromise ultimately would have to be found because the
3 global assessment is just so inadequate in terms of the
4 sensitivity.
5 DR. BYRN: We're going to have time for
6 discussion, so I think we should go ahead with Dr. Adams
7 now, who's going to give us the recommendations of the
8 subcommittee.
9 Thanks very much, Dr. Meyer.
10 DR. ADAMS: Good morning, ladies and gentlemen.
11 I'm pleased to be here and talk about our nasal
12 bioavailability/bioequivalence guidance.
13 The issue that we're bringing to the committee
14 today is one of dose response, and I'll get into that. An
15 outline of this would be an introduction to the two
16 questions, what are the two questions, and then the
17 recommendations and conclusions of the OINDP Subcommittee.
18 Introduction to the two questions. This slide
19 is one that Dr. Lee had presented earlier, but I'd like to
20 just have us read through this because it focuses the
21 question, that to establish bioequivalence of suspension
22 formulation nasal aerosols and nasal sprays for allergic
23 rhinitis, the June 1999 draft guidance recommends a series
24 of different pieces of information.
25 It recommends the equivalence of the

1 formulation, both qualitatively and quantitatively. So,
2 we're saying that a test product should be the same in
3 terms of its qualitative composition of inactive
4 ingredients, as well as quantitatively within plus or minus
5 5 percent.
6 That the device should be comparable, either
7 the same device meaning the same metering valve and pump,
8 or one made preferably by the same manufacturer and the
9 same model. If that's not possible, then as close as that
10 can be obtained.
11 In vitro studies and systemic exposure or
12 systemic absorption. The in vitro studies, however, do not
13 assure equivalence of particle size of the suspended drug.
14 Because particle size differences between test and
15 reference products have the potential to alter the rate and
16 extent of delivery of drug to local sites of action, then
17 those differences in clinical effectiveness could result.
18 For this reason, the draft guidance also recommends conduct
19 of a clinical study for allergic rhinitis to confirm
20 equivalent local delivery.
21 Now, what I'd like to do is to skip to a slide
22 that originally I had presented at the subcommittee meeting
23 and I think it is appropriate to present that here. It's
24 not in the packet because I originally wasn't going to
25 present it, but I think it's essential. It's a nice way of

1 explaining what our predicament is.
2 We've indicated that the package of information
3 for bioequivalence for solution and suspension nasal sprays
4 and nasal aerosols is a substantial package, and it's built
5 upon a number of items. One is that the formulation be
6 qualitatively and quantitatively the same. That is
7 expected of the generic or test product going into this
8 issue, that the device be comparable.
9 And then there's a series of six in vitro tests
10 for which we ask for equivalence. Those in vitro tests are
11 unit spray content, which assures the test and reference
12 products are both delivering the same amount of drug from
13 the actuator. Droplet size distribution. Spray pattern
14 and plume geometry, and what those do is to characterize
15 the plume as it comes from the product and provides
16 confidence that the drug will be distributed the same
17 region of the nose in both test and reference products.
18 That is, droplet size, spray pattern, and plume geometry is
19 the same.
20 Particle size distribution, however, is one
21 that, as we've indicated earlier in our presentations
22 today, cannot be determined in a validated method, and so
23 consequently there's an issue about potential differences
24 between test and reference products in terms of the
25 particle size and, at least in principle, that can affect

1 the rate and extent of delivery to sites of action. It can
2 also affect the rate and extent of systemic absorption, and
3 consequently distribution to sites that would cause adverse
4 effects.
5 We also ask for pharmacokinetic information as
6 a means of determining systemic exposure. As Dr. Meyer had
7 indicated, if that's not the case, then we move to a
8 pharmacodynamic measure such as an adrenal suppression for
9 the corticosteroids.
10 Now, this slide is intended to illustrate the
11 package that we're talking about, and what it says is that
12 first off, going into the formulation, the test and
13 reference products will both deliver the same amount of
14 drug from the actuator. They will deliver the drug from
15 our in vitro studies. They will deliver the drug to the
16 same regions of the nose. And so these products are
17 behaving the same in vitro.
18 In terms of the local delivery -- and of
19 course, local delivery here is really the challenge and why
20 this issue comes to the committee in the first place,
21 because systemic exposure, PK levels are not appropriate to
22 assure the equivalence of these drugs because they do act
23 locally. So, the blood levels may be relevant more to
24 safety than to efficacy.
25 We would like to conduct the clinical study for

1 rhinitis to answer this question about equal efficacy on
2 the steeply rising portion of the dose-response curve, but
3 as we've heard from Dr. Badrul Chowdhury's presentation and
4 Dr. Meyer's presentation, we essentially cannot get into
5 this region of the curve with present available
6 methodology. So, we believe that we're up in this region
7 of the curve where the dose response is insensitive.
8 But if we were to conduct a rhinitis study and
9 show that the test and reference products are both equally
10 efficacious, we know then that even at a single dose, that
11 the products would both be working. They'd both be
12 relieving the rhinitis symptoms as long as they're both up
13 here. They would show equivalence. In spite of the fact
14 that a different amount of drug may be getting to the
15 active sites, they would still be showing equivalence.
16 The other concern is that the drug, because of
17 potential differences in particle size distribution, could
18 be delivering different amounts of drug to the systemic
19 circulation, and they could put the test and reference
20 products down here in the region where they may differ on
21 the pharmacodynamic or clinical dose-response curve for
22 safety or for, let's say, adrenal axis suppression. They
23 could differ.
24 Well, we can control that by use of a
25 pharmacokinetic study to show equivalence. Of course, for

1 some of these products in which there's very little drug
2 that reaches the systemic circulation, it may be necessary
3 to do the pharmacodynamic study instead.
4 So, what we would know, then, from this package
5 of information is that the same amount of drug is delivered
6 from the product. The products are equally efficacious,
7 and that they have equivalent systemic exposure or systemic
8 absorption. So, essentially that is the package of
9 information that would be used for these products.
10 Now, to go back to the two questions, does the
11 committee believe that a placebo-controlled traditional 2-
12 week rhinitis study conducted at the lowest active dose is
13 sufficient to confirm equivalent local delivery of these
14 products, and two, does the committee believe that a
15 placebo-controlled park study or EEU study conducted at the
16 lowest active dose is an acceptable option to confirm
17 equivalent local delivery?
18 As we've indicated, two days ago we held a
19 subcommittee meeting to discuss these issues and what I'd
20 like to do is, with four slides, present the outcome of
21 those deliberations. What I'll do is to indicate a summary
22 statement, and then I'd like to try and capture some of the
23 thoughts that were expressed during the meeting on that
24 particular issue.
25 The first conclusion is that based on current

1 technology and methods, demonstration of dose response may
2 not be possible for locally acting drug products for
3 allergic rhinitis. Some of the comments that were made
4 were the limitations of the current study design cannot be
5 overcome at the present time to show a good dose response.
6 We recognize that a dose response may be seen in certain
7 individuals. As you increase the dose, they seem to
8 respond. But that in fact may be due to differences in
9 allergen levels over time. So, in fact that really may not
10 be a true dose response seen in some subjects.
11 And if we were to be interested in a dose
12 response, it was the subcommittee's feeling that that would
13 be a major challenge to develop a model which is sensitive
14 to dose. For instance, it could be a crossover study,
15 possibly a nasal challenge study of some design, but it
16 would require a substantial effort on the part of the
17 agency in order to develop such a possibly more sensitive
18 design. And in fact the feeling of the subcommittee was
19 that it's really not much of a clinical issue.
20 On the topic of Dr. Meyer's issue is this study
21 for bioequivalence of these locally acting suspension
22 products, nasal products. Is it a pivotal study or is it a
23 confirmatory study? All of the individuals participating
24 in this felt this is a confirmatory study. This is not a
25 pivotal study to fill the needs of the bioequivalence,

1 given the other package of information.
2 The second slide, a clinical study is needed in
3 the comparison of suspension nasal products. However, we
4 have as a note that the subcommittee was not in consensus
5 on this issue, but the majority agreed with the above.
6 Now, I looked over my notes from that subcommittee meeting,
7 and in fact almost half of our participants felt that
8 either a rhinitis study was not needed at all in this
9 circumstance, or that it was questionable as to whether it
10 was needed. It's a blunt instrument.
11 However, it was felt that patients and
12 clinicians will have increased confidence in the
13 equivalence of the products if the study is performed.
14 That was one of the benefits of it. As I say, almost half
15 of the participants felt that the rhinitis study either
16 isn't needed, or they felt ambivalent about it. The
17 feeling was that the disease is benign, the study cannot
18 distinguish between doses, and the rhinitis study in fact
19 is overkill, which is the word that was used by some of the
20 individuals.
21 However, they felt that the pharmacokinetic
22 study is an important part of the package, and in fact the
23 question was asked that if this is a high first pass effect
24 drug, or charcoal block study were used in order to prevent
25 drug coming in through the GI tract so that all the drug

1 comes in through the nasal route, that in fact a PK study
2 could be, to some extent, reflective of equivalent local
3 deposition in the nose.
4 If a drug is absorbed substantially from the
5 gut and a charcoal block study is not done, then the
6 systemic levels would simply reflect the overall safety of
7 the drug as it's clinically used.
8 I received a phone call after the subcommittee
9 meeting, and one of the individuals who felt that the
10 rhinitis study was not needed said, upon further
11 reflection, if the drug is a prodrug, he felt that in that
12 case it would be important to do the rhinitis study at a
13 single dose, and the reason for that, he indicated, was
14 potential differences in distribution to the nose for test
15 and reference products. There could be differences in the
16 enzyme levels in different regions of the nose, resulting
17 in different degrees of conversion to the active moiety.
18 So, that was his reason for that recommendation for a
19 prodrug.
20 Slide three, a clinical rhinitis study would be
21 useful to confirm that whatever unknowns remain after
22 establishing equivalence through in vitro performance and
23 pharmacokinetic metrics are not clinically important. The
24 feeling of the subcommittee was, just do a simple one-dose
25 rhinitis study. If the study is to be done, just do a

1 simple one-dose rhinitis study. It doesn't need to be done
2 at two different dose levels. And that the only
3 information presented is the opportunity to show that large
4 differences exist between test and reference products.
5 That would be the only benefit of doing this study.
6 And lastly, of the three study designs in the
7 draft guidance, the traditional placebo-controlled 2-week
8 rhinitis study is the most appropriate. That is saying
9 that the park study and the EEU study, as pharmacodynamic
10 studies rather than clinical studies, the committee felt
11 were not appropriate, at least at the present time, for the
12 needs for establishing bioequivalence.
13 And a single dose level of test and reference
14 products should be used at the lowest labeled dose. And
15 some of the comments which were made were that an EEU or a
16 park study were not clinically meaningful since there's
17 only 1 to 3 days of exposure of the subjects to this drug,
18 and in fact for full efficacy to take place for the nasal
19 corticosteroids, it can take 2 weeks or even longer to
20 establish that efficacy. So, therefore the traditional 2-
21 week study design is the appropriate one for establishing
22 equivalent efficacy.
23 It said that pharmacodynamic endpoints are not
24 suitable at the present time. We don't know that the onset
25 of action in fact, which can be measured from the EEU and

1 the park studies, is more discriminatory, more sensitive to
2 differences between products than the traditional 2-week
3 study.
4 And the question comes up about should the
5 study be done at the lowest labeled dose or the lowest
6 possible dose. The lowest dose would be one spray per
7 nostril daily. If the product is marketed, however, at two
8 sprays per nostril daily, it would be possible to cut that
9 dose in half in an effort to get down into a more sensitive
10 region of the dose-response curve. It would be possible.
11 But the subcommittee's recommendation was to do the study
12 at the lowest labeled dose because that's a clinically
13 relevant dose. People don't take it at lower doses than
14 that.
15 Another thought was that for these products we
16 know from our experience that showing a dose response is
17 very difficult. In fact, dose response may not even exist,
18 as Dr. Chowdhury has indicated. There was some thought
19 that if in the future products are developed which can show
20 a dose response, then this issue could be revisited in
21 terms of the need to show a dose response.
22 Lastly, no one on that subcommittee felt that
23 either the EEU or the park study was appropriate for
24 establishing bioequivalence. Everyone felt the traditional
25 2-week study design was the appropriate one.

1 Thank you.
2 DR. BYRN: I think we can combine now our
3 discussion with any questions people might have for Dr.
4 Adams. On the agenda we have two topics that we need to
5 discuss. But first of all, let's make sure that there are
6 not specific questions about what Dr. Adams said. Any
7 specific questions for Dr. Adams?
8 (No response.)
9 DR. BYRN: Let's go to question 1, which reads,
10 does the committee agree with the OINDP Subcommittee
11 regarding its recommendations concerning the conduct of the
12 local delivery study based on the lowest active dose and a
13 traditional 2-week placebo-controlled rhinitis study? Can
14 we have discussion on that? So, the committee is
15 recommending a 2-week placebo-controlled rhinitis study at
16 the lowest active dose, which would be the lowest labeled
17 dose. So, that topic is open for discussion. Does the
18 committee agree, disagree, have concerns?
19 DR. JUSKO: I have a general concern about the
20 generality of what we were presented with and these
21 recommendations. All of the products being discussed were
22 corticosteroid suspensions, and I would presume that these
23 recommendations should apply to drugs with other mechanisms
24 of action. It seems that these questions are posed to
25 relate specifically to steroids and not in terms of general

1 principles.

2 DR. ADAMS: Dr. Jusko, the questions were posed

3 as they were because at the present time the only marketed

4 products of suspension formulations are corticosteroids.

5 Should other classes of drugs, antihistamines,

6 anticholinergic drugs or cromones be developed as

7 suspension products, then the same issues would apply here

8 with regard to the need for a clinical study and a PK

9 study.

10 DR. JUSKO: I'm not really sure that drugs with

11 other mechanisms might require, as indicated, the lengthy

12 period for full onset of effects. That's sort of what my

13 concern is. If they did not require the full 2 weeks for a

14 good effect, then these other test procedures, 1- or 2-day

15 pharmacodynamic assessments, could become highly relevant.

16 DR. ADAMS: I would agree with that. We would

17 deal with that on a drug class basis and work with the

18 Pulmonary Division in terms of the study designs.

19 DR. BYRN: Judy?

20 DR. BOEHLERT: I have a question I guess with

21 your use of terminology. By using the term "equivalent

22 local delivery," are we implying more than you can deliver

23 because you might get equivalent local action or activity

24 or efficacy, but indeed may not have equivalent local

25 delivery because you don't have the same dose-response

1 relationship that you might want. I think I'm being
2 confusing, but if you don't have dose response, then you
3 may not have equivalent delivery of the drug, but you might
4 have equivalent activity.
5 DR. ADAMS: I think what you're saying is that
6 the way we worded these questions, one might assume that in
7 fact we meant that there was equivalent local delivery to
8 the sites of action. And what we really mean is that
9 there's equivalence in therapeutic response, recognizing
10 the fact that different amounts of drug between test and
11 reference products could be delivered to sites of action.
12 But because the study is done at the plateau of response,
13 it's going to have the same therapeutic effect.
14 DR. BOEHLERT: That is indeed my concern.
15 DR. ADAMS: Yes.
16 DR. LEE: I just want to go back to Bill's
17 question. Is Bill requesting that the wording be made more
18 specific?
19 DR. JUSKO: Perhaps it should because
20 everything we've seen and discussed pertains to only this
21 one class of drugs.
22 DR. BYRN: Just a comment. I mean, this is
23 more how a guidance should be written, I guess. The issue
24 is, I guess related to all this, is really what we're
25 saying here is, as Bill is saying, it's related to one

1 class of drug, yet the guidance appears general. I don't
2 know whether we should put something in the guidance that
3 says it's only for this, and if there's another class of
4 drugs, there might be a supplement or revision issue.
5 DR. ADAMS: Yes, the guidance will be very
6 clear that the particular designs that we're proposing are
7 for the corticosteroids. For instance, the adrenal axis
8 suppression test would be inappropriate for the
9 antihistamines. We would ask for a different package of
10 information for the systemic absorption if PK could not be
11 determined in that case. So, there's an issue about drug
12 class specificity which will be clear in the guidance.
13 DR. BYRN: Could I ask a question about
14 particle size? If, say, some analytical chemists or
15 pharmaceutical scientists could develop a method to measure
16 particle size in suspension and show equivalence, what
17 would be the effect of that on the deliberations of the
18 committee, if you could show equivalence of particle size
19 with a validated method?
20 DR. ADAMS: I would say that the paradigm for
21 the approaches that we're using to take to the committee
22 today did not include that particular issue because we
23 don't have that situation at the present time. Should
24 validated particle size and particle size distribution
25 methodology become available in the future, then a question

1 on OINDP technical committee is, would we be content then
2 with solely in vitro comparative testing for suspension
3 products as well as for solutions? I would say that we
4 would cross that bridge when we come to it. It's not
5 present at the present time.
6 DR. BYRN: Is the problem in particle size that
7 there are carriers in the suspension that the active is
8 bound to? Is that the problem?
9 DR. ROBERT MEYER: The problem really gets down
10 to there are things like methyl cellulose in these
11 suspensions that in fact are present at pretty high
12 proportions compared to the active drug, which are
13 generally in fairly low concentration. So, it is a matter
14 of interference, I think, as much as any binding --
15 DR. BYRN: But if there were fractionation
16 methods or other approaches developed, there may be ways to
17 do it. As a person that's involved in analysis, I hate to
18 hear somebody say there is no method available. It makes
19 me interested.
20 DR. ROBERT MEYER: I do want to stress the no
21 current method.
22 DR. BYRN: Right.
23 DR. BARR: An alternative approach would be
24 possibly to go into some dissolution because the problem,
25 of course, with the particle size alone is that you have

1 all the other factors that may affect the overall release
2 of drug. So, ultimately there may be some dissolution
3 procedure.
4 DR. ADAMS: That's right. Dissolution is
5 something that has been suggested in the past as a means of
6 addressing that issue. In fact, we've looked at that a
7 little bit in one of our laboratories.
8 Fractionation alone, in the absence of a
9 specificity between different fractions would not be
10 adequate.
11 DR. BYRN: Yes. You'd have to be able to do
12 specificity. You could do dissolution and fractionation.
13 This isn't the subject of our discussion.
14 So, let's get back to question number 1. Is
15 there other committee input on topic number one?
16 (No response.)
17 DR. BYRN: I think we have about 10 minutes.
18 We need to decide, I guess, if we're reaching a consensus
19 or starting to agree with the committee, then we would be
20 recommending that a local delivery study of the lowest
21 actual dose for 2 weeks would be required and we would be
22 supporting that recommendation. Are there any concerns
23 about that on the committee? Any other discussion?
24 DR. JUSKO: The way the question is formulated
25 at face value, the answer seems to be no. It's not

1 possible to confirm equivalent local delivery of two
2 products by this type of test.
3 DR. BYRN: So, your thinking, Bill, is that we
4 don't agree with this recommendation, that it's too --
5 well, go ahead and elaborate.
6 DR. JUSKO: I like the phraseology that Dr.
7 Meyer used that this type of test, while it may be
8 advisable to do for reassurance purposes, it in no way
9 provides any confirmation of bioequivalence or clinical
10 equivalence.
11 DR. BYRN: Okay. I guess we're talking about
12 writing a guidance which would use a number of methods.
13 Maybe Dr. Adams can explain what would be in the guidance.
14 I guess this method by itself would not be in the
15 guidance. Is that right?
16 DR. ADAMS: Yes. As Dr. Meyer indicated in his
17 slide, there's a package of information with the
18 formulation/device recommendations and the PK and the
19 rhinitis studies. Furthermore, an acceptable equivalence
20 shown on the rhinitis study does not trump the in vitro
21 data. The in vitro data must show equivalence. We would
22 in no way ask just for the rhinitis study without the other
23 information.
24 DR. BYRN: Does that clarify that, Bill? So,
25 we're talking about a guidance that would have a number of

1 components, including the 2-week study, but the issue is,
2 do we agree that the 2-week study should be included with
3 those components? I guess the choices are more clinical
4 studies or no clinical studies.
5 DR. JUSKO: I find myself most in agreement
6 with the statement on slide 8, a clinical rhinitis study
7 would be useful to confirm that whatever unknowns remain
8 after establishing equivalence through in vitro performance
9 and pharmacokinetic metrics are not clinically important.
10 DR. BYRN: So, it's as a confirmatory study is
11 what you're saying, Bill.
12 DR. JUSKO: Yes.
13 DR. BYRN: I think that's the intent of the
14 question.
15 DR. VENITZ: Can I ask a follow-up question to
16 that because I think I'm with Bill Jusko on this. Is the
17 subcommittee proposing that this study is required? That
18 means everybody has to do it, even if there are no unknowns
19 left after the in vitro and the PK package has been
20 reviewed? Is that what the subcommittee proposes? I guess
21 I'm asking Wally.
22 DR. ADAMS: We're saying that for the
23 suspension products at the present time, Dr. Venitz, that
24 there is an unknown, which is the particle size
25 distribution.

1 DR. VENITZ: So, by default, it would be
2 required for those products to do a clinical study.
3 DR. ADAMS: Yes, and that would be written into
4 the guidance. And even if a validated particle size
5 distribution method becomes available, the issue would have
6 to go back to our internal technical committee to discuss
7 whether we would be happy with scientifically feeling that
8 the in vitro data alone would support equivalence. That's
9 a separate issue, should a validated particle size
10 distribution method become available.
11 DR. VENITZ: So, right now if the in vitro
12 package and the PK package and the clinical package all
13 demonstrate bioequivalence, that product is approvable?
14 DR. ADAMS: Yes, it is.
15 DR. VENITZ: If the in vitro package or the PK
16 package show bioinequivalence, regardless of the clinical
17 study, that is not approvable?
18 DR. ADAMS: That's correct.
19 DR. VENITZ: If we had a test for particle
20 sizing, and that was a validated test, and the in vitro
21 package, the particle size package, and the PK package show
22 bioequivalence, a clinical study would still be required?
23 DR. ADAMS: Until we take the issue to the
24 OINDP technical committee and obtain agreement from within
25 the committee and at higher levels of management that that

1 is acceptable to not ask for the rhinitis study.
2 There are various routes you could take. For
3 instance, it might be that a PK study and no rhinitis study
4 might be appropriate as well. So, we would have to discuss
5 what the various options are. That decision has not been
6 made at the present time.
7 DR. VENITZ: Okay.
8 DR. BYRN: Any other comments?
9 (No response.)
10 DR. BYRN: I think we have consensus on topic
11 one.
12 Shall we go to topic two now? Topic two really
13 relates, I think, to the fact that there is not confidence
14 in -- would you summarize what you think topic two relates
15 to, Dr. Adams?
16 DR. ADAMS: I'd be happy to.
17 DR. ROBERT MEYER: I think the upshot of this
18 is that we really brought in some ways two questions to the
19 committee that are somewhat split out. One of them is a
20 bit in the way they were phrased to the committee, and
21 perhaps a bit covert, or not explicit. That is, should a
22 clinical study be done at a single dose, and if so, should
23 it be sort of a traditional clinical study, or are there
24 reasons to allow for or prefer an EEU study or day-in-the-
25 park study, given the question that's being put to that in

1 the clinical study?
2 DR. BYRN: And you're recommending neither an
3 EEU or a day-in-the-park study would be acceptable. Right?
4 DR. ROBERT MEYER: Yes. There was a consensus
5 coming out of the subcommittee that if a study were to be
6 done -- and again, there was not full consensus on the
7 requirement for that -- that it should be the more
8 naturalistic 2-week study at the lowest labeled dose.
9 DR. BYRN: Now, we've already said a study
10 should be done. The whole committee has reached consensus
11 on that.
12 DR. ROBERT MEYER: Right, and in fact, as long
13 as everybody understands this as being explicit rather than
14 implicit, if you've reached consensus on topic one, you may
15 have already reached consensus that topic two is --
16 DR. BYRN: We may have, but I think we should
17 discuss. So, what we're saying now in topic two is saying
18 we're going to do a study. It's going to be 2 weeks.
19 Under this category we were just discussing, we're not
20 going to recommend, at least at this time, a placebo-
21 controlled in-the-park study or an EEU study. We recommend
22 a 2-week study.
23 So, let's have some discussion. Does anybody
24 have a problem with that? Again, this is recommended by
25 the committee.

1 DR. MARVIN MEYER: Just a quick question.
2 Which are the pivotal studies in the NDA review? The
3 natural study?
4 DR. ROBERT MEYER: Yes.
5 DR. BYRN: So, this would parallel an NDA, in
6 effect.
7 DR. ROBERT MEYER: Yes, it would.
8 DR. JUSKO: My comment on this one is a little
9 bit of a repetition. Once again, if this pertains to
10 corticosteroid suspensions, it is entirely reasonable, but
11 if a new class of drugs came up, that should be addressed
12 separately.
13 DR. BYRN: Now, I think it's pretty clear that
14 if a new class of drugs comes, the committee would want re-
15 evaluation of a guidance. I think the agency would, too,
16 from what I'm hearing.
17 DR. ROBERT MEYER: Yes, I think it depends a
18 little bit on just how much of a departure it is. I would
19 point out that the first study that Dr. Chowdhury showed
20 was a solution product, but it was also not a
21 corticosteroid product, and that was a day-in-the-park
22 study. We've not seen differences to date between
23 suspension and solution products, or between drug classes
24 in the failure to show a good dose response, nor in the
25 ability of these other alternative study designs to be more

1 discriminatory of dose.

2 So, I think we wrote the guidance to be fairly

3 general, but with an understanding of what the current

4 universe is. I think if that universe were to change, we

5 might need to take that back. But I think it would have to

6 be a change in the universe as it is for these drugs right

7 now.

8 DR. BYRN: Is that okay with you, Dr. Jusko?

9 DR. JUSKO: In part, but I find that first

10 study to be the most flawed, with the baseline being so

11 weak that it would be impossible in that type of study to

12 see real efficacy when you're looking for an improvement

13 from a possible range of 30, when the baseline starts at 10

14 and you look for a score to drop below 10. It's just

15 awfully difficult to see changes.

16 DR. ROBERT MEYER: I guess my point is that if

17 we just simply saw, say, for whatever reason, a suspension

18 antihistamine nasal spray come along and no data from the

19 NDA that we should view that differently in terms of the

20 sensitivity or discriminatory ability of these studies,

21 then I don't think we'd need to rethink the guidance. I

22 think there are a number of things that could change that

23 would lead us to come back to you folks, and we might be

24 talking about new methods of assessing drugs with an

25 ability to better discriminate between doses. It might

1 mean being able to particle size within the suspension.
2 There are things that could change that, and we understand
3 what you're saying but we did write this to be general for
4 what we know now about these drugs.
5 DR. BYRN: So, I think we're reaching consensus
6 on topic two, that we would require a 2-week placebo-
7 controlled study.
8 Go ahead, Wallace.
9 DR. ADAMS: Dr. Byrn, I just wanted to
10 supplement what Bob said. If there were another drug,
11 let's say a suspension antihistamine, to come along, we
12 would intend to use the present paradigm in this guidance
13 for that drug, in terms of what is the universe of drugs
14 that we're talking about here. So, the present paradigm
15 would apply not only to corticosteroids but it would apply
16 to other products, should they be available as suspensions.
17 Yes, we'd have to change some aspects of it in
18 terms of the systemic absorption study. But the basic
19 paradigm would be the PK study and a clinical study
20 conducted for multiple weeks I would presume, a rhinitis
21 study conducted for multiple weeks.
22 DR. MARVIN MEYER: Maybe this relates more to
23 how a guidance works. The draft guidance says the guidance
24 covers studies of prescription corticosteroids,
25 antihistamines, and anticholinergic products. So, if one

1 includes what we are talking about in the framework of that
2 draft guidance, one would assume then that the
3 anticholinergics and antihistamines also require a 2-week
4 natural exposure study, without some specific statement of
5 categorization of the drugs, in line with what Bill's
6 concerns are.
7 DR. ROBERT MEYER: Yes, I think we note the
8 concern is the best way to put it at this point. We'll
9 consider that in the redraft.
10 DR. BYRN: Yes, I think it's appropriate that
11 it's just been noted because the agency would, I'm sure,
12 not apply a guidance unless it was appropriate, unless it
13 had been shown to be appropriate in a submission. So,
14 because it is still just a guidance, if it's not
15 appropriate, some action will be taken.
16 Yes, John.
17 DR. DOULL: I think it might be useful in doing
18 this guidance that the language that says lowest active
19 dose would be a little more precise. Lowest active.
20 You're talking clinical dose. In the dose response slide
21 that you gave, you have a toxicity dose response and you
22 have an efficacy dose response. So, you need to tell us
23 which dose in fact you're looking at. In that case you're
24 looking at --
25 DR. ROBERT MEYER: Yes, it will. And in fact,

1 the subcommittee recommended it be the lowest labeled dose.
2 We, I think somewhat purposely, chose a vague term there
3 because it wasn't clear to us. There are various ways to
4 define the lowest dose. There's the lowest feasible dose,
5 there's the lowest dose that might be active, or there's
6 the lowest labeled dose. The subcommittee felt unanimously
7 that it would be the lowest labeled dose that would be
8 examined for the efficacy purposes, and that a higher dose
9 should be examined for the systemic bioavailability
10 purposes.
11 DR. DOULL: That's fine, so long as you don't
12 call it a threshold.
13 DR. BYRN: Any other comments? Wallace?
14 DR. ADAMS: Dr. Byrn, it would be helpful for
15 us if we could have a vote on these two questions rather
16 than simply a consensus.
17 DR. BYRN: Okay. When we say a vote, let's
18 just go ahead and have an aye or nay vote on the two
19 questions. So, question 1 would be, as topic one is
20 stated, do we agree with topic one? We would say the
21 committee agrees with the OINDP Subcommittee regarding its
22 recommendations concerning the conduct of a local delivery
23 study based on the lowest active dose and a traditional 2-
24 week placebo-controlled rhinitis study considering the
25 comments we've had on the lowest active dose, and all the

1 other comments we've had.
2 So, we'll ask for a vote now. All that are in
3 favor of that, please say aye.
4 (A chorus of ayes.)
5 DR. BYRN: Opposed?
6 (No response.)
7 DR. ADAMS: Can we have a show of hands on that
8 so we can get a count?
9 DR. BYRN: Okay, all in favor? And I guess
10 we're only voting, official members. I'm not sure who that
11 is.
12 (Laughter.)
13 DR. BYRN: Raise your hand.
14 (A show of hands.)
15 DR. BYRN: Is that 10, Nancy? Eleven? Eleven
16 in favor and none opposed.
17 DR. ADAMS: Eleven to zero then?
18 DR. BYRN: Eleven to zero.
19 And then the second topic, the committee agrees
20 with the OINDP Subcommittee regarding its recommendations
21 that the local study be based on the lowest active dose. I
22 guess that really covers it, doesn't it? Do you want a
23 specific consensus against a day-in-the-park and an EEU, or
24 does that cover it?
25 DR. ROBERT MEYER: I think if the committee's

1 comfortable with the 1 precluding 1, then --
2 DR. BYRN: The way it says it, a traditional 2-
3 week placebo-controlled, I think it covers it.
4 DR. BARR: I would just like to ask a question,
5 though, because I think again it comes back to this issue
6 of duration. If you have compounds that you expect to have
7 long duration, that seems to be the primary reason for the
8 traditional 2-week. Is that correct? For example, the
9 cromolyn type or the corticosteroid type, you would expect
10 you would have to have longer exposure in order to
11 determine efficacy. But would that be true for a
12 sympathomimetic or an anticholinergic?
13 DR. CHOWDHURY: Currently the drugs which are
14 approved available for allergic rhinitis are
15 antihistamines, anticholinergics, steroids, and cromolyn.
16 And to answer the question, steroids would require a couple
17 of days to have efficacy. The question here is the
18 suspensions. And all the steroids are suspensions. So,
19 therefore, for suspensions, we're talking about steroids.
20 Therefore, we would require a couple of days for the drug
21 to be active. So, one day of dosing would not necessarily
22 mean the drug would have its efficacy.
23 DR. BARR: My question related to the other
24 compounds. Would alternative methods be appropriate if
25 duration of activity wasn't a consideration because they

1 appear to be more sensitive in some ways.
2 DR. BYRN: Dr. Meyer.
3 DR. ROBERT MEYER: Yes, I was just discussing
4 this with Dr. Adams. I think that perhaps we actually
5 should ask for the vote on topic two. The subcommittee did
6 recommend against giving the option of a park study or an
7 EEU study. I think we should get a vote from the committee
8 whether in fact the guidance should continue to include
9 these as options, in addition to the placebo-controlled.
10 DR. BYRN: Okay, let's finish Dr. Barr's
11 question, though. I think your question, Bill, really is
12 addressed because we've sort of agreed that we're going to
13 reevaluate the guidance if it involves a suspension other
14 than a steroid.
15 DR. BARR: Right, and that's really what I was
16 dealing with.
17 DR. BYRN: That's the general consensus of all
18 of us here, I think.
19 DR. ROBERT MEYER: We just need to be clear. I
20 think that it is a guidance, and should we learn something
21 else that changes the way that's applied, we may either
22 rethink the guidance or choose to apply it somewhat
23 differently. But we don't want to leave here with the
24 understanding of the committee that we absolutely will come
25 back to the committee for these kind of changes, should

1 something evolve.
2 DR. BYRN: Right. We're just giving kind of a
3 general policy overview on this.
4 The second topic, then, would be that the
5 committee would agree with the OINDP Subcommittee
6 recommendation that a day-in-the-park study and an EEU
7 study would not be sufficient. I guess we can just say
8 that. Would not be an option, and maybe that's a better
9 term.
10 Is there any discussion of that, any further
11 discussion?
12 (No response.)
13 DR. BYRN: All in favor, please raise your
14 right or left hand.
15 (A show of hands.)
16 DR. BYRN: Ten in favor.
17 Opposed?
18 (A show of hands.)
19 DR. BYRN: One opposed. So, that is also a
20 consensus.
21 Any other discussion?
22 (No response.)
23 DR. BYRN: Let's take a break. We're running
24 about 10 minutes behind. Let's cut five minutes off the
25 break, if we could. So, we'll come back here at 10:50.

1 (Recess.)
2 DR. BYRN: I think we'll get started. We have
3 three new members up here at the table, but we won't
4 introduce you, if you don't mind, until you're actually
5 speaking because some additional members from the CMC group
6 are coming. So, we'll go ahead and go to the Nonclinical
7 Studis Subcommittee report, and John Doull will introduce
8 the issues.
9 DR. DOULL: Well, I've been asked to introduce
10 this issue. I'll be brief because I know we're all anxious
11 to hear the reports of the working groups.
12 Those of you that have been on this committee
13 for a while will probably recall that our subcommittee, the
14 Nonclinical Studies Subcommittee, was created about two
15 years ago. The charge for this committee was to evaluate
16 the use of nonclinical studies in the development of drugs.
17 In developing the charge to the committee, we really have
18 pushed this a little and we're now more focused on the use
19 of biomarkers to identify both the effects of drugs and
20 also particularly to identify adverse effects, toxicity.
21 We had a second charge, and that second charge
22 was to link nonclinical studies that could be also used in
23 the clinical evaluation of drugs. So, those were our
24 scientific objectives.
25 We were also asked to facilitate the

1 interaction of our subcommittee and Food and Drug with
2 industry, with academia, with other public groups, and
3 we've tried to do that. Yesterday Helen called that
4 leveraging, and I thought about that last night. I'm not
5 sure it's leveraging. It's more win-win, hopefully.
6 I borrowed a couple of slides from Jim
7 MacGregor from his PowerPoint, and let me turn to those.
8 Those are the objectives. I think I've talked about those.
9 The next slide has the history. In order to
10 decide which biomarkers we would focus on initially, we
11 started out in our committee activities by bringing in a
12 lot of experts in different areas. We had several people
13 who came to talk to us about genomics and proteomics and
14 the other "omics". We evaluated that and decided the drug
15 houses are really using those techniques powerfully in the
16 development of new drugs, but they are not quite at the
17 stage where we felt that it would be useful to have a
18 working committee on the use of genomics or proteomics in
19 toxicology, or perhaps even in efficacy. So, we did not
20 include that as a working group at the present time.
21 We also had a number of experts who came and
22 talked to us about noninvasive imaging, both PET scanning
23 and NMR. That one we were really intrigued with, and we
24 thought perhaps that was one where we could recommend a
25 working group to develop some of those ideas. Since then

1 there are some difficulties with PET scanning. It isn't at
2 the stage yet where it's available in medical school
3 teaching, for example. Few places have the equipment, so
4 that one also we are not making as a recommendation for a
5 working group at the present time.
6 Now, the third area that we talked about is the
7 one Dr. Collins talked about yesterday. He talked about
8 the need for biomarkers for liver injury, for cardiac
9 injury, and for vascular injury. We felt that there are a
10 lot of groups that are collaborative groups that are
11 looking at liver injury and that it would be more
12 profitable for our subcommittee to focus more on cardiac
13 toxicity, biomarkers for cardiac effects, and biomarkers
14 for vasculitis. And those are in fact the two committees
15 which we agreed on.
16 We did that last year. By the fall we had sent
17 out notices to the Federal Register, to scientific
18 societies. We asked Food and Drug for suggestions. We
19 asked our members for suggestions, and we got a slew of
20 them. We sorted through all those, and in January we put
21 together two panels, one for cardiac toxicity and the other
22 for vasculitis. I thought, well, gee, we got that all done
23 in January. Perhaps we can meet shortly and start this
24 process. It took an immense amount of effort, and Jim
25 MacGregor really worked long and hard to get through that

1 process. We're learning, and one of the things we've
2 learned is it takes a long time to get these working groups
3 established.
4 But they are now established, and as you can
5 see from the history there, we had the meeting in May, and
6 in that meeting we met with the designated members of those
7 two groups and got off to a start.
8 The next one indicates the members of the
9 committee, and let me just go through that. Jim MacGregor,
10 of course, is from NCTR CDER. Well, he was with CDER.
11 He's now the designate for NCTR. And Dave Essayan is CBER.
12 Dr. Reynolds is PhRMA. Joy Cavagnoro represents Bio.
13 Jack Dean. Is his term up? He was on this committee, but
14 I think his term is up. Anyhow, he's also from Sanofi.
15 And Gloria and I are the two members from this committee
16 that serve on the Subcommittee for Nonclinical Studies.
17 Jay Goodman is a toxicologist from Michigan State. Ray
18 Tennant is from NIEHS. He actually was concerned primarily
19 with knockout mice, but he is now in charge of the genomics
20 program at NIEHS, which I understand will be the lead in
21 the genomics effort of this country. Dan Casciano is the
22 new head of NCTR. So, there are a couple of new members on
23 the committee since we originally got it formed. So, we
24 are doing our best, Helen, to leverage these activities.
25 I'd like to go ahead at this point and

1 introduce then our speakers today, and I'd like to
2 introduce the vasculitis speaker first. This is Dr.
3 William Kerns.
4 DR. KERNS: Thank you, John, for that
5 introduction. I'm here as a representative of my
6 committee, and this is still work in progress. We have met
7 only one time, and I'm here to provide just an update, a
8 report of what we have done to date.
9 Our committee is composed of members that
10 represent approximately 50 percent from industry and 50
11 percent from academia and the regulatory side. David
12 Essayan is our liaison from the agency representing CBER,
13 and myself and Lester Schwartz are co-chairs of the
14 committee.
15 Following the introduction from Dr. Doull and
16 Dr. MacGregor, we met the first time on May 3-4 of this
17 year, and we tried to interpret our charge, as we
18 understood it. Following that meeting, we understand our
19 charge the following way.
20 One, to first develop a common understanding of
21 exactly what the problem is that we're here to resolve. As
22 you noted from the previous slide, our membership is
23 composed of a wide variety of disciplines, clinical
24 toxicologists, pathologists, pharmacologists,
25 immunologists, and so on. It was clear from our first

1 meeting, within the first hour, that we all did not clearly
2 understand the issue that we were there to discuss, and we
3 did spend a lot of time on the first day trying to zero-
4 base the discussion so that we all understood what we were
5 talking about.
6 The primary reason for that is the term
7 "vasculitis" is confusing to many, especially clinicians.
8 When clinicians think of vasculitis, they usually think of
9 hypersensitivity, drug-induced vasculitis. That is not
10 what we were here to describe within this committee. It's
11 something quite different. So, having clinicians on our
12 team is, A, very important but, B, created some
13 communication problems early on that we had to sort out.
14 Second, we were asked by Dr. Doull to address
15 the criticality of the issue and understand whether or not
16 this was a question that needed to be answered, and that's
17 item 2.
18 And if so, develop an initial list of
19 biomarkers that we might pursue.
20 And following that, then, in the second day we
21 surfaced three or four other issues that will become very
22 important for us to resolve as we move forward.
23 In the process of developing new biomarkers and
24 new assays, the opportunity for intellectual property
25 development is tremendous, and this will become an issue

1 within the committee that we have to deal with as we move
2 forward.
3 Secondly, funding issues are critically
4 important in the research that needs to be done to discover
5 and develop the assays and validate them in the next slide,
6 validate them to the point where they become acceptable as
7 decision making tests within Pharma, as well as within
8 agencies around the world.
9 And lastly, resolving issues of
10 confidentiality, both within the membership and between the
11 membership and the agency. And this is an issue that we
12 have yet to deal with, but one that we will have to come to
13 understand more clearly so that we can all communicate more
14 clearly within the team.
15 So, if we tackle the first issue, understanding
16 the problem, I thought I would present a few slides so that
17 those of you in the audience could understand the problem
18 as we do. So, is this drug-induced vasculitis as we know
19 it in humans, or is this drug-induced vascular injury as we
20 see it in animals?
21 The clinical versus pre-clinical impressions
22 I've already alluded to, but in clinical medicine drug-
23 induced vasculitis is usually associated with
24 hypersensitivity vasculitis, a specific morphological kind
25 of disease that patients usually recover when drug is

1 removed. Sometimes it gets worse, and they redevelop
2 disease when you rechallenge them.
3 Preclinically in animal models, we don't see
4 this syndrome. We see something quite different, and I'm
5 going to show you what that looks like. Of the seven major
6 categories of vasculitis, some drug-induced in humans,
7 none, or rarely are they observed in animal studies in
8 routine and toxicology studies in normal animals. This
9 then becomes a problem.
10 I want to go through a few slides to help
11 educate the audience as to exactly what we're talking
12 about. Unfortunately, we didn't have these slides when we
13 first met, but since we've exchanged them by e-mail. I
14 think there are four or five currently approved marketed
15 products on the U.S. market that cause lesions as you're
16 seeing in rodents and dogs and sometimes primates. This
17 happens to be a mesenteric artery from a rat treated with
18 fenoldopam mesylate, a DA-1 agonist. Fenoldopam is an
19 approved drug for hypertension in critical care units.
20 The lesion is characterized macroscopically by
21 intense medial hemorrhage in the mesenteric artery. And if
22 you look at the artery ultrastructurally, you can see
23 tremendous compromise of the vascular endothelium. The
24 endothelium is swollen. There are white blood cells
25 attached. The endothelial cells are retracted, and in some

1 cases endothelial cells can be seen sloughing from the
2 surface. The endothelial cells I was alluding to you can
3 see here sloughing from the surface.
4 You can see down here normal medial smooth
5 muscle. If you remember from the previous slide all the
6 hemorrhage in the media, you can see the cavernous areas
7 where the medial smooth muscle has disappeared, and the
8 empty spaces are filled with red blood cells.
9 And if you look at it from another perspective
10 in transmission electron microscopy, you can see that there
11 not only red blood cells have replaced the normal media,
12 the media is filled with platelets as well.
13 I show you these slides because it should bring
14 to mind different kinds of biomarkers that we might pursue
15 in this effort. And also for those of you that know,
16 morphologically this syndrome is very different from what
17 we see in humans with drug-induced vasculitis.
18 If you look at an arterial lesion three days
19 after injury, you can see that unlike human disease, there
20 are no eosinophils in this lesion, and the lesion is
21 primarily characterized by a neutrophilic inflammatory
22 response. There's separation of the endothelium from the
23 internal elastic lumina. There's medial smooth muscle
24 necrosis and hemorrhage, and there's inflamation in the
25 periadventitial tissues that is primarily at this stage

1 mononuclear.
2 Enough about morphology, but the point being
3 that this syndrome that we're here to characterize is
4 different than what we routinely see in humans. That
5 doesn't make it unimportant. It makes it perhaps more
6 important because we need to understand how to detect these
7 kinds of changes if they occur in humans.
8 So, number two, confirming the criticality and
9 validating the problem. In the 1980s and 1990s, we worked
10 with a variety of different cardiovascular agents that at
11 high doses caused hypotension, reflex tachycardia,
12 myocardial necrosis that Dr. Holt will talk about, and also
13 vascular disease. And we were quite comfortable with that
14 for reasons that, on reflection, may not seem realistic,
15 but quite comfortable with that and thinking that if we did
16 not induce hypotension and reflex tachycardia in humans
17 then we would not induce vascular disease. This is clearly
18 true for myocardial toxicity, but unproven for vascular
19 toxicity.
20 So, we now have a series of new drugs that
21 we're working with in Pharma and within the agency that
22 cause vascular disease but they do not cause changes in
23 blood pressure and heart rate.
24 Once again, lesions that we see in humans are
25 not observed in routine toxicity studies in normal animals.

1 The common drug-induced lesions that we do see in animals
2 are not known to occur in humans and have unknown
3 relevance. There are, as I said, five marketed products on
4 the market that cause these lesions.
5 But lastly and importantly, even though they
6 are unknown to occur, there are, however, no methods for
7 detecting drug-induced vascular injury as I've described in
8 animals or humans prospectively.
9 So, drug-induced vascular injury in animals
10 does warrant an investment of resources to define early and
11 predictive biomarkers of injury and possibly mechanism.
12 The EWG then recommends proceeding to organize the funds
13 and the process necessary to develop and validate specific
14 markers.
15 The next item we took in our charge was then to
16 develop a list of prospective biomarkers. Although the
17 pathogenesis of vascular injury in animals is not clear, it
18 is clear to the pathologists that have looked at these
19 changes that the initial events appear to occur by
20 perturbations of endothelial integrity. And secondly, it's
21 clear to many of us who've worked in the field that the
22 changes that we see are not a result of direct toxic action
23 of compounds on the endothelium, but more importantly
24 probably an effect of altered function, changes in blood
25 flow, changes in fluid dynamics, changes in shear stress,

1 and lastly, changes in hoop stress within the vascular
2 wall, and that these factors are probably more important
3 than direct toxicity.
4 Endothelial compromise, then, appears to play
5 an important early role in the development of this
6 syndrome, and therefore our biomarkers might be targeted to
7 endothelial compromise.
8 So, the charge then is to develop noninvasive
9 methods to monitor endothelial and vascular smooth muscle
10 cell damage in a variety of preclinical animal species.
11 Equally important, in the inflammatory process
12 that ensues in this disease, there are many other
13 inflammatory cells, neutrophils and platelets, involved in
14 the process, and we're also thinking that these platelets
15 and neutrophils, taken ex vivo, might be able to tell us
16 something with regard to new biomarkers, proteins that
17 might be upregulated in these cells that we can look at ex
18 vivo in animals and potentially in humans.
19 And lastly and importantly and probably most
20 difficult, once new markers are identified, then validating
21 the new marker both in preclinical species and transferring
22 that to practice in phase 1.
23 The markers that we are targeting initially as
24 of our initial meeting and as a result of several e-mail
25 discussions in the interim, would be vascular endothelial

1 growth factor and its soluble receptor, sF1t-1, von
2 Willebrand factor, thrombomodulin, CD62E, E-selectin.
3 Circulating endothelial cells. There have been
4 a few publications recently from Europe looking at
5 circulating endothelial cells following angioplasty. I can
6 tell you just briefly the baseline for circulating
7 endothelial cells is undetectable, and post-angioplasty,
8 you can pick up 6 to 10 cells per cubic micrometer. If we
9 can translate that to this kind of a model, that could be a
10 very sensitive and specific indicator of vascular injury,
11 and we need to look at funding research in this area.
12 VCAM-1, soluble beta thrombomodulin, P-
13 selectin. Endothelin 1, also an important soluble factor
14 to look at. PECAM, ICAM-1. And lastly, soluble FAS
15 ligand. I think there's some data that's evolving showing
16 that the endothelial cell death that I showed you in the
17 scanning EM is probably associated with apoptosis and not
18 necrosis. A lot more work needs to be done in this area,
19 but if that is true, we might be able to detect soluble FAS
20 ligand in the plasma as an acute marker of endothelial
21 compromise.
22 Additionally, with regard to biomarkers and
23 other "omics," as Dr. Doull refers to, I think there's
24 tremendous opportunity here to look at the cells involved
25 in the pathogenesis of these lesions for different

1 expression patterns of different messages, different
2 proteins, and so on. I think there's great opportunity
3 here to do that if we can put together the right mechanism.
4 Funding. Critically important to the success
5 of our mission, and it's very early days yet in my
6 committee. To be quite honest, we're struggling to figure
7 out how to accomplish this, and we're looking for guidance
8 from your committee. I have made some phone calls to NIEHS
9 and there are potential funding mechanisms there, and I've
10 been speaking with Ray Tennant and one of his colleagues.
11 Yesterday I spoke with Denise Robenson at ILSI. ILSI does
12 have a reputation of developing large projects like mouse
13 tumors and hepatotoxicity and so on and funding them. They
14 would be interested to see an application. That's just a
15 beginning, unfortunately.
16 I think eventually we would anticipate Pharma
17 would be interested in providing funds to support research
18 in this area, but it's early days yet. Any advice or
19 thoughts you may have, I would be appreciative.
20 With regard to funding, then, whatever the
21 mechanism, I think we need to be looking at animal model
22 development. As I said early on, the current animal models
23 don't really predict what actually happens in humans, and
24 what our current animals predict is something that we think
25 doesn't happen in humans, but we want to prove that it

1 doesn't by developing the right biomarkers. We need animal
2 models that predict what really does happen in humans, and
3 I think this is an area of research that we might look
4 into, as well as the biomarkers.
5 We need novel and specific markers of
6 endothelial and vascular injury that can be validated and
7 reduced to practice. The monies and the research efforts
8 will go into doing this.
9 Our immediate plans. We have a conference call
10 lined up for the 31st of July to continue our discussions
11 and expand and explore what I'm telling you today. I think
12 we need to submit an ILSI application, if that's what the
13 committee wants to do. I haven't mentioned this to my
14 committee yet, so I need to review that with them. We need
15 to look at the other funding mechanisms through NIEHS,
16 which we're actively exploring. We're looking at setting
17 up a workshop in collaboration with the ACT and/or the SOT
18 meetings coming up in the fall and spring of '01 and '02.
19 At the SOT meeting in '02, we have already organized a
20 workshop on vascular toxicity and biomarkers. Dr. Schwartz
21 and I are co-chairing that, and that is on the slate to be
22 presented and we hope to organize some sidebar meetings
23 around that for a broader participation and discussion.
24 There are the IP issues that I mentioned before
25 that we are looking to understand more clearly. Maybe it

1 isn't an issue, but we need to understand it more clearly.
2 We need to understand the issues of confidentiality so
3 that we can communicate more effectively between the agency
4 to understand clearly what the issues are, what they see if
5 possible, and how we might help. Validation strategies are
6 also key.
7 So, lastly, our recommendation then is that
8 this particular topic does warrant the investment of
9 further energies and monies to bring new biomarkers to the
10 table that we can use in preclinical and clinical medicine.
11 The methods need to be noninvasive. They need to be
12 robust. They need to be specific. They need to be
13 sensitive. And we need to be able to reduce them to
14 practice so that we can translate them to phase I.
15 Thank you. I'm happy to answer any questions.
16 DR. DOULL: Thanks, Bill.
17 Our other working group is the cardiotox
18 working group, and Dr. Gordon Holt is going to tell us
19 about activities of that group.
20 DR. HOLT: I'm very pleased to be here to
21 present our findings. From the moment that we constituted,
22 it was, from a personal standpoint, a great relief really
23 to find that we had been constituted with a good group with
24 diverse experience from Pharma, academia, and then the
25 governmental backgrounds to help us with all the ins and

1 outs of things that we needed to consider, as you can well
2 imagine.
3 Perhaps you're hearing between the lines right
4 now, that frankly, to a certain extent, our work is in
5 progress. Our particular charges are likely to change in
6 tune as time goes on. Our particular goals are likely to
7 change as well, too.
8 I wanted to emphasize, too, that Ken Wallace
9 wasn't able to be here today to serve as chairman in
10 talking to you about what is going on, so I get the
11 privilege, since I live 10 miles up the street.
12 Major points to be considered, as Dr. Kerns has
13 just described. In all cases it's very much needed, we
14 found quite quickly, to make sure that we're talking the
15 same language and that we believe we're sitting at the
16 table for the same reason. After we did that, we were able
17 to come up with key questions, what we thought were the
18 real pressure points for the information that we needed to
19 gather to address our charge. We came up with some
20 specific things that we can be doing in the very near
21 future to address these charges, and I'll talk about each
22 of those in time. Then we also started amassing a list of
23 resources that we were quite clear that we did not have
24 that we'll be looking to the committee at large for input
25 on how we can do these things.

1 Again, I emphasize this is work in progress,
2 and if I say something that seems challenging, then I
3 really strongly encourage everybody to bring it to our
4 attention so we can move quickly toward some tangible
5 outcome.
6 In terms of our charge -- this was given to us
7 -- identify opportunities for collaboration, develop valid
8 markers that effectively predict drug-induced myocardial
9 toxicity. We quickly tuned it a bit. What we believe
10 we're trying to do is to find a path for implementation
11 because that, as far as we are able to identify, does not
12 clearly exist right now. So, find markers, find a path to
13 implement them, at the same time clarify what the benefits
14 would be of doing this action, and then finally to identify
15 resources that are needed to bring this to bear.
16 In terms of getting our language straight, one
17 person's biomarker is another person's target, so we had to
18 be sure that we were working in the same zone with our
19 language. We quickly discerned that there are biomarkers
20 we could break down into major categories of
21 susceptibility, exposure, and effect, and then subdivide it
22 further. It's quite obvious that it's a matter of
23 semantics. You kind of run out of words to separate the
24 difference between exposure and effect.
25 Nonetheless, we believe we're down at the

1 bottom end of the spectrum where we believe that we should
2 be focusing our attentions on effect, in particular effect
3 that takes a patient or an animal from a state of
4 integrity, wellness, homeostasis, into something that is
5 not that, stress, and perhaps injury/damage. And
6 injury/damage in our minds is that next step where the
7 patient, whether it be a preclinical animal or a human, has
8 actually had some effect that is long-lasting and adverse
9 to the animal.
10 We wanted to also figure out what the
11 characteristics of an ideal biomarker are. We discerned
12 that we needed to have some idea of a goal in mind for what
13 we were shooting for. I won't go into this list in detail.
14 It's just here as a matter of record, and I emphasize
15 ideal here. This is clearly a wish list because I think in
16 many circumstances we and regulatory agencies will have to
17 take what they get, what biology presents with. But
18 generally speaking, I think there's probably going to be
19 useful agreement that any biomarker will have to be
20 specific to toxicity. It has to be sensitive, predictive,
21 robust. There's no point in going through these things if
22 all the work has to be done in a very expensive academic or
23 very high IQ setting. That's just not going to hold true.
24 As you just heard from Dr. Kerns in the case of
25 vasculitis, this is going to be a very challenging issue,

1 whether preclinical and clinical markers will bridge both
2 forward and backwards n the case of vasculitis. It looks
3 like it will be less of an issue with cardiotoxicity.
4 There are examples that do bridge already. And then
5 ideally these would be noninvasive. In the case of
6 cardiotoxicity, it's an important point to stress that you
7 don't want to induce cardiac damage in trying to monitor
8 it.
9 Key questions that we came up with are listed
10 here. I'll briefly touch on each of those in turn. What
11 cardiotoxicity markers are already accepted? Can we look
12 to existing models and get a paradigm in place for what we
13 should do next?
14 We believed that we had to split that into two
15 zones. One is what the FDA has accepted, and then what the
16 toxicology research, academic, and industrial community is
17 doing right now. Those are two different commodities, we
18 felt.
19 How are new biomarkers quickly identified and
20 validated? How can they be quickly identified and
21 validated? There is an existing committee, the ICCVAM
22 committee, that we looked to for some guidance on paradigms
23 for bringing new markers on board. We also looked to the
24 toxicologist community to help us with this task, and we
25 are, in turn, addressing both of these. I'll talk about

1 that briefly.
2 Then also, as you've also already heard from
3 Dr. Kerns, we have considered what the FDA could do to
4 enable this process, and particularly with confidentiality
5 and some kind of funding vehicle.
6 So, with respect to the current cardiotoxicity
7 biomarkers, I can just summarize a lot of work that we did
8 in our two days of sessions in trying to identify whether
9 or not there are existing guidelines. It looks like there
10 are no biomarkers for toxicity. Again, we're talking about
11 serum markers or something like that that's validated. QTC
12 is not covered under our charge as a biomarker, so we
13 didn't consider that further.
14 So, the FDA doesn't have an accepted guideline.
15 How about the community? In fact, I should register there
16 was a certain degree of surprise because there are some
17 biomarkers that I'll talk about iin a second. Troponins
18 are really highly regarded by most toxicologists as very
19 good markers of toxicity, but they're really not. I'll put
20 that forward. There is quite a long shopping list that we
21 went through, that I just listed here for your information,
22 of proteins, changes that are well known, or at least
23 somewhat well known, in the literature to be associated
24 with cardiotoxicity. But we concluded quite quickly that
25 troponins are by far and away the most advanced of any of

1 them. They are approved for some aspects with myocardial
2 infarction in the regulatory community, but not for
3 cardiotoxicity.
4 The key thing here is validation. With all
5 these markers, how can this information be bridged into the
6 regulatory setting? It's all about validation and some
7 kind of consensus-reaching.
8 I'll also emphasize, too, that we had a strong
9 sense -- and in fact, to a certain extent, personal
10 knowledge -- that these "omics" are in fact in the wings
11 and they have identified very, very compelling markers, and
12 we want to be able to bring this information on board for
13 us as well as to help advance that so that it's a
14 community-wide process.
15 Again, we feel that while there's probably lots
16 of statistically significant identifications that have
17 already been made out there, that again, even without
18 knowing more about what's going on there, that they too
19 will face a validation problem.
20 So, how to validate? The group is looking for
21 models to help us to identify how validation already
22 occurs, and also how we might suggest that things go on in
23 the future. The ICCVAM, the Interagency Coordinating
24 Committee on Validation of Alternative Methods, already
25 exists and has a very important role in bringing new marker

1 paradigms into regulatory acceptance. These tend to be
2 investigator-driven. That is, the person comes forward and
3 says, I'd like to get acceptance on this.
4 They have a very well-described path -- not so
5 much a path but a set of attainments that they look for
6 markers to be advanced to, both in animal testing and human
7 testing, frankly quite an involved process. The difficulty
8 as we perceived it is that it wasn't as clearly milestone-
9 driven as one would have hoped, and it had a certain degree
10 of all or nothing policy to it. But nonetheless, it's an
11 important guideline for us to look to to see if there's a
12 way to help bring things to regulatory acceptance. We very
13 much hope that the ICCVAM members will help us to explore
14 if there's any possible interface between this group and
15 our group to see if we can bring things forward.
16 We also looked for methods where we can get a
17 consensus finding information from the toxicology
18 community, and we have particular example that we propose
19 to do this already. These may well be driven by expert
20 working group people. Many people in the group, we came to
21 find out, know people who know people who can basically
22 bring some of the power of the toxicology community to bear
23 on the kinds of things that we're interested in.
24 We hope to be able to establish some kind of
25 expert consensus on specific biomarkers. This is probably

1 not going to be a huge finding exercise, but in fact a very
2 specific method.
3 We propose using toxicology conferences as
4 forums. These are public forums with speakers and
5 platforms, discussion, the usual sort of things that go on
6 in these conferences, to reach some kind of a gathering of
7 information that will eventually lead to a report. And our
8 working hypothesis right now is that that will be akin to
9 an NIH consensus conference. Not binding, but just a way
10 of collecting information.
11 That's very effective for the kind of
12 information that's already in public domain. What it does
13 not address is the information that we have a strong sense
14 and, to a certain extent personal knowledge, of markers
15 that are out there that the new markers, with the new
16 technologies that have recently come online, where these
17 discoverers and innovators were likely to require
18 maintenance and nondisclosure to ensure their market
19 preservation, at least to a certain extent of time.
20 How can that be dealt with? It's going to be
21 complicated because there is clearly going to be some
22 complexities with multi-party confidentiality. We don't
23 have any suggestions for how to deal with that other than
24 to say we're heartily enthusiastic to do what we can to
25 help in any way to bring that to bear. Perhaps there is

1 some subgroup forming that we can bring at least some
2 information into a private forum so we can make sure that
3 we're seeing the best information available.
4 As Dr. Kerns has already talked about, there's
5 almost certainly going to be some need for funding
6 resources. The idea here is that you probably need to have
7 something to help support academic researchers to focus on
8 specific things that the agency and the committees know
9 they need to find more information on, and there's got to
10 be some enablement there by some funding.
11 There also is likely to be some need for a
12 clearinghouse, a warehouse of samples and standards too so
13 that everybody can be testing to the same methods and
14 qualities. There may come a time when there's a need to
15 have a specific independent testing method done to make
16 sure that everything is going along as it's supposed to be.
17 How's this going to be accomplished? Probably
18 industry and PhRMA should be looked to. I think even as an
19 industry member myself think that industry should be
20 footing some of this bill. It's really no different than a
21 patent application. If industry knows what's supposed to
22 be accomplished, what will be accomplished with success,
23 then they can help work that into their cost of doing
24 business.
25 Certainly the existing granting agencies and

1 the NIH universe are also a great place to do some of these
2 things. It will require some integration.
3 And last but not least, the FDA hopefully can
4 bring some resources to bear on this.
5 What tangible things can we do that we are
6 doing right now to move things forward? We are holding,
7 internal to the expert working group, although it is open
8 to the public, a troponin workshop to be held, I guess,
9 here on the 29th. This is again focused on troponins. We
10 will be reviewing existing data. We will be trying to
11 identify data gaps in the validation pathway as we see it,
12 and then we'll be drafting suggestions on how to take
13 troponin as a particular example of a new marker that we
14 believe can be brought on board or, at the very least, can
15 be put through paces that will let us know whether it can
16 be brought on board.
17 Secondly, we have already taken the privilege
18 of having some contacts within the group to conduct a fall
19 workshop at the American College of Toxicology specific
20 mostly to troponins. We've already scheduled this and
21 started looking for speakers. This, of course, will be
22 conference attendees, where there will be a presentation of
23 current biomarkers on myocardial injury, again heavily
24 weighted towards troponins. And then we are anticipating
25 that there will be some sort of a satellite working group

1 meeting, again that should be open to the public, to review
2 the status of troponins and also to update on novel
3 reporters. That may well be a time when we're going to
4 need to start addressing confidentiality.
5 What's the outcome of this? We really do
6 believe that fairly quickly we can at least prioritize the
7 markers that are out there right now for bringing them
8 online to help with better understanding of toxicology,
9 cardiotoxicity. We also believe that the outcome of this
10 is we will be able to set up a help form of paradigm for
11 bringing new markers on board too.
12 I think I'll stop at that.
13 DR. BYRN: Thank you very much.
14 I think because of time, are there any major
15 questions anybody would like to ask of any of these two
16 speakers?
17 DR. DOULL: I think our intent was simply to
18 inform the committee about the kind of science that's going
19 on and to acquaint you with some of the problems that the
20 working groups have already brought to bear, which our
21 committee, of course, will deal with in its future
22 meetings.
23 DR. BYRN: Thanks very much, John.
24 Helen is now going to give a sort of overview
25 or a what-next talk on these two issues.

1 MS. WINKLE: I'll try to make my talk real
2 quick, since time is limited.
3 I do want to say to Dr. Doull, though, that I
4 agree with the word "leveraging." I don't consider this
5 leveraging it either. I consider it more partnering. I've
6 always had a difficulty with that term, so I thought about
7 it long and hard, too.
8 I want to thank Dr. Kerns and Dr. Holt for
9 coming and giving us this overview of the expert working
10 groups.
11 Just to remind the committee as to what these
12 groups are responsible for, they're basically fact-finding
13 groups for the subcommittee. They will bring the
14 information that they come back with to the subcommittee,
15 and the subcommittee then will, in turn, make
16 recommendations to the full committee.
17 As I think most of you on the committee know,
18 Dr. MacGregor was basically the champion of this
19 subcommittee. He's worked very hard with Dr. Doull and
20 others to get the subcommittee up and running. Also I
21 think it's already been mentioned by Dr. Doull that Dr.
22 MacGregor has left CDER and gone to NCTR.
23 At that time, there was some question as to
24 what should be the future of this subcommittee. So, I want
25 to talk a little bit about that just so you as the advisory

1 committee will know what our thinking is in the agency.
2 Dr. MacGregor and myself talked many times with Dr.
3 Woodcock and Dr. Casciano on this subject and have really
4 been looking at the concept of possibly moving this
5 subcommittee under the auspices of NCTR.
6 Basically the purpose of this committee, which
7 I think Dr. Doull has already addressed, is to provide
8 advice on improved scientific approaches to nonclinical
9 drug development and to foster scientific collaboration or
10 partnering.
11 Here are the objectives. I won't go through
12 those. I think we've already talked about that. I
13 basically want to talk about the future of this committee,
14 as I said.
15 The committee will continue to focus on
16 nonclinical safety assessments. We think this is very
17 important. It's something that's very important to us at
18 CDER. NCTR has a mandate and structure to lead in this
19 area, so as I said, we've been having conversations within
20 the agency as to whether to move this subcommittee under
21 the affiliation of the NCTR Science Advisory Board, and
22 basically too those conversations have included how this
23 affiliation should be accomplished.
24 We've talked about the advantages of the
25 transfer of the subcommittee. Already the subcommittee's

1 liaison, Jim MacGregor, is part of NCTR. Also the ICCVAM
2 process, which has already been mentioned, in the agency
3 also resides in NCTR. NCTR is oriented in doing toxicology
4 research, and it has the resources to support that
5 research. They also have a scientific advisory board,
6 which has experience in supporting such working groups as
7 this.
8 And I may want to just back up a few minutes to
9 talk about CDER's position on research. I think that most
10 of you on the subcommittee know that our resources
11 dedicated to research are limited in CDER. So, we feel
12 that NCTR is in a much better position to support any of
13 the research that comes out of these working groups.
14 Basically they also have the resources to support the
15 working groups. And NCTR -- I talked to Dr. Casciano on
16 numerous occasions -- really has the interest of being
17 involved more in this area.
18 However, should we decide to make these
19 decisions, we feel that CDER is still going to play a very
20 important role in the future of this subcommittee and with
21 the recommendations that come out of this subcommittee
22 because most of this is affecting how we make regulatory
23 decisions on pharmaceuticals.
24 So, we will continue at CDER to support the
25 NCSS if it is moved through participation in working

1 groups. Based on the recommendations we'll bring issues
2 relating to research and regulatory issues to the advisory
3 committee so that we can have further discussion on these
4 issues as they relate to our regulatory process. CDER will
5 bring regulatory questions to NCTR's Science Advisory
6 Board, as appropriate, that relate to this subject.
7 So, we still feel that we'll play a very active
8 part in the role of this committee, should it move to NCTR.
9 We see this committee as very important in helping us set
10 future standards, and also see that there are important
11 things that will come out of this subcommittee as far as
12 our guidance development.
13 Basically where to from here? NCTR has not
14 finalized a decision as to whether to adopt this committee
15 as one of their own. They're convening a team right now to
16 review the appropriateness of the subcommittee and make a
17 determination whether it should, in fact, become a part of
18 the Science Advisory Board. CDER will receive a report
19 back from that team. Dr. Casciano said that he would hope
20 to give this to me in the fall, which we will then in turn
21 share with the advisory committee.
22 Until that time CDER will continue to take on
23 responsibilities for this subcommittee. There are a lot of
24 things happening with the subcommittee, including
25 workshops, working groups, meetings, et cetera, and we'll

1 continue to support those until a final decision has been
2 made. So, I don't want you to think that this is sort of
3 going to go down the tubes if we do make this transfer. In
4 the interim, we'll continue to support it, and after that
5 we'll be an active part.
6 Any questions, comments? Yes, sir.
7 DR. MARVIN MEYER: The focus of today's
8 discussion seemed to be toxicology. Are there other issues
9 that aren't toxicological that would fit within the
10 Nonclinical Studies Subcommittee, and will they fit at
11 NCTR?
12 MS. WINKLE: That's a good question. I think
13 if we come across other issues, we'll have to make some
14 decisions then how we want to handle them internally, if
15 they're not toxicology issues. Right now, as you can see,
16 all the issues that have come up are in the toxicology
17 realm, but you're right, there are other questions that
18 could arise.
19 DR. MARVIN MEYER: I'm thinking perhaps some of
20 the issues from the bioequivalence side, with ways to
21 determine permeability of drugs, in an in vitro setting.
22 That wouldn't really fit necessarily with NCTR.
23 DR. WINKLE: Right. And we would probably
24 bring those issues independently to the advisory committee.
25 Any other questions? Okay, thank you.

1 DR. KERNS: I just had a point for
2 clarification. So, as I understand it, we're to do nothing
3 different in the interim. We just proceed.
4 DR. WINKLE: That's right. Just proceed. And
5 we'll continue to support you. We feel the work is very
6 valuable, so we don't want it to sort of fall to the side
7 while we're making this decision.
8 DR. KERNS: And you'll deal with the politics.
9 DR. WINKLE: Right. We'll deal with the
10 politics.
11 DR. BYRN: It sounds like the prospects for
12 funding at NCTR are more advantageous than FDA. So, that
13 could be an advantage to the investigators.
14 Is there any committee discussion on this
15 issue? Any additional questions, concerns?
16 DR. DOULL: I might just say, Steve, that the
17 subcommittee was, of course, very concerned about
18 maintaining the link with CDER because we feel that what we
19 do in this committee will have great impact for writing
20 guidelines and regulatory approach and so on. So, we need
21 a very strong link and a very effective link in order to
22 make those things benefit in a two-way kind of situation,
23 so that our feeling is that we are very concerned about
24 this and we'll follow this very closely and, hopefully, can
25 work out something that benefits us all.

1 DR. BYRN: Let's go on to the next session. I
2 think we'll just go ahead. I had some discussions about
3 whether we could break this up, but because of other
4 meetings, I think we'll just go ahead until the CMC section
5 is done. So, Dr. Chiu will start out and give us an
6 overview of the CMC section and the AAPS workshop.
7 DR. CHIU: We are here to give you a progress
8 report of this new initiative, the risk-based CMC review.
9 We also are here to seek your advice on two questions.
10 Just to refresh your memory, we brought this
11 topic to you last November, and this is a program with a
12 three-tier process. We are actually in tier 1 of this
13 process. Tier 1 is to establish scientific attributes and
14 acceptance criteria for drug substance, drug products,
15 microbiology, and CGMP, to define what is considered low
16 risk with respect to product quality. With these
17 attributes and acceptance criteria in place, we would be
18 able to compile a list of low risk drugs.
19 Then the second tier is we would show this
20 list to our medical colleagues in CDER and ask a
21 determination of a safety factor, whether any of the drugs
22 on the list should not be considered low risk from the
23 safety perspective.
24 Then the third tier would be evaluation of the
25 GMP status of individual firms, and to see whether a firm

1 would be eligible for this program.
2 A drug, if it is under this program, then the
3 agency will have less oversight. There are three elements.
4 The first one is we will minimize the types of
5 post-approval CMC changes requiring a submission of prior
6 approval supplement, for changes-being-effected supplement.
7 We will reduce the amount of CMC information
8 needed to be reported in annual reports to our approved
9 application.
10 The third one is if the drug is on the list,
11 then if a genographer would like to make a copy and this
12 firm has good GMP historical status, then we will reduce
13 the amount of CMC information needed to be filed in an
14 original ANDA. We call it a truncated ANDA, and this ANDA
15 will mirror the amount of data required in an annual report
16 for an approved application.
17 So, we have many internal discussions. We
18 presented this to ONDC scientific rounds, and we had brown
19 bag meetings numerous times internally to seek comments,
20 inputs. As I said, we talked about this last November in
21 this committee. In June of this year, we presented this
22 program to AAPS workshop. We had a one-day full discussion
23 from the participants, and we seek their scientific input,
24 how to put together the attributes and the acceptance
25 criteria. Therefore, we can start to compile the list of

1 low risk drugs.

2 So, today we're going to give you four reports

3 on what happened in this workshop. We will cover drug

4 substance, drug product, microbiology, and GMP. The

5 speaker for GMP, Ms. Pat Alcock, could not attend, so

6 therefore Dr. Eric Duffy will be her substitute.

7 DR. BYRN: Eric, as we go on, I would like to

8 introduce two invited guests for this session, Dr. Leon

9 Lachman and Dr. Gary Hollenbeck. And our guest speakers

10 are speaking. Of course you just heard from Dr. Chiu, and

11 now Dr. Duffy will be speaking, and then Dr. Sayeed, and

12 Dr. Hussong. So, Eric, please proceed. Thank you very

13 much.

14 DR. DUFFY: I'd just like to give a very brief

15 overview of the discussions that took place at the AAPS

16 workshop on drug substance issues. We had a brief

17 presentation in the morning, to try to frame some of the

18 issues, and then multiple breakout sessions, which were

19 very active and really quite productive.

20 Overwhelmingly, the participants felt that the

21 major criterion that would define "low risk" with respect

22 to drug substance manufacturing was the manufacturer

23 themselves. What are the capabilities of that particular

24 manufacturer? Are they capable? Do they know their

25 process? Can they reproducibly manufacture the product?

1 These seem to be the recurring themes in most of the
2 responses from the industry participants.
3 Secondly and close behind the quality
4 parameters of the manufacturer themselves was having
5 adequate specifications and the capability for adequate
6 quality assessment. This seemed to be a recurring theme as
7 well.
8 Lower down on the scale of critical issues
9 seemed to be issues of stability, inherent stability of the
10 particular drug substance. What the discussions pointed
11 out was that people felt that if you really understood the
12 inherent stability of the product itself, that would seem
13 to be adequate, a good understanding. The discussion
14 centered around whether a drug substance which is flat-
15 line, no degradation, would that be the paradigm. Or would
16 it be acceptable if you had degradation, but if it were
17 well understood and predictable? Would that be acceptable?
18 Well, people tended to think that the latter might be an
19 acceptable paradigm with respect to stability.
20 Some of the issues that we had brought forth in
21 the presentations at the beginning of the workshop had to
22 do with whether one could define complexity of structure as
23 a parameter that one might use as a measure of low risk
24 versus otherwise. And I think people's consensus was that
25 the degree of complexity may not necessarily be of any

1 relevance. Furthermore, how one would define complexity
2 seemed to be extremely difficult, and I think we have
3 struggled with that particular issue as well in other
4 contexts. But the degree of complexity is not relevant
5 because primarily there are analytical capabilities,
6 regardless of the degree of complexity, to understand the
7 quality parameters of the particular drug substance.
8 Another issue that we had brought forth was
9 whether one could use manufacturing process complexity as a
10 parameter to define a drug substance which might be of low
11 risk. The consensus I believe was that it really wasn't
12 necessarily a defining criterion, but simply that the
13 process should be well understood, that the manufacturer
14 should understand their process. And this hearkens back to
15 the initial point that I made, that it really depends upon
16 the manufacturer and their degree of understanding of the
17 process. It was considered essential that the
18 manufacturers themselves understand exactly the complexity
19 of the process and have it well controlled. Another reason
20 for really not regarding this as a defining criterion would
21 be the difficulty in defining what constitutes a complex
22 versus simple process.
23 One other criterion that we had considered was
24 the inherent reactivity of a drug substance. Is it robust,
25 or is it susceptible to reactivity with atmospheric and

1 environmental issues? Or would it be sensitive to various
2 formulation excipients, et cetera? This was considered to
3 be something that could be quite reasonably assessed in the
4 context of the drug product itself, in terms of its
5 stability.
6 Some of the other issues had to do with quality
7 measures. Primarily the discussions focused on
8 specification. It should be well justified. The set of
9 specifications, the tests and procedures should be well
10 defined and justified. And typically for drugs that have
11 been around for a while, in most cases the specifications
12 should be upgraded to contemporary practice and guidance.
13 There were, however, some concerns expressed by
14 many of the industry participants having to do with the
15 notion of upgrading specifications and maybe test
16 methodologies where one might observe, for example, in an
17 enhanced impurities test or assay, new impurities arise.
18 The concern was expressed that if one did observe these new
19 impurities, what would you have to do? Would a new safety
20 qualification have to be conducted? Would toxicology
21 considerations have to be considered? There were some
22 concerns based upon that and there were a number of people
23 who said that a more clear definition of in-use
24 qualification from a safety perspective would need to be
25 put forth by the agency. So, this is something that I'm

1 sure we will have to consider.
2 With respect to the set of specifications as
3 the measure of quality, it was considered appropriate by
4 many participants that that may not be sufficient for
5 assessment of change, impact of quality on change, sort of
6 in the realm of BACPACs, where one needs to assess the
7 impact of a change in manufacturing that is made, and maybe
8 a set of protocols would be appropriate to establish with
9 respect to assessment of change.
10 With respect to process characteristics, I've
11 mentioned that it was considered essential that the process
12 be well understood and controlled, and that also a set of
13 in-process controls need to be in place, and that those
14 controls need to be well justified. In terms of process
15 characteristics, simple versus complex. As I had
16 mentioned, it was considered not particularly relevant, and
17 the definition of how one would do this is, furthermore,
18 very difficult. Would one define it in terms of yield,
19 number of process steps? The type of manufacturing
20 process, very difficult to define. It was overwhelmingly
21 considered that the process should simply be robust. Now
22 how that's defined is another issue.
23 There were some concerns expressed, and I've
24 listed a couple here that some of the manufacturers had a
25 concern that if a drug was put on a list, would it then be

1 mandatory that they engage in this process, upgrading the
2 specifications and going through whatever registration
3 process there might be. That would certainly have to be
4 considered by the agency. Furthermore, if a drug was put
5 on the list, would the agency promulgate kind of a
6 monograph where there would be a universal specification?
7 There was some concern about that.
8 That's really about all on drug substance.
9 Steve, we're going to take questions afterward, or shall we
10 do it now?
11 DR. BYRN: Maybe because of the number of
12 speakers, we should do it now, right after each speaker.
13 So, are there any questions for Eric? Gary?
14 DR. HOLLENBECK: Sort of three questions, Eric.
15 First of all, this process, the streamlining process,
16 relates to drug products. Is that not correct?
17 DR. DUFFY: Well, one of the issues that did
18 come out in the discussions that wasn't necessarily
19 specific to drug substance breakout sessions was the notion
20 of whether or not one could have a drug substance
21 considered to be low risk, but the drug product that it's
22 used in is not considered so, or vice versa. That is
23 certainly something that needs to be discussed. I'm sure
24 Vilayat is going to mention something about that as well.
25 But yes, we need to decide whether you can split it.

1 DR. HOLLENBECK: So, you are not talking about
2 changes in the manufacturing of the active in this context?
3 DR. DUFFY: Oh, yes, we would be.
4 DR. HOLLENBECK: You are talking about that.
5 DR. DUFFY: Yes, and certainly the BACPAC
6 initiative would go a long way toward addressing the issue
7 of change in manufacturing process. I think we have to
8 think about whether or not the BACPAC initiative would need
9 to be enhanced in any fashion for those drugs that are on
10 this low risk list or not. It's something we haven't fully
11 explored.
12 DR. CHIU: Originally we were talking about
13 drug product, drug dosage form. However, because drug
14 substance is part of the drug product, of course if the
15 drug product is low risk, then drug substance must be also
16 low risk. You cannot have a high risk drug substance and
17 have a low risk drug product. We think the two are linked.
18 However, we did receive comments we should
19 consider if the drug substance is stable, but if the drug
20 product, the dosage form is not stable, then we should not
21 just forget. And then we could have a program, drug
22 substance part can be low risk. So, that's something
23 internally we have to discuss.
24 This program is not about post-approval changes
25 because once it is on this program, there's no preapproval

1 CB supplement anymore. So, therefore, the BACPAC does not
2 apply at all. There's no need to report those changes.
3 DR. DUFFY: You said you had a few questions,
4 Gary.
5 DR. HOLLENBECK: Yes. I guess just following
6 that up, I guess there was a presumption, at least for me,
7 that we would always be using quality active pharmaceutical
8 ingredients, and that the danger of establishing new
9 specifications for them in this context really wouldn't
10 help streamline the process.
11 DR. CHIU: For the initial program, of course
12 we will only consider stable bulk drug substances. We will
13 not include the proteins or other labile substances.
14 However, the industry's view is it really doesn't matter if
15 it's unstable, as long as you know the degradants, you know
16 the degradation process, you know how to control it, you
17 have a good specification to detect degradants. Therefore,
18 they should not be out of consideration.
19 DR. HOLLENBECK: My other main question. When
20 I saw this category come up, I kind of expected some
21 consideration analogous to SUPAC, the permeability,
22 solubility, therapeutic kind of screen for active
23 ingredients as part of the classification system. Is that
24 involved at all?
25 DR. CHIU: Of course, the BCS classification

1 could be used as a consideration, but we think you should
2 not be limited to the class 1 because other substances
3 which may be not soluble, not permeable as well, but from a
4 quality aspect, they are probably low risk.
5 DR. HOLLENBECK: It kind of gets to what Yuan-
6 Yuan had mentioned in her presentation, is that the
7 considerations presently are the tier 1, which are quality
8 attributes and other performance and in vivo performance
9 attributes are a different consideration.
10 DR. BARR: Basically does this group then
11 relate just to the stability and perhaps sterility of the
12 unit, as opposed to the release or the performance?
13 Because I'm kind of confused. I think like Gary that it's
14 very difficult for me to separate what's already been done
15 in SUPAC and the bioequivalence classification and those
16 kinds of things to identify problem drugs and non-problem
17 drugs. Apart from the stability, I don't see much
18 difference between the two. Could you clarify that?
19 DR. DUFFY: In terms of product performance,
20 that's the object eventually, how does the product perform
21 in use. Now, certainly for drug products that would be
22 subject to performance problems due to quality attributes,
23 that would certainly be a major consideration for us.
24 Vilayat is going to mention a bit about that in his
25 presentation. So, ultimately that's the prime

1 consideration, how the product actually performs.
2 DR. BARR: Perhaps a low risk drug would be a
3 drug which had excellent stability based upon some set of
4 criteria, and would meet, say, pharmaceutical
5 classification class 1 or something like that. Is that a
6 fair statement?
7 DR. DUFFY: We're not necessarily considering
8 the BCS as tied directly to the quality attributes. We're
9 really focusing more on manufacturing capability, whether
10 the product can be manufactured in a consistent and
11 predictable fashion. Is the drug product itself robust, is
12 the drug substance itself robust, where the degree of FDA
13 scrutiny over manufacturing issues would be considered to
14 be maybe passed over to the manufacturer, provided the
15 manufacturer has the capability to provide proper controls.
16 It's really that approach.
17 DR. CHIU: I would like to add. This program
18 is just to reduce the oversight of FDA. It does not reduce
19 the responsibility of companies to make assessments
20 whenever they want to make a change, whether the change
21 will impact the product performance, product quality. They
22 continually have to do those things, and they just do not
23 need to provide the documentation to the FDA, paper
24 documentation or electronic documentation.
25 However, we also plan to have a joint

1 inspection. Periodically we will go to the site and
2 inspect and make sure companies continue to do the things
3 that they are supposed to do.
4 DR. DUFFY: I'm going to say a bit more about
5 it when I talk about GMPs, but that's an integral part of
6 this whole program, that the manufacturing capability and
7 adherence to GMPs and having quality systems in place on
8 the part of the manufacturer. It's a quality issue
9 primarily.
10 Any further questions?
11 DR. RODRIGUEZ-HORNEDO: Yes. In the case of
12 solids that are drug substances, were any specific
13 scientific attributes considered beyond what you presented,
14 such as solid state structure, functional groups, melting
15 points. I wonder if there is a similar paradigm to what
16 has been used in the bioequivalence, biopharmaceutical
17 classification system to the vulnerability of a solid in
18 meeting the expectations we have with respect to quality
19 beyond what you have mentioned here.
20 DR. DUFFY: Yes. Certainly physical attributes
21 are very important, and some physical attributes are well
22 understood and well controlled. And others might be less
23 easily understood and controlled. Polymorphism, for
24 example, very important, but might quite easily be
25 controlled and understood. Less well understood might be

1 particle size distribution, where that's important for the
2 drug product performance.
3 What constitutes a defined particle size
4 distribution and how does one assess the change in that
5 particular size distribution is a difficult thing, and in
6 fact we're hoping that some of the initiatives that PQRI on
7 that score can really help the industry and the FDA come to
8 an understanding of what constitutes a good understanding
9 of particle size distribution.
10 But you bring up a very good point that the
11 physical attributes certainly can't be neglected in terms
12 of assessing whether or not it's a drug substance. It
13 might be vulnerable to vagaries of manufacturing problems
14 or atmospheric problems.
15 DR. CHIU: I would like to add. Polymorphism
16 and particle size, all those things were discussed in the
17 workshop. However, the feelings of the participants were
18 although those are important attributes, as far as they are
19 analytical tools to define them, to detect the change, then
20 they should not be used as a barrier for defining low risk
21 drugs.
22 DR. RODRIGUEZ-HORNEDO: I thought the objective
23 was to also reduce the regulatory burden. We also have
24 very good techniques to identify the bioequivalence, and
25 yet the impact of the biopharmaceutical classification

1 system is there.
2 DR. CHIU: Let me add, because if it affects
3 the bioequivalence, then the case is requiring in vivo
4 studies, we're not removing that oversight because based on
5 FDAMA, whenever there's a need for in vivo studies, it
6 needs a prior approval supplement. So, we must comply with
7 our law. So, therefore, your concern is that this will
8 change FDA with our oversight, then if you affect in vivo
9 performance, then we will not know, that won't happen
10 because it would still need prior approval supplement when
11 in vivo bioequivalent studies are required.
12 DR. DUFFY: Yes, Dr. Anderson.
13 DR. ANDERSON: If I understand this correctly,
14 the most crucial element of this whole thing is the
15 manufacturer.
16 DR. DUFFY: That was the consensus of the
17 participants at the conference.
18 DR. ANDERSON: I'm not questioning that. My
19 question is, will you have some criteria or some standard,
20 some kind of guidelines for deciding in this area?
21 DR. DUFFY: I'll be getting to that in the GMP
22 discussion, but the short answer is yes.
23 DR. ANDERSON: That's good.
24 DR. DUFFY: You like short answers.
25 DR. ANDERSON: Well, my students always give me

1 short answers.
2 (Laughter.)
3 DR. ANDERSON: Under your quality controls,
4 underneath the upgraded to contemporary guidance, what
5 happens if new impurities are discovered in the drugs?
6 DR. DUFFY: Well, this certainly was an area of
7 concern that the industry had expressed. It's always a
8 safety issue. If one finds new impurities, you need to
9 assess the impact that it may have upon the safety profile
10 of the drug. How one does that is something we do need to
11 work out, and the discussion of in-use qualification is one
12 thing, but there is the standard ICH approach to
13 qualification from a safety perspective. These issues
14 certainly need to be addressed. There's no question about
15 it. There is tremendous concern on the part of the
16 industry.
17 DR. CHIU: Let me add. If we have a drug on
18 the low risk list, even though we reduce the oversight, but
19 if the company makes a change, new impurities occurred
20 because of the change, because of the change of that kind,
21 it will affect the specification because when you have a
22 new impurity, you will have a change of specification. You
23 need a test or you need a change in the substance criteria.
24 Therefore, a change in specification under FDAMA requires
25 a prior approval supplement.

1 So, therefore, we will still have oversight
2 when a new impurity is discovered. The firm needs to
3 submit a supplement. We saw the qualification data, tox
4 data necessary. So, this program will not affect when a
5 new impurity is discovered.
6 DR. ANDERSON: One final thing. Under
7 structure, it is generally known that the analytical
8 methodology is less reliable for complex structures than it
9 is for simple ones. Under the process where you have
10 simple versus complex, and you said that's considered not
11 relevant, it is usually known that the more complex the
12 process is, that is, the number of steps in a reaction, the
13 more likely you are to encounter a lot of other problems,
14 including additional impurities and things like that.
15 DR. DUFFY: Well, there is greater opportunity
16 for things to foul up, yes.
17 DR. ANDERSON: I think this is under not
18 important or something like that, but that may be something
19 you want to look at.
20 DR. DUFFY: We are going to be considering
21 that, indeed. What I maybe should stress is that my
22 presentation and the following presentations are really an
23 attempt to summarize what the consensus of the workshop
24 participants was, and not necessarily the specific
25 recommendations that FDA will have. These are

1 considerations that we're going to take back and work on in
2 our further deliberations.
3 Yes, Gary.
4 DR. HOLLENBECK: Not to prolong this, but would
5 it be possible for a drug that's classified as a narrow
6 therapeutic index drug, given the comments that you've
7 made, to be considered low risk? You've gotten into tier 2
8 of our considerations, which is discussions with our
9 medical folks.
10 DR. CHIU: I'm sure our medical colleagues will
11 not agree.
12 DR. BYRN: If I can just give you an idea of
13 what we're going to do now, based on our agenda and so on.
14 We're going to go until 12:45, so if we can adjust the
15 presentations and such. We had a lot of discussion right
16 now, and we'll try to compress the committee discussion.
17 Then we'll break for lunch at 12:45 and will come back with
18 our open hearing at 1:45. So, everybody got about the
19 allotted time.
20 Dr. Sayeed is next. He's going to talk about
21 drug product.
22 DR. SAYEED: As pointed out by Eric, the
23 workshop was like a morning presentation followed by a
24 breakout session. So, what I'm going to do is go briefly
25 into what was presented in the morning session, and then go

1 into the input we got in the breakout sessions.
2 In the morning session, these two distinct
3 approaches were presented to the audience. As you see, the
4 first approach was based on developing a set of attributes
5 or criteria for defining low risk and use this set of
6 attributes, once they're developed, to identify low risk
7 drugs. And the second approach basically deals with the
8 knowledge and the understanding we have for a given drug
9 product and identify these drug products based on the
10 understanding we have, and then go ahead and perform a
11 quality risk assessment to define low risk.
12 Given the nature of the approach one, which is
13 basically a global approach, the determination was made to
14 get the input from the audience on only this approach.
15 There were certain questions that were raised in the
16 presentation, and based on these questions, we expected a
17 little bit of input in the following breakout sessions.
18 So, I'm going to go over the questions and the attributes
19 which were presented to the audience in the morning session
20 based on this approach one.
21 Here I have a set of attributes which were
22 actually presented in the morning session for the
23 discussion in the breakout sessions. The attributes were
24 dosage form, strength, manufacturing, specification, and
25 stability.

1 On the next few slides, what I'm going to do is
2 I'm going to go into each of these attributes and then go
3 into the input we got from the audience for each of these
4 attributes.
5 Dosage form. The question raised was, should
6 all the dosage forms be included in this risk assessment or
7 in this initiative. The general consensus was, yes, maybe
8 we can consider all of them, but it wasn't further defined
9 what that maybe is. So, due to the time restraints and all
10 that, the general thing was, yes, depending on the
11 understanding, maybe all the dosage forms can be considered
12 for this initiative.
13 The question for the strength was, should
14 strength be used as a factor in determining risk? Should
15 there be a line drawn below which a product can be
16 identified as either high risk, or above a certain point,
17 it can be identified as a low risk? The general consensus
18 of the audience was, it should not be considered. Strength
19 should not be a factor for defining risk in terms of
20 quality.
21 Moving on to the manufacturing, this is where
22 we spent most of the time. Almost all the issues relating
23 to manufacturing were covered, including the physical
24 attributes of the drug substance, the excipients, the
25 interaction of the excipients with the drug substance, and

1 the various manufacturing processes that can be used in
2 manufacturing a given drug product.
3 Having discussed all of that, the input was,
4 regardless of how complex or how difficult the process is
5 in making a given drug product, it should not be used. It
6 really doesn't inherently contribute in defining risk. In
7 other words, what the audience was trying to tell us was,
8 if we understand the process, if there is a control and the
9 process is controlled and validated, then the manufacturing
10 should not be an issue in defining low risk.
11 But there is one thing which clearly came out
12 in that session. If there's any functional packaging
13 attached to the product that includes like a delivery
14 system or something like that, then that product should not
15 be considered as low risk.
16 In specification, the thing which was dealt
17 with in specification was, is it adequate to just have the
18 USP specs? Or for this initiative, should the
19 specifications be updated to the current standards. The
20 general consensus from the audience was, yes, there is a
21 need to update that standard to the contemporary standard
22 in order to adequately define or assess the risk for this
23 initiative.
24 In terms of the stability of the product,
25 again, the questions and the things which were discussed in

1 the breakout sessions were, do you need to have a profile?
2 Do you need to have a complete understanding of the
3 mechanism of degradation? Does the degradation have to be
4 predictable, or there should be some sort of a limit
5 placed, and depending on the level of the degradation, is
6 there any way to define the product, whether it's a high or
7 low risk, depending on the level of the degradation?
8 So, the general consensus was the level should
9 not be a determinant, regardless of what you see in the
10 degradation as far as you understand the degradation, as
11 far as the degradation is predictable. The level of the
12 degradant should not be a criterion in determining the
13 risk. But the consensus was, yes, there should be an
14 understanding for the mechanism of degradation, and the
15 behavior has to be predictable in order to adequately
16 define risk for this initiative.
17 The outcome of this discussion was, in summary,
18 it's hard to define or identify quality attributes so that
19 those attributes can be used for defining a product,
20 whether it's a low or high risk. They said approach one is
21 a good approach but it was difficult for the audience to
22 actually pinpoint the attributes that could be used for
23 defining low risk. They were telling us, give us a product
24 and tell us what the product is and how it's being made,
25 then we can tell you whether it's a low or high risk

1 product. That was the basic outcome from the breakout
2 sessions.
3 Thank you.
4 DR. BYRN: Questions for Dr. Sayeed?
5 DR. SHARGEL: Yes. I have perhaps a need for
6 clarification. When you're saying strength, are we really
7 talking about dose in terms of a very low dose drug, maybe
8 in micrograms with a large excipient concentration versus a
9 drug that's a relatively high dose versus a very small
10 excipient?
11 DR. SAYEED: Well, that was a question which
12 was raised when we said low dose, if you have micrograms or
13 milligrams, or something going into like 500 milligrams
14 versus a microgram. The general consensus and the input we
15 got from the audience was it really doesn't matter whether
16 it's 1 microgram or 500 milligrams, as far as they
17 understand the process, as far as the process is under
18 control and validated. The strength should not be used as
19 a determinant for defining risk.
20 DR. SHARGEL: May I have a follow-up?
21 Concerning then the dose response -- and that may go back
22 to the drug substance -- are you considering a drug in
23 terms of nonlinear or having a very steep dose response
24 versus one that's relatively flat, that small doses doesn't
25 make much change?

1 DR. CHIU: No. The project is really only
2 related to product quality. We are not talking about in
3 vivo response. And if a nonlinearity response becomes a
4 safety factor, we will evaluate in our tier 2 of the
5 process.
6 DR. SAYEED: Are we going back into the
7 clinical effects, and we really don't want to get there.
8 That's part of the tier 2, and we're dealing with tier 1
9 only here.
10 DR. SHARGEL: However, if you were dealing with
11 a nonlinear product, then small changes might affect its
12 delivery.
13 DR. SAYEED: Well, that's something which will
14 be considered, but what I'm trying to present here is what
15 we got in the breakout session. It really doesn't mean
16 that we're going to follow up on that but that's what we
17 got there.
18 DR. BYRN: Any other questions? Leon and then
19 Bill.
20 DR. LACHMAN: I think we're talking about
21 trying to control these active ingredients and dosage forms
22 by the measurement of the quality of the active ingredient
23 and the product from a reproducible point of view. I think
24 we have to consider the inherent characteristics of the
25 active ingredients, the complexity of the synthesis and

1 complexity of the molecule, as was indicated before, as
2 well as the complexity of the process.
3 I'm sure you can control it. It doesn't mean
4 that everybody can control it to the same degree. And I
5 think that's where you run into a problem. I think in
6 order to have a tier 1 set of characteristics for active
7 ingredient products, you're going to have to somehow cut
8 the totality of the product mix that you're talking about
9 here. If you're looking at the outcome of the workshop, I
10 don't think you'll ever get to that tier 1 set of compounds
11 and products that you can use. That's just an observation.
12 DR. CHIU: I think you made some good comments.
13 This is a difficult issue because most of the companies
14 think there are no high risk drugs. There are only high
15 risk companies. And I'm not one of them.
16 (Laughter.)
17 DR. CHIU: At the agency we have to establish
18 objective criteria. So, we will proceed from a scientific
19 point of view.
20 DR. LACHMAN: What I'm trying to say here is
21 we're going to have to consider the basic sciences here,
22 physical and chemical sciences, not just the practicality
23 of coming up with a dosage form. If you do enough work,
24 I'm sure you'll come up with it, but the amount of controls
25 you're going to have to implement to assure the

1 repeatability of that is going to be enormous.
2 DR. SAYEED: That was the intent of the
3 workshop, to get some input like that. But unfortunately
4 what we heard was, for a given company if the process is
5 under control and if it's validated, we are fine. As Yuan-
6 yuan mentioned, there is no high risk product. It's all a
7 high risk company.
8 DR. BARR: It seems to me that the ideal goal,
9 that what you're really seeking is to try to find those few
10 substances which may be so stable, so safe, and be so
11 easily manufactured that you can reduce the amount of work
12 that you have to do. That would be tier 1, as I understand
13 it. You have to use simply physicochemical measurements
14 and characteristics to put them into tier 1.
15 Most drugs I think are going to fall into a
16 category in which to some degree they're going to be
17 dependent on some of their pharmacologic properties and
18 their critical manufacturing variables. There, just to
19 comment on one point just as an illustration, the dose and
20 the strength is very important. I know at least two
21 companies that have had great problems manufacturing
22 levothyroxine because of the very low dose and the
23 difficulties of manufacturing it. That to me is an
24 inherent difficulty, and the minute I would see a microgram
25 dose, I would say, somebody's going to mess up.

1 DR. SAYEED: I totally agree with you.
2 DR. BARR: And next, we have to get into
3 somehow the pharmacologic linkage to that.
4 And then it seems to me the next linkage is the
5 dosage form linkage. Obviously, stability in an oral
6 tablet is going to be different than the stability for
7 intravenous products that maybe have to be sterilized. So,
8 the dosage form is going to be critical.
9 But it seems to me that ultimately what you'll
10 need to do is to come up with the critical manufacturing
11 variables for that particular dosage form, maybe for that
12 particular company, but maybe in general, and then define
13 the stability or the range of stability about that critical
14 manufacturing variable, whichever they are. In other
15 words, how sharp that peak is on that variable, or how flat
16 that is and how much area you can have on either side of
17 those variables. I think that probably is workable.
18 DR. DUFFY: You mentioned probably the poster
19 child of problem drugs in levothyroxine. Not only is the
20 drug substance itself problematic, but how you then
21 formulate it. It's probably one of the more difficult you
22 could come up with. So, that's the kind of consideration
23 we certainly would be making. Is the drug substance itself
24 inherently stable, and is it subject to problems depending
25 upon how it's handled and how it's manufactured? That

1 example was very well put.
2 DR. BYRN: Now we're really running out of
3 time. I'm not sure how we should do this. Maybe try to do
4 it like the next two talks in two minutes apiece or
5 something.
6 (Laughter.)
7 DR. BYRN: If we could do that, and the
8 committee also may need to limit their comments a little
9 bit or we'll never get to lunch. We'll just start our
10 hearing.
11 DR. HUSSONG: Good afternoon to all my
12 hypoglycemic friends here.
13 (Laughter.)
14 DR. HUSSONG: The AAPS conference on
15 streamlining the CMC regulatory process had two sessions on
16 microbiology issues, one concerning the post-approval
17 changes to applications and the other was to try and define
18 specific characteristics to qualify drug substances and
19 drug products as low risk. The discussions focused on
20 sterile products, but we also got some comments concerning
21 non-sterile products.
22 Now, participants felt that sterile drugs could
23 be separated into risk-based groups based on sterilization
24 processes used in their manufacture. For example, the
25 terminal moist heat sterilization processes were considered

1 to have greater reliability than the aseptic processes for
2 manufacturing. Although this generality was noted to have
3 exceptions, aseptic processing is universally agreed to
4 offer greater challenges.
5 Certain changes to the processing of what might
6 be considered low-risk products will still require
7 supplements, however. These examples might include major
8 changes in sterilization technology. For example, if you
9 were switching from filtration to gamma irradiation.
10 Additionally, if you were deleting steps in the
11 sterilization process. For example, if the sterilization
12 process used aseptic filling methods, followed by a short
13 heat process, and if you dropped one of those, that would
14 certainly require a supplement.
15 Also, changing critical parameters in the
16 specifications concerning the sterilization process. Those
17 would be the control parameters for the sterilization.
18 However, many changes, about 20 of them, were
19 noted that do not negatively affect sterility assurance,
20 and for these it was recommended the route of annual
21 reports could be used. Now, some of these included minor
22 changes to container and closure systems. Also offered as
23 an example were equipment items used prior to the
24 sterilization steps. Additionally, terminal sterilization
25 autoclave loading patterns were felt to be kind of low risk

1 concerns. And several people argued that the
2 lyophilization cycle really didn't have that much to do
3 with sterilization. We didn't even use to sterilized
4 lyophilizers until recently.
5 Concerning non-sterile products, there are very
6 few microbiological concerns. Participants said none, but
7 I disagree. For oral dosage forms, transdermal,
8 suppositories, and products that are inherently
9 antimicrobial, they felt that these should be streamlined
10 and of reduced review and scrutiny. And certainly non-
11 aqueous products, such as the metered dose inhalers, nasal
12 sprays, dry powder inhalers, were offered as examples of
13 additional low risk category drugs.
14 There were a lot of requests for guidance
15 concerning manufacturing process-associated changes. These
16 requests asked in particular for information concerning the
17 categories of filing changes and more examples and
18 definitions so that people could feel confident that they
19 were doing what the agency wanted and communicating
20 properly.
21 The other advantage to having these guidances
22 is, it was felt, that the agency was in need of internal
23 help here, and this might be a side benefit to it because
24 of many complaints from the industry that recommendations
25 were not consistent, either between offices, between

1 centers, and sometimes between the centers and the field.
2 So, in summary, we have a lot of evaluation to
3 do internally. We need to determine what we can do to best
4 address these concerns, and we do feel that we can
5 accomplish a lot using process based evaluation rather than
6 drug product based.
7 Thank you.
8 DR. BYRN: Questions for Dave.
9 (No response.)
10 DR. BYRN: Our next speaker is Eric Duffy again
11 with GMP.
12 DR. DUFFY: Steve wants me to talk fast. Now,
13 I'm not from New York, but I'm from Boston, so I can
14 probably keep up.
15 I'm presenting this on behalf of Pat Alcock who
16 is out of the office today.
17 The GMP breakout sessions were really central,
18 I think, to most people's consideration of this whole
19 initiative, where the capability of the manufacturer really
20 was a recurring theme all the way through. There was some
21 discussion initially of what the current system was, and
22 I'll kind of breeze by that, however, simply just to say
23 that there was, to me, surprisingly a consensus that the
24 current system really works quite well. The inspectional
25 paradigms that we have in place for ensuring GMP compliance

1 seem to be working quite well.
2 But for this particular program, there was some
3 discussion about whether or not there should be some what
4 was termed GMP-plus system established where there's
5 something a little bit further than what the current system
6 was. A number of different suggestions came up with
7 respect to how one evaluates the firm's capability for
8 adherence to GMPs and to have quality systems in place to
9 ensure consistent quality manufacturing.
10 What are the measures of these? How would the
11 agency assess the capability of this firm to demonstrate
12 exemplary adherence to GMPs?
13 Some of these suggestions were recall history,
14 for example. It could be an assessment of the body of PAI
15 inspections that had been conducted, review of 483
16 comments, the recurrence of particular issues. Basically
17 what is the regulatory status, inspectional status of a
18 firm? So, I think what we need to do is try to develop a
19 paradigm to assess the history and a means of demonstrating
20 the capability of a particular manufacturer.
21 There were other issues that could certainly be
22 measures which might concern whether a firm had been under
23 any consent decrees. Would then some sort of probationary
24 period need to be established to provide the firm an
25 opportunity to demonstrate good manufacturing practices and

1 adherence to GMPs? That might need to be defined?
2 There was another consideration of the
3 implication this might have with respect to the mutual
4 recognition agreements that we're currently engaged in
5 negotiating with the Europeans, and I think in the future
6 with Japan, that this may have some impact on that. And we
7 certainly need to take all that into consideration.
8 Further concerns were that if we were to create
9 this GMP-plus system, that it might create a different set
10 of GMP standards for the drugs on the list versus those
11 that are not. This approach may have a differential impact
12 upon large firms versus small firms, new firms versus
13 experienced firms. So, a fairness issue essentially was
14 expressed.
15 How one would handle situations where there are
16 multiple companies involved in a supply chain. What
17 clearly comes to mind is drug substance manufacturing where
18 one might have three or four firms involved in
19 manufacturing various stages of a synthesis? Manufacturing
20 intermediates, how would we handle that? Certainly an
21 important thing to consider.
22 Also, how one would handle changes in ownership
23 or management. Would that have an impact upon our
24 consideration of the reliability and capability of the
25 particular manufacturer?

1 I think I hit two minutes. There we are.
2 DR. BYRN: Questions for Eric?
3 DR. LACHMAN: Eric, you're now discussing a lot
4 of GMP and administrative issues that are ongoing right now
5 within the agency's activities on inspections. So, there's
6 nothing really novel here. I still think we're getting
7 away from the inherent characteristics of the drug and
8 dosage form and controls necessary to assure
9 reproducibility.
10 DR. DUFFY: It's a totality of approach in this
11 case, Leon. We're not really divorcing the attributes of
12 the drug itself from manufacturing capability. It's going
13 to have to be interwoven in some fashion.
14 DR. LACHMAN: Right now there's an intensive,
15 proactive regulatory environment out there from a
16 compliance point of view, GMPs, and so on. They consider
17 all these elements on inspections and what to do next to
18 the firm and so on. So, that's really nothing new that you
19 addressed. And these additional GMPs that you can apply
20 are being applied if you're out there in the field. So, I
21 think we still have to get back to the basic science of the
22 drug and dosage forms and the reproducibility of the
23 controls for the products and active ingredient.
24 DR. DUFFY: We don't disagree with that at all.
25 DR. LACHMAN: I think we're muddying the waters

1 a little bit here with bringing in all these GMP issues
2 because they exist now.
3 DR. DUFFY: Well, we were simply trying to
4 express what many of the participants at the workshop
5 expressed, and that is that we need to have some way of
6 measuring the capability and qualifications of a particular
7 firm to enter into this program for reduced regulatory
8 scrutiny. If they have a demonstrated history of a
9 capability to adhere to GMPs, to manufacture in a
10 consistent manner, and produce a quality product in a
11 predictable fashion, well, then that's a plus for them for
12 involvement in the program.
13 DR. LACHMAN: I think the FDA has that now.
14 They have quality profiles of firms based on their
15 inspectional history.
16 DR. DUFFY: Right, and some firms are turned
17 down for approvals.
18 DR. LACHMAN: That's right. That's what I'm
19 saying. So, that's nothing I think that we don't have
20 already. That's all I'm saying.
21 DR. DUFFY: Were there any other questions?
22 Comments? Judy?
23 DR. BOEHLERT: Just a comment. While I agree
24 with everything that Leon said, I just wanted to add a
25 comment on this concept of up-to-date and meaningful

1 specifications. I don't think industry realizes what kind
2 of task that may be for them, particularly on old products
3 that are compendial. They're following compendial methods.
4 There are no physical tests in the compendia to begin
5 with. So, that's something that needs to be addressed.
6 Those will probably result in submissions to update old
7 methods, old tests, new impurities that they've now found
8 that have always been there but they didn't see them
9 before.
10 DR. DUFFY: Those concerns were amply expressed
11 at the workshop.
12 DR. BOEHLERT: Yes, I'm sure. And it's a lot
13 more work than I think industry is realizing. On a new
14 product that has good controls, perhaps not, but on old
15 products.
16 I don't know how everybody gets up to the same
17 standard in that case because the methods aren't published
18 in USP. The physical tests, the process impurities. They
19 don't list those.
20 DR. LACHMAN: I think we need to look at some
21 of the history here for existing products that have been on
22 the market a long time and they've been safe. They haven't
23 caused any health hazards. As the methodology and
24 analytical techniques become more sophisticated, we're
25 going to find more impurities in the products that have

1 been on the market. That's something that we have to
2 consider in addition and not part of this mechanism, I
3 don't think, because those exist now for existing products.
4 DR. DUFFY: Those concerns were expressed
5 repeatedly.
6 DR. BOEHLERT: I think if impurities have
7 always been there, that's a different situation than
8 creating a new impurity because they could, indeed, be
9 qualified for use.
10 DR. DUFFY: It's just that you now see it.
11 DR. LACHMAN: That's right.
12 DR. DUFFY: Shall we move on? Any further
13 questions? Gary, you had something?
14 DR. HOLLENBECK: Just a similar comment. I
15 think that the essence of this presentation shows that
16 maybe you don't have tier 1, tier 2, and tier 3. These
17 things are so interwoven that they almost have to be
18 considered simultaneously. I'm a strong advocate for
19 rewarding a company that has a history of good GMP
20 compliance, and I think that's a critical part of the whole
21 process.
22 DR. BYRN: Dr. Chiu? We're going to go to the
23 next steps, and then if people can be looking at these two
24 questions. I think we've discussed many of these issues
25 already.

1 DR. CHIU: As you can see, we were a little bit
2 disappointed with the outcome of this workshop because we
3 went in seeking scientific input. What we received were a
4 lot more questions, and also the consensus is not the way
5 we think we can readily handle.
6 However, I do believe -- and I think our
7 working group also believes -- there is a way to establish
8 criteria, attributes to characterize safe, so-called low
9 risk drugs. Actually the terminology was discussed in the
10 workshop. Many people felt it has a bad connotation
11 because if a drug is on the low risk list, they feel other
12 drugs become high risk. They would like us to think about
13 changing the terminology. So, internally we have discussed
14 maybe we could call it predictable drugs, established
15 drugs, robust drugs. Some people suggest low impact drugs.
16 So, if you care to discuss, maybe you can come up with a
17 better term than low risk.
18 But everybody understands what low risk means,
19 that from the quality point of view, the product is really
20 prone to defects and they are with those more
21 physicochemical characteristics. Therefore, not much will
22 happen to them regardless how you handle it.
23 Based on the discussion you had the last time
24 and today and also the workshop and the internal
25 discussion, we thought we need to modify our program a

1 little bit. A lot of people told us internally and
2 externally when I see a drug, I work on a drug, and I
3 review the drug, I know it is low risk. When I see one, I
4 will know it. But if you ask me to define the
5 characteristics in a broad sense, it's very hard.
6 So, we thought then maybe we should take a
7 parallel approach. In addition to considering stability 5
8 years, stable at the room temperature, it has no
9 polymorphism, et cetera, maybe in the meantime, we can also
10 solicit from people what drugs through their experience
11 they think are low risk. Then we can evaluate the
12 characteristic of those drugs and then come up with
13 objective, scientific criteria. So, if we do those things
14 parallel, maybe you can reach there faster.
15 So, we're going to form subgroups under our
16 current working group to separately address drug substance,
17 drug product, and microbiology issues.
18 We also formed a group to address GMP. But as
19 Leon said, GMP is GMP. Everyone has to be in compliance,
20 otherwise you already get in trouble.
21 So, the other input we had from the workshop
22 is, as I said, this is really the concern of so-called high
23 risk manufacturers. The manufacturers will now know what
24 they're doing. Therefore, regardless if the drug is low
25 risk or high risk, the drug made by such a company would

1 become high risk.

2 So, therefore, the feeling is it is important

3 that you tie in the GMP status not only with the historical

4 status, but also with the GMP status of a specific product

5 on the list. So, if we do that, then that company, to be

6 eligible for this program, must already have experience in

7 making that particular drug. If we move from that

8 direction, that means the original ANDA must contain full

9 information because the company would not be eligible for

10 this program because they have not made that product yet.

11 So, if we move in that direction, there will be no TANDA,

12 no truncated ANDA.

13 Therefore, this comes to the two questions we

14 pose to the committee to discuss. The first question is

15 really whether we should take the parallel approach, we

16 should seek input from people from industry, from our

17 reviewers to find the drugs through their experience that

18 are considered to be low risk. Then we use those drugs and

19 analyze the characteristics and see whether from there we

20 could establish a set of objective attributes and

21 acceptance criteria.

22 The second question is whether we should tie

23 the GMP status to a specific product. And if the answer is

24 yes, we will not for the moment entertain TANDA, and the

25 program temporarily will exclude truncated ANDA

1 submissions.

2 DR. BYRN: Let's spend a couple moments on each

3 of these. On the first question, any comments from the

4 committee as it reads here, is the approach of establishing

5 attributes and acceptance criteria for drug substance, drug

6 product and microbiology based on the characteristics of

7 potential candidates of low risk drugs appropriate? Is

8 that approach appropriate? Any comments?

9 DR. HOLLENBECK: I think the list is

10 inevitable. It is something that's necessary.

11 But your comments about the process I think are

12 really good. It's like my view of art. I don't know what

13 it is, but I know it when I see it. Here, I think you

14 would be better served to do kind of a retrospective rather

15 than prospective approach. If we sit down and try to

16 identify everything that might be on the list, it's almost

17 impossible to make the list small enough or have any drug

18 ever qualify as being low risk.

19 However, if you do go through this exercise, I

20 think what you usually find is there's one thing that kicks

21 things off the low risk list, and if you do that for a

22 series of compounds, you'll begin to compile this set of

23 criteria.

24 DR. DUFFY: We're doing precisely what you're

25 suggesting, Gary. We're kind of delving back and doing a

1 little data mining, one might refer to it as, to really
2 see. We have a product that appears to be robust and
3 perform in a consistent fashion. What is it that makes it
4 do that? We are doing it.
5 DR. BYRN: I agree. I think you have to do it
6 almost compound by compound early on anyway.
7 Other comments on number one?
8 DR. MARVIN MEYER: Is the question whether one
9 should have a subgroup that looks at the chemical and a
10 subgroup that looks at the dosage form, or will they be
11 studied simultaneously by a group? For example,
12 hydrochlorothiazide immediate release tablet versus some
13 type of a controlled release dosage form? If you want to
14 get this thing off dead center, if you took a product that
15 everyone says, well, it doesn't matter what the dose is,
16 it's effective, it's safe, it's stable, it's blah, blah,
17 blah, that's our poster boy, if you will, for a low risk
18 drug, and then kind of build around that and come up with a
19 list and then float the balloon and see how it flies.
20 Or is the question saying should the agency
21 even be concerned about reducing the regulatory burden
22 based on these attributes.
23 DR. CHIU: No. The question is the former, not
24 the latter.
25 DR. MARVIN MEYER: The approach.

1 DR. CHIU: Yes, it's the approach because even
2 though we formed subgroups, if we identify lists of already
3 the candidates, we will have the subgroup to go back to our
4 files to look at the characteristics of the drug substance
5 of that product, and the characteristics of that drug
6 product as a drug product subgroup. Then we will talk to
7 each other and then put the things together. So, the
8 reason we want to form separate subgroups is then we can
9 become more focused.
10 DR. BYRN: Is there general consensus that the
11 response to question number 1 is affirmative, it's a good
12 idea? Okay. I don't think we need a vote on this one.
13 Question number 2. In effect, this would
14 eliminate the TANDA mechanism right now. Basically what's
15 being said now is that the CGMP status and also its history
16 of that specific product would go into consideration. Are
17 there thoughts on that?
18 DR. SHARGEL: As a member representing the
19 generic industry, I was, of course, compelled to address
20 this issue. I think the history of GMP certainly is
21 suitable and for new products that generics make or new
22 generic drug products, there are already in place pre-
23 approval inspection and validation batches and other
24 approaches. So, I would like to keep it broader, not
25 specific to a history of GMP.

1 DR. LACHMAN: I would say that the GMPs apply
2 across the board. They're not geared for any single
3 product. Even on pre-approval inspections, you do a
4 vertical review of the documentation and records to support
5 that product, but you also go broader because your
6 environmental system or your water system doesn't just
7 apply to a product. You got to look at the totality of the
8 GMPs and the training program. So, you can't just isolate
9 GMPs in a vertical manner. It has to be horizontal.
10 The quality systems are broad. It's not only
11 for one product. If you're making tablets, you've got to
12 have a quality system for tablets. You make injectables,
13 you got quality systems for injectables. They're not
14 exactly the same as tablets. So, you got to look at the
15 system and not an isolated element.
16 DR. CHIU: So, you do not think the
17 manufacturing history or experience for a specific product
18 is important related to GMP.
19 DR. LACHMAN: No, because I think it's all
20 broader than just a specific related to a single product.
21 DR. BYRN: Where I think some of the problem
22 may come in is in the drug substance side. I don't know,
23 but that's where know-how and so on may play a bigger role
24 in many cases. I guess if you started talking about
25 extended release products and so on, it may play a role in

1 drug product. But certainly to me I would like to see
2 somebody have made some drug substance and see what their
3 record is on making that prior to. So, I don't know
4 whether there's a way to do it with drug substance and not
5 with drug product.
6 DR. CHIU: Well, I think there is. Maybe we
7 could split this question into two: 1a means whether GMP
8 status to a specific drug substance is important; the
9 second one is whether GMP status to a drug product is
10 important. Then if the committee can vote on both
11 subquestions.
12 DR. BYRN: Well, I'm just saying that the
13 manufacturing history might be more important for a drug
14 substance than a drug product.
15 DR. CHIU: Yes. I mean manufacturing history
16 for a specific drug substance. That's the GMP part.
17 DR. BYRN: You know, that wouldn't preclude a
18 generic firm from buying it from a well-known manufacturer.
19 This is more like a new manufacturer.
20 DR. CHIU: Right, a new supplier.
21 DR. LACHMAN: The API firm supplying an
22 innovator company or a generic company also undergoes
23 inspection by the FDA, and their process is evaluated with
24 regards to repeatability. In certain cases, both innovator
25 companies and generic companies don't manufacture their own

1 API or they manufacture part of their API and farm out part
2 of it. So, your drug master file becomes an important part
3 in the evaluation of this low risk to high risk. I think
4 that needs to be taken into account, the controls like we
5 have for dosage form. What are the controls for the active
6 pharmaceutical ingredient? I think, Steve, that's an
7 important piece.
8 DR. CHIU: Can the committee vote on these
9 questions? Because it's important for us to establish the
10 scope of this project.
11 DR. BYRN: I'm not sure what your question is.
12 DR. CHIU: The question is whether we should
13 eliminate TANDA, if we could put into two parts the TANDA
14 for drug substance and TANDA for dosage forms.
15 DR. BYRN: Yes. We need to try to reach a
16 consensus because we are going to have to start at 1:45
17 again.
18 DR. LACHMAN: I think there can only be one
19 TANDA. I don't think you can break it --
20 DR. BYRN: TANDA would just be a drug product.
21 An ANDA would be a drug product. It would be the DMF --
22 DR. CHIU: I understand. DMF supports the
23 TANDA, so DMF is part of TANDA.
24 DR. LACHMAN: So, the TANDA would be affected
25 if the DMF wasn't any good. I mean, if the bulk drug

1 supplier wasn't any good, you won't get approval of the
2 application.
3 DR. CHIU: I understand. Maybe let me explain.
4 The ANDA contains a drug substance part and a drug product
5 part. A drug substance could be supported by a DMF. So,
6 TANDA means truncated ANDA. We couldn't have a truncated
7 ANDA, both truncated in drug substance information and drug
8 product information. So, if we say the drug substance part
9 of the information is essential for TANDA, then the
10 truncated submission would not apply to the drug substance
11 part.
12 So, therefore, if I can have a reading from the
13 committee whether the drug substance information should be
14 fully submitted in a TANDA. That's the first question.
15 DR. LACHMAN: I think it's an integral part of
16 the TANDA. You can't get a TANDA without an active
17 ingredient.
18 DR. CHIU: Sure, but it will be reduced
19 information. It's not eliminated. Under TANDA, there will
20 be reduced information to be submitted for a drug substance
21 and for a drug product.
22 DR. LACHMAN: All right, so that has to be
23 still determined.
24 DR. CHIU: To be determined, yes. We will
25 eventually write a guidance, what would be adequate

1 information for an annual report, and then we thought we
2 could start with the summary, CTD summary of the quality
3 section. That type of information, if it's sufficient for
4 an annual report, it will be sufficient for a TANDA.
5 So, if you tell me the drug substance cannot be
6 truncated, then we will say the annual report will also be
7 required to have the full drug substance information and
8 the TANDA will have full drug substance information, only
9 reduce the information on the drug product part.
10 DR. BYRN: Is it possible just to make a list
11 of drugs from the safest to the less safe and just draw a
12 line somewhere and say these are so safe that it doesn't
13 make any difference who makes them?
14 DR. CHIU: That's the objective.
15 DR. LACHMAN: Well, I'll tell you, I wouldn't
16 go that far, Steve, because I wouldn't want to have metal
17 in the active ingredient --
18 DR. BYRN: Yes, well, we're assuming that they
19 pass compendial specs.
20 DR. CHIU: Compendial specs are not adequate
21 for all products.
22 DR. BYRN: I think we have to stop now. I know
23 we haven't gotten a full conclusion yet, but I think we
24 should stop. I think the agency could come back to the
25 committee with more detailed proposals, but continue along

1 both of these lines, and from what the committee said, not
2 kill TANDA. Do not kill a TANDA, but consider our comments
3 and continue.
4 DR. CHIU: That's fine. We will come back if
5 we have more specific questions. Thank you.
6 DR. BYRN: That's what I think we should do.
7 We're going to meet back here at 1:45.
8 (Whereupon, at 1:10 p.m., the committee was
9 recessed, to reconvene at 1:45 p.m., this same day.)
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7 AFTERNOON SESSION
8 (1:57 p.m.)
9 DR. BYRN: Welcome to our afternoon session.
10 This is the open public hearing part. We have had no
11 requests from the audience that's attending to make a
12 presentation, but we do have four five-minute presentations
13 from the Inhalation Technology Focus Group.
14 The first speaker will be David Radspinner,
15 Ph.D., who's going to give us an update on ITFG/IPAC-RS DCU
16 Working Group progress. He'll explain all this.
17 (Laughter.)
18 DR. RADSPINNER: It's only fitting to have more
19 acronyms, isn't it?
20 DR. BYRN: That's fine. We're used to that.
21 DR. RADSPINNER: As mentioned, my name is David
22 Radspinner. I'm a member of the IPAC, which stands for the
23 International Pharmaceutical Aerosol Consortium on
24 Regulation and Science. This is an industry association.
25 We formed a collaboration with the Inhalation Technology

1 Focus Group which is a subgroup of the American Association
2 of Pharmaceutical Scientists.
3 Together what we have done is last year we
4 formed a collaboration to look at CMC issues and also BA/BE
5 issues related to the FDA draft guidance. These technical
6 teams have actually presented some of their concerns at
7 this meeting back in November. What we'd like to do today
8 is give you an update as to some of our activities.
9 As you see here, we've been working quite
10 diligently on proposals around issues of CMC with relation
11 to the draft guidance. Also, the BA/BE technical team has
12 been looking at dose-response studies.
13 With regards to CMC, there are four critical
14 issues we look at, that is, dose content uniformity,
15 particle size distribution, tests and methods, and
16 leachables and extractables. What I'd like to do is
17 briefly update you on dose content uniformity, and then
18 I'll hand it over to Dr. Evans.
19 Back in 2000, we collected and analyzed the
20 dose content uniformity database and submitted the findings
21 to the FDA. This was back in July. The reference is
22 listed here.
23 In November, there was a meeting and we
24 reported at that meeting that 68 percent of the products
25 that were analyzed did not comply with one aspect of the

1 dose content uniformity criteria within the draft guidance.
2 We also met with the FDA back in November, and
3 we met once again in May 2001 to discuss the findings and
4 plans for future work.
5 What we've done is we've kind of moved on from
6 the review of the database itself, and we've worked very
7 hard on developing an improved dose content uniformity
8 test, and that's what I'd like to focus on here.
9 The foundation of this test is originally based
10 on some ideas coming from Dr. Walter Hauck, which I'm sure
11 most of you know, and it's based on a parametric tolerance
12 interval approach. The test design is also similar to some
13 concepts that were developed and discussed within ICH with
14 regard to content uniformity.
15 We've looked at quality standards implied
16 within the guidance, and it's sort of an approach where
17 we've taken the draft guidance and sort of reversed
18 engineered a definition of a quality statement.
19 We've also looked at the capabilities within
20 the industry of modern inhalation technology and considered
21 it while developing this test.
22 The parametric tolerance interval approach,
23 when we compared it to the current guidance -- the
24 advantages are increased efficiency in using the sample
25 information. So, we're not really collecting different

1 sample data, but we're using the information much more
2 efficiently we believe.
3 By doing a parametric tolerance interval test,
4 we're also improving the consumer protection -- this is in
5 a statistical sense -- while at the same time improving
6 producer protection. So, we're trying to avoid those
7 batches that fall in the middle.
8 What's important is we have an explicit quality
9 definition, which is a proportion of doses within a batch
10 that fall within a given target interval.
11 The acceptance criteria is based on a sample
12 mean, a standard deviation, and what's called an acceptance
13 value, which actually combines the two.
14 It's a consistent quality standard, but we
15 offer a flexible testing schedule to the producer.
16 There's also a single test for both within-unit
17 and between-unit variability, and this has been achieved
18 through a parametric tolerance interval test. One of the
19 aspects of that has also been an increased average sample
20 size for testing within the industry.
21 Where do we go from here? There's a draft
22 report currently under review within the IPAC-RS
23 consortium. We anticipate submitting this in the fall of
24 this year. We also anticipate having a meeting following
25 that with the FDA to discuss this, and we do recommend that

1 this become part of the draft guidance.
2 I guess I take questions either now, or if
3 you'd like to move through all four presentations before
4 taking questions.
5 DR. BYRN: I think we will go through all four
6 and then take questions together.
7 DR. RADSPINNER: Thank you.
8 DR. EVANS: Good afternoon. My name is Carole
9 Evans, and I'll be presenting on behalf of two of the teams
10 today, the particle size distribution team and the test and
11 methods team.
12 The particle size distribution team have
13 addressed two concerns on the draft guidance, firstly, the
14 concern that there is a requirement for mass balance within
15 the particle size testing be established as a drug product
16 specification. In this case, the mass balance actually
17 attempts to measure emitted dose, which is appropriately
18 controlled by separate specifications and test methods.
19 However, we agree that this mass balance measurement could
20 be appropriate as part of a system suitability control, but
21 it should not be a product specification. Furthermore, if
22 we're to use mass balance as a system suitability, the
23 limits should be determined during validation studies and
24 not set arbitrarily in a guidance.
25 Additionally, one of the concerns is that the

1 label claim may not necessarily be reflected by the mass of
2 drug collected on all stages and accessories. For example,
3 there are some products for which label claim is defined by
4 the pre-metered dose rather than the emitted dose, and in
5 these cases, there would not be a match there.
6 Finally, we've also reviewed some data that
7 we've collected from a number of products and have found
8 that, in general, the majority of products do not meet this
9 requirement. To date we have collected a large database of
10 data from 35 products and found that only 11 percent of the
11 products -- that's 4 of them -- will actually meet this
12 criteria. We've submitted this initial assessment of the
13 database to the FDA in a paper last August.
14 As a next step, we'd like to meet with the
15 agency and try and determine the actual purpose of this
16 requirement to try and understand better what the objective
17 of the agency with this requirement is and work with them
18 towards finding an alternate method of addressing their
19 concerns. To this end, we've submitted a proposal to PQRI
20 to have further discussions on the subject.
21 The second area that the particle size
22 distribution team is working to address is for the use of
23 particle size distribution profiles in bioequivalence
24 testing. The draft guidance proposes a chi-square
25 differences approach to comparing the profiles with test

1 and reference products. The concern is that the chi-square
2 method was developed for one particular product and we're
3 using one particular type of equipment, and the
4 applicability to other products and other test
5 methodologies may be limited and hasn't been demonstrated.
6 Furthermore, the equivalence criteria have been set
7 somewhat arbitrarily.
8 The team are currently pursuing an
9 investigation of alternate approaches. Amongst those are
10 the approaches based on bootstrapping of data. Their
11 objective here is to try and find other approaches which
12 may be more discriminatory, would have wider applicability,
13 and would provide a consistent approach for comparisons of
14 profiles. They've submitted a proposal to PQRI to have
15 some work pursued to look at alternate approaches and to
16 look at what metrics for comparisons of profiles may
17 actually have some clinical relevance to help us evaluate
18 bioequivalence.
19 I'll move on to the test and methods team. The
20 test and methods team has been reviewing the test methods
21 proposed in the guidance, and our objective has been to
22 select methodologies that would be based on development
23 data providing meaningful information about product
24 quality. Our concerns are that some of the tests proposed
25 in the guidance offer little added assurance as to product

1 quality and in some cases may be redundant.
2 We've collected data on a number of the tests
3 and have developed a database consensus and recommendations
4 to the FDA. We submitted a paper to the FDA in May of this
5 year which proposes alternate language for a number of
6 tests for MDIs. Again, our objective here is to maximize
7 the value of the controls and tests and minimize the
8 redundant testing.
9 I will not read all eight. We submitted
10 comments on the tests listed here. Our paper provides a
11 critical assessment of the value of these tests and the
12 development data that may be used to support new product
13 control. We've concluded that a fixed list of tests may
14 not be appropriate as guidance and that the guidance should
15 stress the importance of defining the tests used for a
16 product during the development process, and that we should
17 eliminate those controls which we feel are redundant.
18 We're at the moment working on developing proposals to put
19 forward to PQRI.
20 Thank you.
21 DR. BYRN: The next speaker is James Blanchard
22 who is going to address leachables and extractables.
23 DR. BLANCHARD: Thank you and good afternoon.
24 I'd like to update you on the work of
25 leachables/extractables team.

1 We have reviewed both guidances very carefully,
2 basically trying to look at them from a user's perspective.
3 From an implementation perspective, we feel that we can
4 more effectively implement the guidances if we have some
5 thresholds to work with which we can agree upon and the
6 agency can agree upon as well. So, one of our concerns is
7 proposing or trying to propose adequate, appropriate
8 thresholds for reporting, identifying, and qualifying
9 leachables and extractables.
10 Also, we have found some terms that are very
11 important that are a bit unclear in terms of how to
12 interpret them. So, we are also looking for clarity to
13 define concepts such as correlation, particularly how a
14 leachable will be correlated with an extractable because
15 that's actually a very important in implementing the
16 guidelines and further testing.
17 Also, there is a term called "critical
18 component." What exactly is a critical component? What
19 has to be actually done to test a critical component? So,
20 we'd also like some more clarity on that definition as
21 well.
22 So, what we've done to start this process is
23 that we've started gathering data from the industry and the
24 one set of data we did collect was for leachable and
25 extractable data on specific drugs to see if correlations

1 did exist between these leachables and extractables for
2 this.
3 We've also collected other types of data.
4 We've also formed a toxicology working group of expert
5 toxicologists from industry to look at the qualification
6 issues, and together we have put together a report which
7 we've now submitted in March.
8 So, I'd like to go through some of the
9 highlights of some of the areas in each of the guidances
10 that we think would help for clarity or some help with the
11 agency.
12 First of all is the definition of a critical
13 component. We're proposing that a critical component would
14 be any part of the device that would be in direct contact
15 with either the formulation, the patient's mouth or mucosa.
16 That would be what we would be testing going forward in
17 our characterization of the extractables and the
18 leachables.
19 Next, getting to the idea of thresholds, we are
20 proposing a reporting threshold of 1 microgram per gram in
21 the controlled extraction studies of the raw materials. At
22 this level, we are thinking that you won't get complete
23 structures, but maybe you can an idea of at least the class
24 of the compound you're dealing with. Then when you have
25 100 micrograms per gram, we would set that as the

1 identification threshold where we would have confirmed
2 structures.
3 Now, moving ahead to leachables, basically
4 these are when you're really working with the dosage form
5 and the excipients. The guideline right now calls for
6 doing toxicological qualification on extractables, and we
7 really want to make a strong case to only do the tox
8 evaluation on leachables.
9 Secondly, getting back to the point of
10 correlation between extractables and leachables, we would
11 like to say a correlation exists between those two when you
12 can qualitatively, either directly or indirectly, relate a
13 leachable to an extractable.
14 Third, again getting back to the concept of the
15 threshold, we are proposing a reporting threshold of .2
16 micrograms total daily intake, TDI, as a reporting
17 threshold and a 2 microgram TDI for identification
18 threshold for each leachable.
19 Then lastly, in the routine extraction studies,
20 which we would be doing to maintain or to make sure that we
21 have adequate control over the components coming in, we
22 would like clarity in terms of what is the actual purpose
23 of these studies. We are proposing that these should be
24 used to ensure that the extractable profiles of components
25 used in commercial manufacture remain consistent with

1 profiles and components used in the pivotal development
2 studies, and they are not a substitute for in-process
3 control or supplier qualification.
4 So, we've put together two flow charts to help
5 capture some of these issues. Also, the second flow chart
6 will give us more detail on the tox qualification, which I
7 haven't got into yet.
8 But we're starting off. This is taking us down
9 through the routine extraction, controlled extraction
10 studies, and into leachable studies. The first box here is
11 starting off with the critical component, again a component
12 in direct contact with the formulation, the patient's mouth
13 or the nasal mucosa. And we're saying that if that's true,
14 yes, then you do a controlled extraction study where we
15 would do qualitative and quantitative assessment of all
16 peaks greater than 1 to 20 micrograms per gram.
17 And then going down to the next blocks, we
18 would then go on an do a leachable study on this material,
19 and we would do that using aged registration batches
20 through end of shelf life to quantify in drug product the
21 extractables identified above. And in this process, we
22 would quantify all peaks greater than .2 micrograms TDI.
23 And we would provide identity and quantity of all
24 leachables to the toxicologists for assessment, which is
25 the next box.

1 Just going over, if the critical component did
2 not contact the formulation or patient's mouth or mucosa,
3 then we go over to the no box. Then we can do other
4 testing that would be sufficient such as identity,
5 dimensional properties, and so forth.
6 Going forward on to our routine extract
7 studies, then we would be doing that and other testing if
8 necessary. So, we have it all boxed up.
9 Now, going on to the qualification thresholds
10 here, we have individual leachables above .2 micrograms TDI
11 and if we are saying that's true, then we go down a couple
12 of paths. We'll go down the easy route. Greater than 5
13 micrograms TDI would be our upper threshold. And then we
14 say we confirmed structure, and then we would basically do
15 a full tox assessment of that.
16 However, if there are greater than .2
17 micrograms and less than 5 micrograms TDI, we would assess
18 whether there are structural activity concerns, and then we
19 would do a tox assessment or not, depending upon what's
20 happening with that assessment.
21 If we go up here to the top, if it's no, if the
22 leachables are less than .2 microgram TDI, then we would do
23 no further evaluation.
24 So, these are the thresholds we're laying out
25 for the qualification.

1 I'd also like to make the point we are also
2 opening up a category for special compounds which may have
3 SAR concerns or be nitrosamines or PNAs that are known to
4 be a problem. So, we would treat those on a case-by-case
5 basis. These thresholds may or may not apply to them.
6 So, going forward, we strongly encourage
7 incorporating into the guidances these thresholds for
8 identification, reporting, and qualification, and we are
9 proposing that we have an ongoing discussion through
10 various fora with toxicologists and chemists to work
11 through these thresholds. We also have submitted our
12 proposal to PQRI.
13 So, just to sum up what we've talked about
14 here, the ITFG/IPAC-RS collaboration plans to bring several
15 proposals to PQRI and continue discussions with the agency
16 regarding the new DCU proposal.
17 We hope that through the meetings of the OINDP
18 Subcommittee, Advisory Committee on Pharmaceutical Science,
19 PQRI, and other appropriate fora, the work of the
20 ITFG/IPAC-RS collaboration will be carefully considered.
21 And we believe that FDA and industry will be
22 better able to respond to the needs of patients by
23 expediting the availability of new OINDP products while
24 maintaining appropriate standards for safety, efficacy, and
25 quality.

1 We appreciate your consideration. Thank you
2 for your consideration. I'll turn it over to the BA/BE
3 presentation.
4 DR. BYRN: We're going to go ahead with Dr.
5 Sequeira, and then we will have any questions or comments
6 from the committee after this presentation.
7 DR. SEQUEIRA: I'll be brief. I'll try to keep
8 it to under 5 minutes.
9 I'm a member of the BA/BE team, and this team
10 has been in existence for a year and a half. During that
11 time, we have been very productive and worked
12 constructively on this very difficult issue, and some of
13 our efforts are described on this slide.
14 We've made four presentations on this topic at
15 meetings like these, and we've also submitted three reports
16 to the FDA on this topic.
17 We've conducted a review of the current
18 literature on this, a task which has stretched over this
19 the year and a half. We do not have substantive new
20 approaches on dose response, but we feel that risk
21 assessment and risk management must be done first to put
22 this whole issue of nasal drugs into proper perspective, as
23 I'll discuss a little bit later.
24 The in vitro study designs in draft BA/BE
25 guidances are useful for comparability of products, but

1 unproven in value for establishing clinical equivalence and
2 substitutability.
3 Based on the data presentations made by the FDA
4 at Tuesday's meeting and this morning, we agree with the
5 OINDP Subcommittee recommendation of selecting one dose
6 between the test and reference in the clinical study and
7 the inclusion of a placebo.
8 We also agree that the traditional treatment
9 study offers the most appropriate study design for
10 assessing nasal drug products intended for local delivery
11 and concur that the typical 2-week duration of this study
12 is appropriate.
13 However, there is a need for the draft BA/BE
14 guidance to further develop the statistical requirements
15 for this study, even if it is to be used to confirm the
16 comparability and substitutability of reference and test
17 products. As most of you know, the weakness of this design
18 is its dependence on seasons and the measurable placebo
19 effect.
20 I'd like to present here a case study that is
21 very relevant to this topic. This is work done by Casale,
22 Azzam, Miller, and others and published in 1999 in the
23 Annals of Allergy, Asthma, and Immunology. It deals with
24 the demonstration of therapeutic equivalence of generic and
25 innovator beclomethasone in SAR. I'd like to point out

1 three issues with this paper.
2 The first, the authors state that the primary
3 objective was to compare the test product, which in this
4 case was a generic, at two doses versus the placebo. And
5 their secondary objective in the paper was to compare the
6 test versus the reference innovator product. We clearly
7 think that a reversed hierarchy is more appropriate here
8 and that the secondary objective should have been the
9 primary objective.
10 Secondly, the study was designed as a different
11 study, not really as an equivalence study. The sample size
12 was adequate to distinguish between active and placebo, but
13 inadequate to distinguish between the two types of BDP, had
14 there been a difference. This is a typical common design
15 error. Failure to differentiate between the two products
16 dose not mean that a difference does not exist, had the
17 design been more robust to pick up this difference.
18 The third issue is the order of administration.
19 The active was followed by a placebo, and the treatments
20 were not randomized. Hence, we have the bias of washoff or
21 washout by the placebo.
22 We really didn't mean to critique this paper,
23 but only to present it as an example of the need for
24 further work in this area.
25 Therefore, this leads me to the key steps to

1 confirming the correct study design, which are summarized
2 on this slide. Firstly, the draft guidance must address
3 the issue of substitutability and not confuse this with
4 comparability. Secondly, we need to develop statistical
5 requirements for this study design for comparing the test
6 and reference products. And the team seeks the agency's
7 guidance concerning this issue.
8 One way to deal with open questions on
9 bioequivalence study design is to use risk management to
10 focus scientific investigation on those critical elements
11 whose uncertainties should be given priority as the
12 development of the guidance progresses.
13 We've highlighted here three risk areas present
14 with locally acting nasal products in the context of
15 clinical comparability and substitutability. The first is
16 the comparability of the container closure system to assure
17 comparable spray delivery. Here I must add that the FDA
18 has done an excellent job with the guidance they have given
19 for Q1 and Q2, but that takes care of the formulation.
20 What we need is something like I'd like to coin, Q3, to
21 give us some measurable parameters on the packaging of this
22 particular product so we can be assured that the spray is
23 comparable between the test and reference product.
24 The two other issues concern particle size
25 differences between the test and reference product and the

1 implication of these particle size differences on both the
2 onset of action and a systemic exposure of the product.
3 As Dr. Adams very well knows, people use
4 different micronizers throughout the industry and end up
5 with different particle size distribution products for the
6 drug substance. People also know that you can essentially
7 nanosize the drug product using microfluidization
8 techniques and achieve drug product with very fine particle
9 size. And people also know that you can make a mistake and
10 do a lousy job on micronization. So, you end up with
11 particle size being a very critical issue here.
12 And it cannot be presumed that an in vitro test
13 that correctly correlates with the local actions will also
14 be predictive of the systemic outcome.
15 My last slide is missing, but I'll read it out
16 to you. The container closure system and particle size are
17 two key risk areas that remain to be addressed regarding
18 clinical comparability and substitutability. We agree with
19 the agency and the OINDP Subcommittee that particle size is
20 important in determining standards for orally inhaled nasal
21 drug products. We agree that Dr. Adams and the FDA have
22 rightful concerns on drug particle size in the emitted
23 spray as being one of the most critical parameters that
24 could affect local efficacy and safety. In fact, their
25 sister division on the pulmonary side considers dose

1 delivery and particle size distribution of that dose to be
2 a very critical element for these products, even if they
3 are line extensions of new products.
4 So, after giving you all those thank you's, I
5 would like to now throw out a challenge, and I'd like to
6 recommend that an efficacy study be developed to
7 investigate the onset of action, via either a park study or
8 an EEU study, so that we could at least be assured on
9 substitutability of these products because a very important
10 parameter of these products is onset of action. So, in
11 addition to the traditional treatment study, we'd like to
12 suggest a short-term 1- to 3-day study in the park or in
13 the EEU to get a feel for onset of action.
14 Thank you.
15 DR. BYRN: Thank you very much.
16 Are there questions from the committee for any
17 of these speakers? Judy? For Dr. Sequeira.
18 DR. BOEHLERT: Yes, for Dr. Sequeira. I have a
19 question regarding particle size. It's very easy to
20 control and measure particle size on the active ingredient.
21 That can be done. The techniques are available and you can
22 show comparability very readily.
23 In your experience, does that particle size
24 change once it's formulated, and are you going to see a
25 difference from one product to another?

1 DR. SEQUEIRA: Yes, in fact, Dr. Boehlert, Dr.
2 Poochikin gave us a dissertation on the five or six factors
3 that can change the particle size of the drug in the final
4 formulation, because after the drug is compounded by one of
5 many, many techniques where there can be homogenization or
6 they can use other kinds of techniques, there could be
7 changes occurring during compounding, during filling, and
8 then finally on stability. And he listed a few more
9 factors that I have the time to cover.
10 DR. BOEHLERT: Is that reducing the particle
11 size or increasing the particle size, or both?
12 DR. SEQUEIRA: Sorry?
13 DR. BOEHLERT: Does the particle size go down
14 or up or either?
15 DR. SEQUEIRA: It could go either way,
16 depending on the manufacturing.
17 DR. BYRN: Dr. Meyer.
18 DR. MARVIN MEYER: This wasn't your
19 presentation, but I was curious how the threshold limits
20 were established for the extracteds and items leached.
21 DR. BLANCHARD: If you wanted, I could give you
22 slides. We have prepared slides to describe this if you
23 want to go through the process, or I can give you just a
24 high level -- very high level?
25 High level. Basically we worked from the 5

1 microgram TDI. We compared that to daily exposures a
2 person would get to ambient air pollution. So, basically
3 we're trying to look at what are people exposed to every
4 day and what do we accept as being safe every day.
5 So, there's actually a study called the Harvard
6 Sick Cities Study that measured air pollution
7 concentrations and related them to mortality and
8 cardiovascular problems. In that study, they found one
9 city that was actually very, very clean. It was Portage,
10 Wisconsin, and it had a concentration of 18 micrograms per
11 cubic meter of these particles. Actually that's very, very
12 clean air compare to all the other cities in the U.S.
13 We used that as a reference point, realizing
14 we've got an added safety factor just by being the fact it
15 was very clean air. We calculated what people would be
16 exposed to in that city at different ages and also for
17 people with disease, and said basically these are the
18 different ranges they would be exposed to, then looked at
19 the safety factors we're talking about. So, basically the
20 5 microgram TDI stands up very well when you do that
21 analysis. We're talking about being 3 percent or 9 percent
22 of what you'd be exposed to due to ambient air pollution in
23 those cities.
24 We've also done comparisons with being exposed
25 to different MDIs, high dose MDIs, low dose MDIs,

1 acceptable residues from metered dose inhalers. So, we
2 have a four-pronged rationale based upon that.
3 So, basically the ambient air pollution one is
4 the top one actually in terms of what's driving that.
5 Do you want to get into the analytical
6 thresholds at all?
7 DR. MARVIN MEYER: No. I was just curious.
8 I'm not in a position to debate whether that's good or bad.
9 I just wanted to know how you did it.
10 DR. DOULL: Steve, let me follow up on that,
11 Dr. Blanchard.
12 I don't know whether you're aware. Alan Rulis
13 has put together a threshold of regulation for Food and
14 Drug. It has to do with packaging materials. It really is
15 in the food section, but it's a very similar concept.
16 DR. BLANCHARD: Right.
17 DR. DOULL: And I was struck by the fact that
18 your TDI is similar really to what Rulis has --
19 DR. BLANCHARD: Are we talking about the
20 threshold regulation which is a .5 parts per billion?
21 DR. DOULL: Yes.
22 DR. BLANCHARD: Right. We're familiar with
23 that. We actually reviewed that, and we were looking to
24 incorporate some of that rationale in our thinking. So, we
25 are aware of that.

1 DR. DOULL: His argument is that no matter what
2 the agent is, even if you take the carcinogens, whatever
3 list of carcinogens that go with that rationale, that is in
4 fact a threshold of concern that is reasonable.
5 DR. BLANCHARD: And the rationale there was
6 that even if it was unknown to be carcinogenic today, if it
7 was later found to be carcinogenic, it was still be so low
8 to be trivial.
9 DR. DOULL: I had one other question. You
10 talked in there about using SAR, structure activity.
11 DR. BLANCHARD: Yes.
12 DR. DOULL: Are you talking about components of
13 the molecule or are you talking about the molecule itself?
14 You're saying if it's cleared by SAR, then --
15 DR. BLANCHARD: With SAR, you're looking at
16 components where basically you find a functionality that
17 would be of concern. Then that would raise a red flag for
18 you. We could work this through with the agency, but you
19 could take a conservative approach and say, well, if we
20 know this is problematic in functionality, then we would
21 put that into a special category and give it further
22 analysis.
23 DR. DOULL: You mentioned nitrosamines, for
24 example. You could say all those agents that are similar
25 you're going to put them in the same bag and be concerned

1 about them.
2 DR. BLANCHARD: Right.
3 DR. DOULL: Or you could be looking for
4 quaternary ammonia or something which should be a part of
5 the thing.
6 DR. BLANCHARD: So, I'm thinking we're going to
7 look at functionality groups, not the whole compound.
8 Both. The nice thing about nitrosamines is that you know
9 going in that these are well characterized compounds. You
10 know you should be looking for them and you are expected to
11 be looking for them.
12 DR. DOULL: It's kind of a decision tree.
13 DR. BLANCHARD: Right, and we can handle it on
14 a case-by-case basis.
15 DR. DOULL: Well, that's interesting.
16 DR. BYRN: Thank you very much. We'll be sure
17 to provide this information to the people who are writing
18 these guidances, and I'm sure they will take it into
19 consideration.
20 Now we're going to go on with the next session,
21 and let me introduce Dr. Lachman and Hollenbeck who are our
22 guests for this session also. Both of them have spoken
23 before and are on the left.
24 First, Dr. Ajaz Hussain is going to give an
25 introduction. Dr. Hussain is acting Deputy Director in

1 OPS.

2 DR. HUSSAIN: Good afternoon.

3 The afternoon session is actually taking a look
4 at some future directions. I will not ask you to vote on
5 any of these, but I think we would like comments,
6 recommendations on what your thoughts are on the two topics
7 that we present to you this afternoon and start to take a
8 look at some of the new directions and bringing new science
9 and technology into manufacturing.

10 The topic I have chosen is optimal application
11 of in-line or at-line manufacturing controls in
12 pharmaceutical product development. For the last couple of
13 years, our labs within FDA -- actually more than a couple
14 of years -- have been working with some of the new
15 analytical methods which offer, we think, significant
16 opportunity. A number of publications that I provided to
17 you in your handout material were to illustrate the type of
18 applications that are feasible, and other chemical
19 industries -- indeed, in fact, food industries -- have
20 adopted some of these and are benefitting from these
21 technologies. Pharmaceuticals have not done so and I feel
22 that's an opportunity that we can have significant public
23 health and economic benefits if we can have optimal
24 application of modern in-line and at-line process controls
25 and tests in pharmaceutical manufacturing.

1 One could look at that as a hypothesis, and
2 that's what I'm presenting to you. The goal here is to
3 initiate public discussion on opportunities and challenges
4 associated with regulatory application of what we call
5 process analytical chemistry tools in the pharmaceutical
6 industry.
7 I have invited Dr. Raju from the MIT Sloan
8 School of Management and Chemical Engineering Program which
9 is focusing on pharmaceutical manufacturing to discuss with
10 you anticipated win-win opportunities. The MIT program is
11 in conjunction with a number of companies that has looked
12 at modern manufacturing methods. I hope you get not only
13 the time and cost saving type of information from him, but
14 a sense of what engineering applications to pharmaceutical
15 productions can do for us.
16 As an introduction of what I mean by process
17 analytical chemistry, here are the many different
18 technologies that are part of process analytical chemistry,
19 and the goal here is to have real-time characterization
20 analysis of samples or material and to have those decisions
21 as close to the processing step as feasible. Generally
22 these are accomplished without sampling and are
23 multivariate in their nature.
24 Two very common examples are near infrared and
25 Raman spectroscopy in the transmission mode, as well as the

1 reflectance mode. These essentially can be within the
2 processing unit itself or would be close to the processing
3 unit, so that you don't have to collect a sample, and
4 information about the sample is gathered at the site, and
5 decisions could be made rather quickly, as opposed to the
6 conventional method where you collect the sample, do the
7 analysis, wet chemistry, and so forth. So, you're looking
8 at a difference between wet and dry chemistry here in some
9 ways.
10 My presentation is more focused from a
11 formulator's perspective, how we think a formulator would
12 benefit from these technologies. To give you a sense of
13 what these tools are, here is an example of gasoline
14 analysis. On the top, you have four different attributes
15 being tested by different methods. You have octane engine
16 taking 40 minutes, RVP analyzer, a GC method, and a density
17 meter. All of those attributes can be measured on line or
18 quickly with near infrared with the same spectra. So, one
19 method is able to characterize or to gather information
20 about various physical and chemical attributes.
21 So, in this case, the difference here is you
22 essentially use pattern recognition tools to understand the
23 relationship between the spectral attributes and those
24 physical or chemical attributes of interest. Based on that
25 calibration curve or the statistical model, you have a

1 system that can evaluate a new sample that comes along.
2 So, that's the framework under which many of these process
3 analytical chemistry tools operate.
4 I have taken this from a website of a company,
5 which I have obviously blocked the name our, for
6 pharmaceutical applications. Here from the website it
7 says, "from incoming raw material inspection to final
8 product release, instruments, software," and all these
9 technologies have been available. You can see the progress
10 that has occurred in this area over the last 10 years.
11 These obviously are available but are being
12 currently used as an alternate. These are not generally
13 regulatory methods. These are alternate methods which are
14 in addition to the regulatory testing.
15 I would like to focus my thoughts on what I
16 perceive as the impact on product quality could be by
17 adoption of some of these technologies. In my opinion, the
18 current situation begs us to take a hard look at this at
19 this time. Combinatorial chemistry and high throughput
20 screening essentially have created a scenario where the
21 number of interesting, promising new chemical entities is
22 humongous. As a result, development, including product
23 formulation development, is becoming rate limiting.
24 There are two aspects which are challenging.
25 Formulation development has always been considered as a

1 black box because of the inability to reliably predict
2 product performance changes when formulation/process
3 variables are varied. Also, variable physical functional
4 attributes of raw materials that are known to conform to
5 USP or NF standards. Compendial standards have always
6 focused only on chemistry, not on the physical attributes.
7 So, functionality of excipients has not been a public
8 standard, and it's not likely to become a public standard
9 because of the complex nature of the excipients, as well as
10 multiple uses of excipients. It's a very difficult process
11 to build public standards based on physical attributes.
12 Process analytical chemistry tools focus both
13 on physics as well as chemistry at the same time and at the
14 right place actually. So, here is an opportunity which in
15 pharmacy at least we have not, in my opinion, taken full
16 advantage of. The number of publications are humongous.
17 Some of those you have seen in your handouts, and they're
18 very impressive. But I think in terms of evolution, I see
19 bringing these technologies in would really help move
20 pharmaceutical manufacturing to the next stage quickly.
21 From my way of looking, over the last 100
22 years, tablets that we make today are the same as we made
23 100 years ago. In fact, aspirin is over 100 years old, the
24 first tablet ever made. So, we have been making tablets
25 and capsules essentially in the same way, the same process

1 as for the last 100 years.
2 But during those 100 years, we have transformed
3 pharmacy from an art to more of a science and engineering
4 based profession. In the last 30 years, you have seen
5 application of physical chemistry and chemistry principles
6 coming in and engineering principles coming in, but we're
7 not there yet. We still develop our formulations through a
8 trial and error approach, although that's a guided trial
9 and error approach where you have a formulator with vast
10 experience and can guide the formulation development
11 program quickly.
12 But keep in mind, at least from the pharmacy
13 school perspective, pharmaceutics and other disciplines
14 have sort of eroded away, and formulation development is
15 not being taught in schools anymore, literally. So, the
16 experience base and the knowledge base is to some degree
17 eroding away. So, the trial and error has to be guided.
18 In the abscence of that, it becomes very difficult.
19 There has been a tendency towards moving to
20 design of experiments with Professor Bancor and others who
21 had initiated that, but 1994 Professor Shanguard did a
22 survey of the pharmaceutical industry to see how many of
23 them are utilizing statistically designed experiments to do
24 formulation development. That number came to be 5 percent.
25 So, the trend has not moved in that direction. So,

1 although we would like to see more designed experiments and
2 hopefully computer-aided design concepts to come in, they
3 have not occurred.
4 Dosage forms have transformed drug delivery
5 systems. The next stage is obviously intelligent drug
6 delivery systems. If we are able to improve the
7 formulation science, then we actually create more
8 opportunity to look at more creative options. Here's an
9 opportunity. Batch processing to continuous and automated
10 processing is obviously a desired next step in this
11 evolutionary process.
12 However, coming back to the pharmaceutical
13 product development process, here are some of the
14 attributes that we have to address. It is multi-factorial
15 and a complex problem. Significant reliance on formulation
16 development is based on personal knowledge. Historical
17 data is likely to have been generated by a guided trial and
18 error approach. There are many choices of achieving target
19 specification.
20 Therefore, I think from an FDA perspective, to
21 evaluate some of those changes under SUPAC, for example,
22 becomes a challenge. Without up-to-date information,
23 there's a high potential for misjudgments, reinventing the
24 wheel, and mobile institutional memory. We have seen in
25 many situations approved products need frequent changes.

1 They're not optimal.
2 So, if you look at the pyramid of
3 pharmaceutical product development knowledge, I tend to put
4 that knowledge base in low to medium in terms of level of
5 sophistication in the details that it's able to resolve.
6 The reason for that is most of our database is based on
7 historical trial and error. Patent recognition and
8 generalization of that data is extremely difficult. We
9 have heuristic rules of thumb and very few empirical models
10 for developing formulation safety. With respect to
11 mechanistic modeling, physical rules, we're not there yet.
12 How are we controlling unit operations now? If
13 I take a simple unit operation, blending, the last two
14 years I have been engrossed in blending problems and the
15 criticisms received from industry of our guidance.
16 Blending is a major thing in my mind right now, and
17 therefore I have asked Dr. Raju to use blending as an
18 example to illustrate some of the issues.
19 How do we control blending? We define the
20 equipment, type, size, operating speed. We define a
21 process time. Then we check whether the blend is
22 homogeneous or not. So, you blend, put thieves in, collect
23 samples, and check.
24 Wet granulation. We define equipment, define
25 fluid addition, composition, volume, and process time, and

1 check for moisture content after we dry those granules.
2 These are fine but are limited in scope with respect to
3 performance predictions.
4 Unit operations are intended to produce in-
5 process materials that possess optimal attributes for
6 subsequent manufacturing steps. We know that.
7 Do current controls always ensure consistent
8 quality of in-process materials? They can't. One reason
9 is the physical attributes of the pharmaceutical raw
10 materials can be highly variable. We don't have a good
11 handle on that.
12 A consequence is processes do need to be
13 adjusted, and if you do adjust those beyond certain ranges,
14 you have to seek regulatory approval or some regulatory
15 evaluation is needed. So, it's an added level of scrutiny.
16 One of the whole initiatives of risk based is to reduce
17 the supplements.
18 So, the current situation, again to summarize,
19 in-process testing is the norm, not controlled. Blend
20 uniformity, for example, if I take that example, I'll stop
21 the blender, test, wait for the answer to go to the next
22 step. That's one way of looking at it. If it was
23 controlled, blending would have been done until it's
24 homogeneous and move on.
25 Process parameters and specification are set

1 based on limited data. Raw materials. We don't know their
2 functionality well. And a combination of all this. In-
3 process sample collection, testing, verification, and as a
4 result, a lot of exceptions that occur contribute to long
5 production cycle time. It was a bit of a surprise to me
6 that it could take 30 to 60 days to manufacture one batch
7 of tablets.
8 Process validation. What are the limitations
9 there and how are we doing that? I found this quote by
10 Harwood and Molnar quite interesting. The publication was
11 called Using Design of Experimental Techniques to Avoid
12 Problems, published in Pharmaceutical Development
13 Technology in 1998. They characterized current practices
14 in validation as a "well-rehearsed demonstration that
15 manufacturing formula can work three successive times." In
16 their experience, "validation exercise precedes a trouble-
17 free time period in the manufacturing area, only to be
18 followed by many hours, possibly days or weeks, of
19 troubleshooting and experimental work after a batch or two
20 of product fails to meet specifications. This becomes a
21 never-ending task."
22 Clearly, companies would not release batches
23 which fail specifications. It's the subject for recall.
24 But here is a situation at least for temptation. If you
25 your batches are failing, it leads to problems. And some

1 of the court cases I was involved with dealt with these
2 issues.
3 I hope that is not a general observation. I'm
4 sure it's not a general observation. But the example does
5 illustrate what happens when quality is not built in, and
6 quality cannot be built in till you really understand your
7 processes and so forth.
8 The type of cycles times that you're looking
9 at, which you will hear from Dr. Raju in more detail, are
10 as follows. It takes 21 to 90 days to qualify a raw
11 material. It takes about 60 days to manufacture and
12 release a tablet formulation, and you'll hear more about
13 this, so I will not deal with it.
14 So, what we are talking about right now is the
15 next step in the evolution of process controls. When I
16 started out in pharmacy school and my industrial training,
17 this is how we did it. Reach out, grab some of the
18 granules, squeeze them, see how they break, and then decide
19 whether the granulation endpoint is reached or not. That
20 was years ago. Things are different now, obviously.
21 But the next step in the evolution is to go
22 more subjective, gather physical, chemical information
23 about the granules to ensure that the granulation was
24 optimal so the tableting next step would be as smooth as
25 possible. And that's feasible now.

1 Modern in-process controls. I'll use near IR
2 as an example because in our labs we have more experience
3 with that right now. It's a noninvasive spectroscopic
4 technique, and you could also use it as an imaging tool --
5 and I'll show you some examples -- which has been in use
6 for the last 10 years in the food and chemical industries.
7 It provides real-time control of processes
8 without having to collect samples.
9 One can potentially process material until
10 optimal attributes are achieved, as opposed to stopping and
11 testing.
12 And using pattern recognition tools, one can
13 relate near IR spectra to both physical and chemical
14 attributes of materials and hence be in a position to
15 predict product performance and therefore improve product
16 quality.
17 If I were to apply near IR technology to a
18 tablet formulation, I chose a direct compression as an
19 example. On the left-hand side, the conventional approach
20 would be get the raw materials, do the compendial tests to
21 make sure they meet the specifications, blend the product,
22 test for blend uniformity, and keep in mind the only
23 component that we test is the drug. One of the culprits
24 that creates problems is magnesium stearate, very small
25 amounts. We never test for that.

1 Compaction. We make the tablets. We check for
2 hardness, thickness, weight, friability, and so forth,
3 content uniformity and dissolution. All of those could be
4 done literally at- or on-line with some of these
5 technologies.
6 I'll give you an example of some of our work.
7 Blend uniformity has been an issue and PQRI has actually
8 developed a proposal on how to address that. The proposal
9 is posted on the PQRI website. But we wanted to look at
10 the near IR imaging technique to see what can be done.
11 So, we were looking at tablets. These are
12 furosemide tablets that I think were made at the University
13 of Iowa. No. These are handmade tablets in our labs.
14 It's a binary mixture of drug and excipient. What you're
15 looking at is a chemical image. The tablets are white,
16 colorless tablets. But the chemical image, the white areas
17 are the drug, and the red spectrum is the excipient. So,
18 looking at each of those pixels in the digital image, which
19 was acquired in less than a minute, or actually in 30
20 seconds, you get that picture. You can actually develop
21 simple metrics to do the analysis.
22 Here is our University of Iowa product where we
23 are looking at the scale of interest right now that's
24 actually a small part of the tablet. So, with the current
25 technology of blending, we can achieve uniformity far

1 beyond what we had anticipated. So, blending should not be
2 a problem. We are doing it right, but we are having
3 trouble proving that we are doing it right right now.
4 So, here is, for example, if you analyze each
5 pixel, you can see the complete distribution of the drug
6 and concentration and so forth and how symmetric it is when
7 it's uniform. When it's not uniform, you can see how
8 things change. This information can be gathered in
9 minutes, if not seconds.
10 I've used another example. Since I mentioned
11 magnesium stearate, here is a slide that Steve Hammond from
12 Pfizer shared with me and what can be done which we could
13 not do before. Two blends, one with good flow properties,
14 one with bad flow properties. Look at the distribution of
15 magnesium stearate in that. So, you can easily associate
16 problems to solutions and develop causal links quickly.
17 Just to go on as an example, near IR is not the
18 only one. Raman. You could have a three-dimensional Raman
19 spectroscopy of a tablet's surface and look at where the
20 aspirin is and where the excipient is, and actually do
21 quantitative analysis at the same time.
22 Here is a very recent publication from Dr.
23 Lodder's group from Kentucky, published in the Pharm. Sci.
24 Tech. of AAPS. Since it was available on the web, I
25 downloaded this. Here you're looking at the ability to

1 analyze aspirin and salicylic acid after it has been
2 packaged. So, this is through a blister pack. You don't
3 even have to wait. Through a blister pack you could look
4 at aspirin and actually look at the moisture content of the
5 tablet without having to open the blister pack.
6 So, the technology is maturing, but there are
7 many challenges. One of the challenges I have heard,
8 talking to people from industry and in a recent trip to the
9 U.K., the New Technology Forum, is the mind set is out
10 there that FDA will not accept it. FDA will accept it if
11 there's good science. Period. There's no question about
12 it.
13 Also, I think the mind set is also in
14 companies. Regulatory affairs departments within companies
15 have to be convinced, and others have to be convinced.
16 There are challenges. Method suitability and
17 validation approaches have to be developed, have to be
18 agreed, a consensus has to be developed.
19 Chemometrics is something which traditional
20 analytical chemists are not aware of, are not fully
21 cognizant of, and don't have expertise in. So,
22 chemometrics, pattern recognition will have to come in and
23 we'll have to learn how to deal with that.
24 Also, mechanisms of regulatory introduction
25 have to be developed so that investment costs and other

1 cost issues can be managed properly.
2 So, to summarize, potential benefits for
3 process analytical chemistry. I believe that manufacturing
4 and quality control cycle times can be reduced and costs
5 can be reduced. It can improve product quality, provide
6 information during processing for feedback control. Direct
7 sampling problems are eliminated and can facilitate
8 establishment of causal links between product and process
9 variables and product performance.
10 Improve patient and operator safety. Keep in
11 mind many of the products are very important, and operator
12 safety is a concern.
13 And I firmly believe there's a win-win
14 opportunity that will require out-of-the-box thinking on
15 both FDA's and industry's side to move forward. I hope you
16 would support my perceptions here, and I would like to hear
17 your thoughts on this.
18 The second presentation will focus more on the
19 opportunities that exist in reducing cost, time of
20 development, and so forth.
21 Questions?
22 DR. BYRN: Questions for Ajaz? I'm sure we'll
23 have a discussion after the second one, but are there
24 questions for Ajaz right now?
25 DR. ANDERSON: Did you say that you are using

1 near infrared in your laboratory?
2 DR. HUSSAIN: Yes.
3 DR. ANDERSON: Could you just take a couple of
4 minutes and comment on it, on the results that you're
5 getting?
6 DR. HUSSAIN: Actually I had planned to share
7 with you some recent information. I had -- Robbe Lyon is
8 here -- the division director, to give me a comparison
9 about HPLC and near IR. They are currently doing
10 furosemide analysis content uniformity. They estimated
11 time to do a USP analysis for furosemide tablets is 34
12 hours, using the HPLC technique. It's 3 hours with near
13 IR. The complete analysis takes 3 hours, everything.
14 The sample costs for a stability study that we
15 are doing again. Costs per sample using near IR, again for
16 the same drug, is about $2.25 compared to $47-something for
17 HPLC. So, that's our experience in our hands.
18 Instrumentation cost is almost comparable. The
19 instrument that we have is about $75,000 for the near IR,
20 and HPLC in high end is $40,000 to $50,000.
21 DR. HOLLENBECK: Ajaz, in the backgrounder,
22 there was the statement that you made that went like this.
23 The regulatory environment under which the pharmaceutical
24 industry must operate is often suggested by many to be an
25 impediment for introducing these tests. I think you just

1 covered that in your slide by saying that FDA won't accept
2 it, but can you expand on that a little bit more in terms
3 of what impediments exist and what steps can be taken to
4 get rid of them?
5 DR. HUSSAIN: The challenge here is I think
6 uncertainty. We don't have a guidance out. There are many
7 parts of the agency that have to deal with this from the
8 field to the center. So, that itself is a challenge.
9 I think the major challenge is validation in
10 terms of how do you validate this. I'll use blend
11 uniformity as an example. Sampling using a thief is a
12 challenge. It creates this problem. But the mind set is
13 to validate near IR, you have to compare it to that method.
14 I think if you're looking at a modern technique, with the
15 potential of becoming the gold standard, you have to
16 compare that to some standard. We had that discussion this
17 morning with clinical. The same issues cross over. So,
18 again, I think we have to think outside the box how you
19 validate some of these tools and bring those in without
20 adding a burden.
21 What will we plan to do is to create a
22 subcommittee. There are a number of challenging issues.
23 In my letter to you all, I suggested that we really need a
24 multi-disciplinary team to look at the feasibility and so
25 forth. So, a subcommittee under this committee would be my

1 proposal.

2 DR. BOEHLERT: May I just make a comment as

3 well? Maybe we need to think even further outside the box

4 when it comes to things like blend uniformity testing

5 because right now things like the Barr decision are forcing

6 manufacturers to take single dosage units, one to three

7 times the size of the dosage units, take it off-line and

8 test it by a technique, and that creates the problems. So,

9 testing is one aspect, but it's other things that are

10 impacting what we have to do today.

11 DR. BYRN: Our next speaker is a good friend of

12 mine, G.K. Raju, who is going to give a case study on in-

13 line process controls.

14 DR. RAJU: I'm not sure if this is a good thing

15 or a bad thing. I haven't been to an advisory committee

16 meeting in my life. I'm not sure that it's a good thing.

17 I'm not a pharmacist. I'm not a doctor, but I want to help

18 make medicine cheaper, better, and faster for patients

19 because I think it's a great thing to do, and I want to do

20 whatever little I can to help do that. I am a chemical

21 engineer, and think of the next few slides as a chemical

22 engineer's view of the pharmaceutical industry.

23 This is the training I come with that affects

24 how I look at things. That affects what I'm going to say

25 when I look at these things. So, I'm going to summarize an

1 outsider's look at the pharmaceutical industry at multiple
2 levels. Hopefully I have something intelligent to say.
3 I'm not really asking for anything. I'm asking really for
4 you to lend me your eyes and ears and hopefully your mind.
5 And this is a summary of what I think I'm going to say.
6 Since I'm new to this field and this audience,
7 I'm going to tell you where I come from. I'm then going to
8 have two very high level looks very quickly at an industry
9 at a very high level. I'm going to go through a lot of
10 slides, and that's because I want to go through a lot of
11 things quickly. So, don't worry if you don't get the
12 details. You have it in your background slides.
13 I'm not from New York. I am from Boston, and
14 I'm also from India so I can talk pretty fast.
15 (Laughter.)
16 DR. RAJU: So, this is the introduction to
17 where I come from, sitting in the chemical engineering
18 department and also in the business school at MIT. We then
19 decided to work together in what we began to call the MIT
20 Pharmaceutical Manufacturing Initiative. And our passion
21 was to begin to describe and capture the opportunity to
22 impact this part of this pharmaceutical industry.
23 What was that part? And we had to draw a
24 diagram. That was one of the first things we were taught.
25 Let's draw a diagram that represents that little block.

1 That diagram has pieces over time and pieces over space.
2 That's pharmaceutical manufacturing. There's the process
3 development over time, and then there's routine
4 manufacturing. We have the chemistry changing in the
5 active ingredient. The dominant physics, which is what are
6 the components. Small aspects of physics which is what
7 form should these components be in and how do I package
8 around it. No chemistry. Physics in the middle two,
9 chemistry here, sometimes biology, and some paper most of
10 the time around it. That's what pharmaceutical
11 manufacturing looked like.
12 So, if I was going to measure and characterize
13 it, I had to measure it in terms of something, and we all
14 know what dollars are. We can debate what quality is, but
15 we have a pretty good understanding of what that is. Time
16 means the same thing to everybody. It's the time on a
17 clock. And safety can mean different things to different
18 people.
19 For this presentation, I now have a choice
20 which one of these to talk about. It seemed like the most
21 neutral and seemingly communicative thing to do was to talk
22 about time because all of us know what that is. It's
23 pretty neutral. It's important. It's the same thing for
24 everybody. So, for the rest of the presentation I'm going
25 to talk about time, looking at it from two points of view.

1 Routine manufacturing. When we first looked at
2 pharmaceutical manufacturing, it seemed like the word only
3 meant routine manufacturing, which was this, and process
4 development somehow was disconnected from it. So, routine
5 manufacturing. The first question was, what is routine
6 manufacturing and where is the time spent?
7 So, we said let's look at some blocks of
8 routine manufacturing. We got together a consortium of a
9 lot companies. Over these I've worked with about 25
10 companies representing 80 or 90 percent or more of the
11 pharmaceutical business. One of the focus areas was the
12 formulation of a particular consortium, and we said, let's
13 start looking together at your plants from an outsider's
14 point of view and measure where the time is spent.
15 Once we decided to do that, the question then
16 became which products do I look at. Everybody makes
17 different kinds of products. So, we said we can do high
18 volume products. Those are the billion dollar products.
19 We can do the complex ones, and we had some discussions
20 about complexity, and then there were liquid lines which
21 have totally different manufacturing and testing
22 priorities. Which one do we choose?
23 Since we had no basis to choose, well, yes,
24 about 80 percent of the products are solid, so we could
25 look at the first category, but liquids were distinct. So,

1 we wanted to know what they were about as well. So, we
2 said we don't really have a basis to choose between, so
3 let's do a little bit of all of them. Let's look at the
4 high volume products, for example.
5 The first step I was taught was to draw a
6 process flow diagram. From a chemical engineering view, we
7 said let's draw so-called unit operations, what is
8 happening in that step, chose the color blue. This is the
9 active ingredient that we don't study, and I showed you
10 that block on the previous slide.
11 The first thing that came to my mind is why are
12 these tests at the two ends of it. I began to understand
13 that, of course. But why is it that we don't measure
14 anything in between? We had two dominant places where we
15 did testing: at the end, at the beginning. We had very
16 minimal in-process testing in my opinion. I was surprised
17 at the very little testing that happened along the way. It
18 was something I wasn't used to, and I kept asking why.
19 I said, yes, we make a product that goes into
20 somebody's body. That's important. We have to make sure
21 its safe. We have to worry about its efficacy. I don't
22 know if it's 210 or 211 on your CFR documentation, but
23 these are the definitions about purity. I read them up and
24 I said, okay, this makes sense that you have to do these
25 tests because they mean something in the body. But why are

1 we doing it at the end? Yes. That's the last place we can
2 do it. We can be pretty sure that when it comes out, it's
3 done.
4 But what are the consequences of only doing it
5 at the end? Maybe we should think about that as well.
6 It's not just a zero sum game here. There are some
7 consequences, possibly, about measuring things here when
8 the causes of that variability may be very early on.
9 Second, raw material testing. I was surprised
10 at how little implications of the physics of the process
11 were captured in that test. If formulation is all about
12 the physics of the process, the main test was really a
13 chemical test. And I wondered why. Again, as you wonder,
14 you start saying, let me look at a few more cases. Maybe
15 this is just one example.
16 So, I used the same colors now, and I simply
17 said instead of drawing a process flow diagram in space,
18 let's draw it in time. So, it's the same colors now. All
19 I did was say let's draw them in time and look at it from a
20 company's point of view. What came out instantly was an
21 observation that the red testing took significantly more
22 time than the making itself. Were we pharmaceutical
23 manufacturers or were we pharmaceutical testers? It's just
24 a general open question to ask. So, testing dominates what
25 we do. Clearly there are important reasons.

1 Is this just process A now? Maybe if you look
2 at a few more, we'll see if there's some pattern here.
3 Another big high volume. Usually now we're talking about
4 close to a billion dollars or more, so significant. I'm
5 not doing products that are not important. It looked like
6 a simpler process, the tests very much defined by the body
7 now. The tests are very much defined by what a tablet
8 should do. And the place is in the same place again, very
9 little in the middle. The consequences in time look so
10 similar. Again, about 20 days from the beginning and the
11 end, less time in the actual making of the tablets. Then
12 there's the API which I don't even count and this inventory
13 afterwards that I don't even count.
14 Let's look at another one. Is there a pattern
15 here? Yes. The tests look very similar, almost expected
16 now. The times keep coming almost similar. So, it's not
17 the company. It's not the location. It's not the product.
18 Maybe it's just the high volume products that look like
19 that because that's what I've seen so far.
20 Here's another high volume product that looks
21 very similar.
22 Just to be sure, let's look at a fourth one,
23 and it looks very similar again. We take a couple of
24 months to go through the system, half or more than half of
25 the time testing it in some way. Does that testing take

1 that long? What drives the timer on those tests?
2 But before I go into that question, let's make
3 sure that we've seen a representative -- if you would go
4 back to the active ingredient manufacturing, you would see
5 a much longer time. And if you look at this time and you
6 add it up from the beginning to the end, you ask yourself
7 is this what we want to do in pharmaceutical manufacturing.
8 What are the consequences of allowing us to do it? That
9 is, if there's some variability here and because of our
10 testing and the way we define it, we see it 100 days later,
11 how are we going to relate the cause and the effect, and
12 what happens to our problem solving of asking why we see
13 something? Does time affect that kind of a thought
14 process?
15 We finished high volume products. Maybe it was
16 just those billion dollar products that look like that.
17 Let's look at a complex process, complexity measured in
18 many ways. One measure would be the number of steps, which
19 in the previous presentation you said wasn't important. In
20 this case it clearly was a complex process. I try to make
21 sure they always fit on one slide, so I don't take too many
22 slides to explain it.
23 But again, you have a process that does a
24 number of things again and again. The way we measure how
25 well we do it is testing at multiple places. If you look

1 at that process in time, this is what it looks like.
2 Again, the testing dominates the time very much.
3 Let's say a liquid line, and liquids are
4 different in the sense the uniformity is a little easier to
5 establish. Micro-testing is a little bit distinct about
6 priorities in terms of testing. So, let's look at a liquid
7 line, although those are not the dominant dosage forms.
8 Yes, the basic tests around it look very
9 similar. The sterility test clearly is going to show up on
10 the next slide. If we now say let's put the process and
11 draw the time around it, you really start wondering why
12 this ratio of the testing to process is so different. If
13 you then say let me try to summarize and see if I can get
14 something important around it, you ask where is the
15 leverage.
16 The first is to make sure you put all those
17 products on one slide and ask do I see a pattern, and we do
18 see a pattern and the pattern being that almost always the
19 testing seems to take at least as much time as the making
20 itself.
21 What shall we do about that? First, we
22 probably have to understand the testing itself. So, if
23 that is at least the single biggest thing we should look
24 at, maybe we should look at it in a little bit more detail.
25 So, the big picture. Let's got to the next

1 level of the picture for each of these red bars. So, we
2 said let's look at those tests. What really are those
3 tests and where is the time there? Let's look at any of
4 those tests, at the beginning, at the middle, at the end of
5 a process, and it always has a unit operation that ends.
6 It stopped. You take a sample from the process. You hold
7 the sample in the plant. You then document your sampling.
8 You transfer it to the lab. You then batch it in the lab.
9 You then actually do your test right here, then data
10 collect. You document. You transfer from review, and then
11 you make a decision about what?
12 If you looked at your test itself, it's this
13 tiny little thing here. And Ajaz says he was comparing
14 HPLC with NIR. What kind of a difference does it make?
15 But Ajaz also said at-line and in-line, and it's those
16 aspects that the opportunity is there. It can be Raman.
17 It can be laser-induced fluorescence. It can be NIR. But
18 it's the fact that at-line and on-line is what takes care
19 of these red bars. That's where the variability comes in
20 in many cases because we as human beings don't like to do
21 the same thing again and again for too long. Sometimes
22 that shows up in many places. But yes, we can do something
23 about the testing, but yes, this is where the pieces are.
24 So, if you look at the technology opportunities
25 around it, the only way to attack this place completely is

1 the word on-line. Along the way we go from off-line to at-
2 line, in-line, and on-line. You can see the transition,
3 and I think there's an opportunity for the whole industry
4 to make that transition test by test, product by product,
5 and I think that's a lot of time that we can do something
6 about.
7 So, to repeat, it's not the test itself. It's
8 the before and the after of the test, which is 98 percent
9 of time opportunity.
10 So, what did we say? We said if we were all
11 about making quality, we measure it very infrequently. Why
12 do we measure it so infrequently? Because it's a lot of
13 work. It takes a long time. The scale of the test is
14 based on the scale of the human being. The manual nature
15 of the off-line test defines the cost-benefit tradeoff of
16 doing that test. Hence, we do it at the end because we
17 have to do it at least at the end we think.
18 But once we make it on-line, the tradeoff of
19 number of tests to the cost of the tests has now changed
20 fundamentally. So, one test and two tests are not
21 necessarily once and twice more expensive in terms of the
22 organization's time, cost, and possibly even quality. We
23 want to make it more continuous. The FDA would be very
24 happy. So would we because we would actually have
25 differences in our times, we would have differences in our

1 processes, and we would attack the off-line test once and
2 for all.
3 So, that's the first message of a chemical
4 engineer looking for a little bit of time at routine
5 manufacturing over space. We covered different products.
6 We thought we had some conclusions. But clearly I had to
7 look at it over time, and there were so many things I could
8 look at. From a chemical engineering perspective, I would
9 love to look at the active. There's something chemical
10 going on.
11 But the consortium, when we sat together and we
12 said we said we can do all of this, we can study all of
13 this, they said look at blend uniformity. Why would we
14 want to do that? You blend for five minutes and all you
15 want to do is figure out whether you're done? That's
16 really boring. No. This is what we want you to do.
17 (Laughter.)
18 DR. RAJU: Okay, I'll do it.
19 We did a lot of other things, but when Ajaz
20 invited me, I said I'm going to talk about all these
21 things. He said blend uniformity.
22 (Laughter.)
23 DR. RAJU: So, I said I'm gong to have to do it
24 here too. So, that's the next set of slides that I have.
25 It's blending.

1 Let's define what blending is. What am I going
2 to try to find out? I've looked at space. Let's look at
3 time now just to be creative. I want to look at process
4 development and the measurement of quality, particularly
5 blend uniformity along the way.
6 Here is my on-line sensor and then benefits are
7 a little less, but it's at-line and in-line compared
8 against off-line. This sensor has many possibilities and
9 near infrared is one. A number of companies have worked on
10 it. We've patented a technology called laser-induced
11 fluorescence within this consortium of companies. There
12 are different aspects and different ways of measuring
13 uniformity. But the conventional way, we're all the same,
14 and we all do thieving because that's how we started off
15 doing it a long time ago.
16 But let's understand what blending is. Before
17 we figure out what on-line do, we've got to figure out what
18 blending is first. So, blending is actually not just the
19 mixing; it's actually a whole bunch of operations before
20 and after it. You clean a blend. You load the active
21 excipients. You then finally mix. Then you sample. You
22 transport to a lab. You analyze, and then you have results
23 about uniformity. You have different kinds of results.
24 You can be undermixed, and so you mix longer. You could
25 get it right, and there's a minimum specification. I think

1 it's RSD 6 percent, and you usually get 3 or 4 percent. I
2 was happy to see that.
3 But sometimes you have this thing called
4 overblending that I never learned in chemical engineering.
5 They call it desegregation. They said sometimes its
6 demixing. But something happens so it really is not a good
7 idea to go beyond that time too. Do we understand it? No.
8 Well, let's not get into that right now.
9 But let's look at the material and information
10 flows. The material flows through as you go forward. The
11 information all comes far away from the lab many, many,
12 many, many hours away. You then make a decision about the
13 material based on another organization, which is what is it
14 about batching the HPLCs? Because they have only so many
15 and they want to make best use of their samples. So, what
16 are the consequences? So, that's blending.
17 If we agree that that's blending, let's see if
18 we can do blending on-line. Here's an example of a
19 collaboration between MIT and Purdue, two universities
20 actually collaborating. We don't have a pharmacy school
21 and we have a chemical engineering school and a business
22 program. Here is a bin blender at Purdue University in
23 their pilot facility. We do the lab scale trials in our
24 laboratories at MIT, and when we scaled up in collaboration
25 with near infrared and LIF together. And this is basically

1 a light-induced fluorescence. There's no laser. It looks
2 at uniformity in three different locations.
3 The question is a very simple one, which is
4 when are you done? There is no deeper question about what
5 are those patterns, what do they mean. When are you done?
6 It's very clear that we could do it very easily and very
7 robustly.
8 We were pretty happy about when we were done,
9 and we said we're very excited. How do we know whether we
10 got it right? You're going to know if you got it right
11 when you compare it against thieving.
12 Okay, I know I'm uniform. I have to compare
13 against thieving. You told me thieving was a problem with
14 the sampling and the manual operation. Now, is it going to
15 be difficult for me to compare a much superior test with an
16 inferior test and that would be my benchmark? Can we look
17 deeper about content uniformity? I can do a lot more
18 tests. I can look at different places. I don't think
19 that's going to work. You have to measure it against
20 thieving.
21 So, we did and we were very lucky that that
22 works well. This is the laser-induced fluorescence, and
23 it's very similar for the near infrared. We can certainly
24 talk about that as well. On average for different active
25 concentrations, and we were able to go very low. For

1 important products, I think we have a great answer. The
2 endpoint was very consistent and less variable. Not
3 necessarily a tradeoff between the FDA and the industry,
4 between quality and cost, but we got them all less
5 variable. What does that mean in terms of time and cost?
6 Well, I told you I won't talk about cost, but I will try to
7 talk about time.
8 So, if Ajaz represented some part of the FDA
9 and he was looking for just this variation, hey, we're not
10 doing too badly. But if we represented the companies, how
11 would this help us? Why would we have to go through this
12 pain of showing equivalence? Hopefully we'll get something
13 out of it. Maybe it's cost. At least it has to be time.
14 So, the answer is so what. We've got to get something out
15 of it. It seemed like we had some variability reduction.
16 The "so what" comes down to let's compare --
17 and I took one of those case studies now, one of these
18 processes that three different excipients were added, one,
19 two, three. Here is the conventional off-line test, and I
20 have the on-line test. And I have the maker of this
21 product, and I said what are your blend process development
22 times.
23 But I said let me not stop there. We have a
24 consortium of seven companies. Let's capture all of those
25 times so that I don't have to then succumb to the argument

1 that says it's just that company that doesn't blend very
2 well or do the process development.
3 So, we collected blend process development time
4 from all the seven companies and everybody was different.
5 So, we said let's capture all their data, but let's start
6 asking questions around the whole blending operation.
7 Let's define the blending operation. The off-line one has
8 a number of components, brown representing the material
9 flow, as I said before, blue representing the information
10 flow. Brown, material. Blue is information. Information
11 flow and material flow are two different tasks.
12 When material is separate from information,
13 what is the space in between called? It's called
14 inventory. When you can combine material and information
15 together, that's when you can deal with the fundamental
16 drivers of inventory. You have to wait to get the
17 information. You wait with the material. And that's
18 called inventory. So, we wanted to get these two things
19 together.
20 And then uniformity is done differently in
21 manufacturing and is done differently in process
22 development. Again, it's done differently if you're a
23 generic versus a brand name. But in many cases, depending
24 on the country, you don't necessarily have to do the
25 content uniformity test at the end of the blend while

1 you're manufacturing. You often do it during validation,
2 often during process development. Some of the generics do
3 it around the manufacturing as well. Some countries would
4 do it in the manufacturing as well.
5 But let's look at process development now
6 because that's what we're going to look at and figure out
7 what is the material/information flow going to be for the
8 on-line technology. Where's the brown? Where's the blue?
9 They are in the same place, and this is the decision.
10 Here is the material/information flow, so complicated.
11 Here is the simple flow. We measured it where the cause of
12 the variability is, and we can do something about it.
13 So, let's collect data from all these
14 companies, and we have the seven companies. How long do
15 you take to clean? How long do you take to load? How long
16 do you take to discharge, sample, transport, test, hold?
17 And we had all the seven data entered in, and we said now
18 let's simulate each of these case studies.
19 So, we said let's take each of these companies
20 and do blend process development the way they did it. We
21 said here's all these tests. We're going to represent all
22 these tests based on the time of what they took. Here is a
23 representation, a model of each of those steps. Modeling
24 is a really not so commonly used thing in this industry as
25 well. But let's look at each of these steps.

1 For example, this is the QC lab. You transport
2 to the QC. I told you about all the components. You hold.
3 You retrieve the samples. You prepare. You test. You
4 analyze. That's inside the lab. Here's the actual
5 blending. Here's the actual charging of the active
6 ingredient and you can say you usually have to clean and
7 then you have to load the active. And you represent all
8 those steps.
9 This is now two years old, and when we were
10 presenting at the consortium of the pharmaceutical
11 companies, we said it's a few more months before it's the
12 start of the millennium. And I said let's start the
13 millennium -- this is way back from our time now -- the old
14 way. Let's do blend process development the way we did it
15 for now I don't know how many years. If aspirin was made
16 this way, then that's a lot of years. So, let's do it that
17 way.
18 So, we're going to start using the actual data
19 from each of these companies. Let's start and do blend
20 process development. And here's the actual time that it
21 takes, and you can see the 1st of January is now the 3rd of
22 January and we're waiting for our first batch to come out.
23 It's now the 4th of January. This is actual time based on
24 the data that we collected. Still waiting. This arrow
25 indicates that we got our first batch with an acceptable

1 RSD. Now, we got one. We are really happy now.
2 We look at our plant and we see a whole bunch
3 of samples waiting to be analyzed, so-called sample blends.
4 We don't know whether this is right. We don't know how
5 many we have to do. We make a lot and we're waiting for
6 the analysis. It's a whole other organization somewhere.
7 This is inventory space, information and material flow
8 being disconnected.
9 Let's go inside our lab and see what they're
10 doing. We go inside our lab and you can see they have a
11 whole bunch of samples to deal with. They're working
12 unbelievably hard, and you can see that it's at different
13 places. Some are being held. Some are actually being
14 tested. Then you can see some are being analyzed.
15 You can now look at the QC people, and there
16 are QC/QA people in that organization, red indicating that
17 they're busy, and you can see they're very, very, very busy
18 in the lab. They're both very busy. We got our first
19 blend.
20 You can now look at all your HPLC equipment,
21 and if it's red, they're busy too. So, if HPLC is busy, if
22 people are busy, there's inventory in your plant, you got
23 one correctly.
24 Now, you have this interpretation of
25 validation, if you remember Ajaz saying in his

1 presentation. This is a lot of work. If I could just get
2 three right. So, you say I've done one. It's now the 4th
3 of January. Let's try to get a couple more. Oh, everybody
4 is working so hard. Everybody is so busy. What should the
5 right head count be? How many HPLCs should I have?
6 Terrible questions asked around a terrible technology. The
7 wrong questions.
8 But you finished one. You got two. It's the
9 5th of January. You took five days. You got it out. Now,
10 there's some people in the organization, so-called
11 processing people, who say you know what? We got it right.
12 We got three done. You know, maybe we should do a few
13 more so that we just understand the area around it.
14 But then you have your marketing people. You
15 have your business people who look at your plant.
16 Everybody is so busy. You have the inventory. And they
17 say it's all about time market.
18 So, what are we going to do? Okay, everybody
19 is busy. This is three runs in a row. This is content
20 uniformity. This is blending.
21 Let's go to the next step. We have an envelope
22 around which we've done data. We have data. Now we're
23 ready to go to the market, and that's now the 5th of
24 January.
25 As another alternative, I also challenged the

1 companies and the consortium to say let's go back in time
2 and start that same millennium, January 1st 12:00 midnight,
3 run everything the same. That is, you clean the same way,
4 you load the same way. The only thing you do differently
5 is the monitoring of content uniformity. So, you start the
6 same time too.
7 Now you figure out what you want to do about
8 it. So, you run your batches. You watch the clock and you
9 do everything else the same. It's 10 o'clock on the 1st of
10 January. I finished one. Let me just take a look at my
11 lab and see what they're doing. Red means they'll be
12 really busy. Wow. Now, is the question now should you not
13 have those QC people? No. You want your QC people to do
14 thinking jobs instead of doing jobs. This is an
15 opportunity for them to be auditors and trainers and QA
16 people. I think they're going to enjoy themselves more if
17 they don't have to move in batch samples.
18 Let's just take a look at our HPLC equipment
19 that Ajaz had I think underestimated at $45,000. You just
20 freed that up too, but you did put a lot of investment
21 around your on-line sensor. But guess what? We're very
22 happy. We've only got one right. It was pretty fast.
23 Let's see if we can get a few more. We got two. It's the
24 first day. In about 24 hours, we just finished three and
25 now we're asked the question, you finished three, one is

1 random, two is minimally a pattern, three is a law in some
2 disciplines. Is this a law? Do we know a blending? Do we
3 know the uniformity of our blending?
4 Shall we do a few more? Yes. QC people are
5 there to analyze the data to figure out what your next run
6 should be. You don't have things sitting around. The
7 costs are making that decision of a few more. You know
8 you're going to succeed. You can do some runs around it.
9 And maybe you can go back to the real deeper spirit of
10 CGMP. That's four. That's five. How many do you want to
11 do? Six. Okay, two days. We did seven runs. We did more
12 than twice as many in less than half as much time. This is
13 what technology can do for us.
14 Now I've asked the companies -- this is
15 obvious. The technology is in place now. This is your
16 data. I presented it to you. Why isn't it done? It's
17 been around for a long time. The first response is I've
18 done so much of this NIR stuff. I have so much data. But
19 the FDA just won't accept it.
20 I actually first met Ajaz at the PhRMA meeting,
21 and he presented right after me, which is when the idea for
22 this came up. I ran after him and I said, Ajaz, why
23 haven't you guys accepted it, and he just said I have not
24 seen one application with near infrared submitted to the
25 FDA yet.

1 Are they wrong? No. They're both right. It's
2 a perception. Number one. Second, it's a limitation of
3 saying you want to do a test-to-test comparison.
4 Together, I challenge this advisory committee
5 to break out of the box to see if we can break through that
6 barrier. I can see the logic for that test-to-test
7 comparison. I can do the same thing too. But let's look
8 back to why we had that test. What does it mean for all of
9 us? A lot, just for that one step. I took the simplest
10 possible step, and it gets better every time. Blending.
11 On-line blending process development. Off-line whether you
12 have one, two or three blends. A factor not 10 percent. A
13 factor of 10 improvement to a factor of 15 improvement of
14 that process development time just for blending.
15 But even better. There is a predictability of
16 that time, which means you know when to start your blend
17 process development, you know when to build your plant, you
18 know how big to build your plant. That is about
19 variability of the organization. It depends less on the
20 organization now. This is the opportunity.
21 I listened to the presentations and everybody
22 seemed to believe uniformity is an important issue. But I
23 challenge that on that important issue, to make an
24 important leap in working together to be able to capture
25 some of these benefits together. I don't even talk about

1 the quality variability issues because I said I will talk
2 only about time today.
3 So, we looked at the top level routine
4 manufacturing, and we quickly got some pictures that told
5 us something and we said where do we look now. We then
6 took the simplest possible operation and we said let's take
7 the simplest technology -- and there are three or four of
8 them -- and look at the opportunity that we have ahead of
9 us.
10 As I come to the end of my presentation, I'm
11 going to take off on a couple of things that I said before.
12 We want to monitor quality continuously. Because of the
13 cost of doing it today, we do it at the end. The
14 consequences are large and we all deal with it together as
15 companies and regulators and society. So, on-line
16 technology, at-line technology allows us to break that
17 tradeoff and measure continuously where we can all win
18 together.
19 We have extended this work beyond blending. In
20 fact, I would have rather talked about all of those. And
21 we've looked at different parts of the process. Being a
22 chemical engineer, I like the first part. But we looked at
23 a lot of these, including some microbial tests, flow,
24 tableting transport. We looked at high volume products.
25 Here is an example of some of the data that I deliberately

1 don't show you the axis on, but here is where you can
2 monitor in the active ingredient. Here's the blend
3 monitoring data. Here's the flow data, and you can measure
4 uniformity during flow and you can measure tablet
5 uniformity.
6 The challenge now is to ask yourself what is
7 content uniformity as the whole process. How do I show,
8 when I bring in revolutionary technology, that I'm actually
9 more uniform over the whole process? How do I get myself
10 out of the way of saying it should be a test-to-test
11 comparison when the case for the test and the manual aspect
12 of a test is the technology problem? With all of these
13 together, I showed you the opportunity for improvement
14 here. I showed you the opportunity for improvement over
15 just blending.
16 If you look at a three blending case -- I
17 wanted to go back to that -- you can see as your off-line
18 and on-line get to see more and more steps, the difference
19 between on-line versus off-line gets bigger because the
20 cause and effect gets separated. So, there's a cumulative
21 benefit as you add on more of these things together.
22 With that challenge, I will end my presentation
23 saying that I took one aspect of manufacturing performance
24 and summarized many years of work around saying we can do
25 something about it. I deliberately don't talk about those

1 aspects, but obviously they're significant and you can
2 imagine that time translates to money and quality.
3 I would gratefully acknowledge my colleague,
4 Professor Charles Cooney from MIT who would have loved to
5 be here, but is on the mountains of Peru and couldn't come.
6 Now for the last five years I've worked very closely and
7 very excitedly with Professor Steve Byrn at Purdue. This
8 is my first introduction with a pharmacy school, and it's
9 been great fun.
10 And CAMP is the Consortium for the Advancement
11 of Manufacturing of Pharmaceuticals that has more than half
12 the pharmaceutical industry associated with it.
13 And in addition, I've also worked with the MIT
14 program on the pharmaceutical industry. We worked with
15 basically almost every one of these pharmaceutical
16 companies in different ways.
17 Last, because I think I'm beginning to say
18 something real about real processes. I feel bad to put
19 this up but I felt I needed to. Nobody is liable for
20 anything I say except me. Some of the data -- I
21 deliberately take out the y axis when it's not relevant.
22 But I think the basic message has to be very
23 clear. I know the way to deal with that message. It's not
24 obvious and not trivial, but that's what we're here for.
25 With that, I'm going to actually see if maybe

1 Steve can have a few thoughts on this because we actually
2 have gone well beyond some of this. Maybe he can decide
3 whether he wants to talk about it or not.
4 DR. BYRN: Thanks, G.K.
5 One thing I should say, before we start and we
6 talk about this, is Purdue is heavily involved in research
7 and developing intellectual property in this area. So, you
8 should know that when I talk about my comments.
9 But G.K. touched on these areas because with
10 one of his slides especially -- and this is probably the
11 only comment I'll make -- we think there's tremendous
12 potential for these technologies, on-line/at-line
13 technologies, to reduce time to market of drugs. That
14 could be achieved by starting using these technologies in
15 development and then moving them through scale-up because
16 you can get instant feedback when something is going wrong,
17 and by using multiple sensors, multiple at-line/in-line
18 techniques. So, there is a huge potential public health
19 benefit because if we can reduce time to market and, like
20 G.K. showed, ensure quality at the same time, then that's a
21 very exciting game.
22 I think that's probably all I need to say.
23 I think we need to have a discussion now.
24 Ajaz' proposal was to, I think, establish a subcommittee of
25 this group to look at these technologies in more detail and

1 report back. But let's have a discussion and see if there
2 are questions for G.K. and go from there. Yes, Vince.
3 DR. LEE: I think this is very intriguing. Is
4 there any other industry using these technologies?
5 DR. BYRN: Yes. I think G.K. can answer that
6 one.
7 DR. RAJU: This is probably one of those really
8 extreme industries where testing takes a lot longer than
9 processing. It usually takes a much smaller fraction.
10 There are many good reasons for it. It's the legal nature
11 of the test, the fact that we're making medicine.
12 But actually I think if we do it right, by
13 moving it up, we can actually capture all of those. We can
14 actually make -- I hate to say the word "better," but we
15 can make equivalent, in a real way equivalent product I
16 think. And we can all be a lot happier and have more fun
17 doing manufacturing. I'm not sure I want to be
18 manufacturing if all I do is doing. I want to do some
19 thinking, and that's part of improving the process along
20 the way within the constraints of the CGMP, of course.
21 DR. BYRN: Just to give one example, Vince, as
22 far as we know, Lay's Potato Chips uses near IR to monitor
23 the water content in a potato chip. They use many more
24 units than we do.
25 DR. LEE: Let me ask one more question. Can

1 you build into dissolution as part of the --
2 DR. BYRN: We do need to be fair. There are a
3 few tests that are more difficult to put at-line or on-
4 line.
5 DR. HUSSAIN: Steve, let me answer that.
6 Vince, I think in the handout there's an article on
7 predicting dissolution rate of carbamazepine. We in a
8 sense can essentially predict or control every parameter or
9 variable that affects dissolution. So, dissolution can
10 essentially come at-line in terms of the predictive mode.
11 You're not actually doing the dissolution, but you're
12 essentially ensuring that dissolution would be acceptable.
13 So, we'll have to think out of the box how to address
14 that.
15 DR. BYRN: Yes. To put the actual test on-line
16 would be difficult, obviously, because you've got a time to
17 dissolve.
18 DR. LEE: You still need personal intervention.
19 Right?
20 DR. BYRN: There are automated units where you
21 can kick a tablet out. You can run a dissolution test
22 automated.
23 DR. HUSSAIN: In our labs actually in St.
24 Louis, we have actually predicted dissolution, just near IR
25 when you know what the dissolution is. Tennessee has been

1 doing some of that right now. So, predicting dissolution
2 from spectra, information gathered from tablet surface.
3 That's a very important point for us. There's potential
4 for misuse of the technology too because now I can predict
5 the dissolution of a tablet without doing the dissolution.
6 Then therefore it raises the question of selectivity in
7 terms of what gets reported to FDA. That's a concern that
8 we have to worry about.
9 DR. LACHMAN: Has anyone considered the
10 validation implications of this activity?
11 DR. HUSSAIN: That is a major issue I think
12 we'll have to deal with, and part of the reason for
13 requesting a subcommittee is to discuss those aspects, how
14 one should go about doing this.
15 DR. LACHMAN: That's going to be something
16 that's going to be very important to address.
17 DR. BYRN: Yes, and G.K. was touching on that.
18 One of the problems in this blending area is how do you
19 validate what we think is a more precise method, which is
20 at-line monitoring, with a less precise method, thieving
21 and off-line analysis. We need to talk to statisticians
22 about how to do that.
23 DR. LACHMAN: I think you have to have the
24 various computer assisted activities and electronic
25 documentation and records that you're developing. So, it

1 gets quite complicated for the validation activity.
2 DR. HUSSAIN: I think the patent recognition
3 and the statistical validation would be a challenge.
4 DR. LACHMAN: Right.
5 DR. BOEHLERT: I was just going to mention that
6 I'm aware of at least one company in this country that
7 makes vitamin blends that has been using near IR since the
8 mid-1980's to test and release product and quite
9 successfully. I don't know if they'd be willing to share
10 that with the group, definitely --
11 DR. HUSSAIN: I'm aware of the OTC and other --
12 DR. BOEHLERT: And that's analogous to a
13 pharmaceutical blend.
14 DR. HUSSAIN: I understand, yes.
15 DR. RODRIGUEZ-HORNEDO: Two points. The first
16 one is I cannot find it now, but in the reading materials
17 you sent us, there is something in the European
18 Pharmacopeia regarding the use of NIR. So, what do we know
19 about Europe using these techniques?
20 DR. HUSSAIN: The European Pharmacopeia
21 introduced the chapter on near IR in 1997. We are working
22 with USP to try to get a chapter in USP.
23 EMEA, our counterpart, has a draft position
24 paper, and that position paper is in your packet also. In
25 their position paper, they have outlined some of the

1 regulatory challenges that they feel would need to be
2 addressed before it comes in. I'm aware of one company
3 which has essentially adopted a lot of this in a new plant
4 in Germany. So, probably Europe is ahead of us in this
5 regard.
6 DR. RODRIGUEZ-HORNEDO: I think it's a great
7 opportunity to have control of the processes by monitoring
8 in-line.
9 Regarding dissolution and the example of
10 carbamazepine you gave us, I'm not sure if the sensitivity
11 to the dissolution is due to the solid state
12 transformation. Are you able to also capture differences
13 in effective surface areas that may affect dissolution?
14 DR. HUSSAIN: Predicting dissolution is sort of
15 a black box. I don't have a mechanistic understanding of
16 that, but based on what I have seen so far, porosity -- you
17 can actually predict hardness of that. All those things
18 are being captured.
19 So, the mechanism by which we are predicting
20 dissolution I'm not sure I understand that, but that's the
21 focus of our lab right now. We asked the labs to focus on
22 how are we predicting dissolution, what attributes that we
23 are getting from the tablet surface are related to that.
24 So, I think as we understand that, more confidence would be
25 developed in this area.

1 DR. RAJU: There's also a more recent public
2 news that the Australian regulatory agency approved NIR for
3 release just a few weeks ago.
4 DR. BLOOM: The other aspect of these
5 techniques is that you can use them off-line also for
6 troubleshooting. In some cases there have been
7 publications of Raman and near IR trying to find some
8 troubleshooting.
9 DR. HUSSAIN: One such example I presented from
10 Pfizer, Steve Hammond, on the bad flow was the
11 troubleshooting.
12 DR. LEE: This is not a quality control
13 question, but how much retooling has to be done to
14 implement this?
15 DR. HUSSAIN: I don't have a good answer for
16 that. That's one of the reasons I thought we will need to
17 gather more information on that. We have done it crudely
18 in our labs. We are doing it off-line. We're using the
19 same. So, it's buying HPLC or buying this, so it's not
20 that. But in terms of putting it on-line, I think G.K.
21 probably will have more information on that.
22 DR. RAJU: I think that people have been doing
23 it in stages and different companies have made significant
24 progress, more than one step at a time. The interface with
25 the regulatory agency, because of perceptions, has been

1 kind of delayed. But the phase has been to first do it at-
2 line and in-line before on-line because you get half the
3 benefit or a little bit more before that. When you go
4 close to the process, the operators start asking questions
5 about the data. Why is it that we call it uniformity?
6 They start looking at patterns, for example, that say, oh,
7 this is probably because we top-loaded the excipient versus
8 bottom-loaded. As soon as they can remember the data and
9 ask why around it, because cause and effect in the same
10 human being gets analyzed and the process gets -- so, it's
11 coming in phases and on-line has been kind of the last step
12 and not everybody has done it yet.
13 DR. BYRN: Other comments from the committee?
14 Is there general consensus that a subcommittee should be
15 formed to pursue these concepts and work with the agency
16 and so on?
17 DR. HOLLENBECK: Ajaz, could you comment a
18 little bit more on the direction you'd expect the
19 subcommittee to take?
20 DR. HUSSAIN: There were three stages in my
21 mind in terms of how this could unfold. One is simply an
22 understanding of the current state of technology. Vince
23 asked about what does it take to do this. Because if that
24 is too a high cost, obviously, it's going to be a slow
25 process and so forth. An understanding of the feasibility.

1 Second would be I think probably understanding
2 of validation procedures. Without that, I think it will be
3 difficult.
4 Thirdly, I think some mechanistic understanding
5 because I think we probably should gather information on
6 how much this is generalizable so that we build confidence
7 in what we are looking at because patent recognition, use
8 of chemometrics and so forth is a different way of looking
9 at chemistry than we have done before. So, we really need
10 to build confidence and understand the mechanistic basis,
11 especially, say for example, about dissolution. If I'm
12 able to predict dissolution, how am I doing this? If we
13 are replacing one with another black box, we need to be
14 careful.
15 DR. BYRN: Any other questions?
16 (No response.)
17 DR. BYRN: Let's take a break till 4:00. We're
18 not very far behind. I think we're in pretty good shape.
19 So, let's take a break till 4:00.
20 (Recess.)
21 DR. BYRN: I think we can begin.
22 I'll introduce the speakers as we go along
23 today, and we should just continue till the end. I know
24 we're running behind, but we're okay I think because we
25 were supposed to finish at 4:45. So, we'll just finish

1 around 5:00.

2 This session is on microbiology. The first

3 speaker is Dr. David Hussong.

4 DR. HUSSONG: Good afternoon. The last time I

5 was up here, we were nearly an hour behind. Now we're only

6 15 minutes behind, so I'd like to congratulate the panel

7 for shortening the cycle times and getting things rolling.

8 (Laughter.)

9 DR. HUSSONG: I'm here to initiate a discussion

10 of applying new technologies to microbiological testing in

11 the pharmaceutical industry. Now, many of these

12 technologies have been around for quite a while. Some have

13 come from a clinical arena and some from academia. But I

14 wanted to give a real quick history. This is microbiology

15 history 101. So, if you'll bear with me for a minute.

16 Historically, to measure growth of

17 microorganisms, you use medium. To detect them, you use

18 medium. Everything is growth-based, and it depends on the

19 medium. So, if you don't have the right nutrient, you

20 don't detect it. You don't get the right nutrient, you

21 can't count them.

22 There are other methods and they will often,

23 when used, show different populations. Now, the USP

24 methods, the compendial methods, for microbiology are very

25 much the simplest and people can do them in most any

1 laboratory. Because they are simple, anybody will do them.
2 They can be standardized, but I don't think that they're
3 necessarily the best.
4 Now, we've been looking at bacteria for over
5 300 years, and in the last 100 years, we have played with a
6 lot of different methodologies. Certainly there has been
7 some pressure driving us to get into the use of them.
8 Towards that end, the Parenteral Drug Association was able
9 to put forth Technical Report 33, a multiyear effort. It
10 came out in May 2000 telling the pharmaceutical industry
11 how to bring these methods on-line.
12 So, today's speakers I'd like to introduce. We
13 have Dr. Bryan Riley, an FDA review scientist, who will
14 give us an introduction to the alternate technologies used
15 in microbiology.
16 We have Dr. Ken Muhvich, who is a consultant to
17 the pharmaceutical industry, and he has a lot of experience
18 with the validation of methods, both the standard methods
19 and the new methods.
20 Dr. Jeanne Moldenhauer is with us who is also a
21 consultant, and she has a tremendous scope of industry
22 experience, and she will discuss her experiences as a user
23 of some of these technologies.
24 We're hoping Roger Dabbah will be able to join
25 us. He seems to be a little late. But he's from the USP

1 and he can provide us some comparative information relative
2 to the compendial methods.
3 So, with that, I'd like to introduce questions
4 that we'll have at the end. What I'd like to have the
5 committee do is keep these questions handy.
6 Question 1. You can see I have a little bit of
7 bias in these methodologies. Considering the advantages
8 demonstrated by some of the new microbiological testing
9 technologies, should FDA take steps to facilitate the
10 pharmaceutical industry's use of these technologies?
11 Then question 2. Since various guidances and
12 compendia offer test acceptance criteria in terms of
13 colony-forming units, is it appropriate to permit changes
14 to the numerical limits to reflect the sensitivity of tests
15 that measure microorganisms using these properties?
16 So, with that, I would like to have Dr. Riley
17 take over.
18 DR. RILEY: Good afternoon. I'd like to spend
19 about the next 10 minutes or so taking a brief look at the
20 methods used for microbial limit testing. What we'll do is
21 look at both the current methods that are now in use, as
22 well as a couple of the new technologies.
23 First I'd like to look at the compendial
24 methods, which in this case means USP. There are
25 essentially two types of compendial methods used for

1 microbial limit testing.

2 The first are called plate counts, which give
3 us colony-forming units, also known as CFUs. This is
4 probably the most common method used for microbial limit
5 testing and is probably the most accurate of the ones used
6 so far. In this case, the samples are applied to a solid
7 medium. The medium is incubated. The microorganisms that
8 are capable of growing on this media will grow, form
9 colonies. These colonies can be counted, and then the
10 results are expressed as either CFUs per ml or per gram of
11 the sample.

12 The other method is called the most probable
13 number method, or MPN. It's based on the statistical
14 distributions of organisms in a sample. It is considered
15 less accurate than the plate count, but it is used
16 sometimes when plate counts can't be used.

17 What you do is you take a parallel series of
18 serial dilutions of a sample in liquid medium. You do
19 these at least in triplicate. So, what you might have, for
20 example, are three tubes of a 1 to 10 dilution, three tubes
21 of 1 to 100, and three tubes of 1 to 1,000, and so on. You
22 incubate these tubes, and then you look for evidence of
23 growth. You take note of how many tubes at each dilution
24 have growth. Then you refer to an MPN table which will
25 give you the most probable number of organisms in that

1 original sample.
2 The advantages of the compendial methods, as
3 Dr. Hussong mentioned a minute ago, is they're very simple.
4 They don't require fancy equipment. Any microbiology lab
5 should be able to perform them. They're sort of tried and
6 true.
7 Also an advantage is it only counts viable or
8 living organisms, which is important because that's really
9 all we're worried about in this case. Are these organisms
10 alive or not, can they multiply?
11 The disadvantages are the incubation time.
12 Despite the fact this says 48 to 72 hours on this slide, it
13 actually can be longer. It can be up to about 7 days or so
14 depending on the organism you're looking for.
15 The other disadvantage is not all organisms
16 will grow on a single medium. So, you're really just
17 getting a subset of the possible viable organisms in a
18 sample.
19 Again, we're only interested in the viable or
20 live organisms. Therefore, the new method must be able to
21 count or differentiate between live and dead, and also must
22 not count microorganisms shaped particles or anything like
23 that. You only want viable bacteria or fungi. Therefore,
24 you need some sort of viability indicator, and I'm going to
25 talk about two different indicators that are used in these

1 two new methods.
2 The first method is called esterase detection.
3 The example I'm going to give is a test called ChemScan
4 from a company called Chemunex. Esterase is an enzyme
5 that's ubiquitous in microorganisms. It's present in all
6 of them. The reagent that is used is called Chem-Chrome,
7 which is a nonfluorescent compound which can be passively
8 taken up by microorganisms. Esterases in these organisms
9 will then cleave that substrate, which will give you a
10 fluorescent compound. The viability is demonstrated by the
11 presence of the esterases in the microorganisms, as well as
12 the intact cell membrane that is necessary to help contain
13 the fluorescein after the Chem-Chrome reagent has been
14 cleaved.
15 To perform the procedure, you sample the filter
16 through a membrane. You expose the membrane to the
17 reagent. You then analyze the membrane by laser scanning,
18 looking for the fluorescence. You will count particles
19 that fluoresce at the appropriate wavelength and also at
20 the appropriate size of the microorganisms that you're
21 looking for.
22 The time for this test is an hour or two from
23 start to finish.
24 The next method I'm talking about is ATP
25 bioluminescence. The examples are the MicroStar and the

1 MicroCount tests by Millipore. This test looks for ATP,
2 which is the primary energy source for all organisms. The
3 reagent used is a combination of luciferin, which is a
4 substrate, and luciferase, which is an enzyme, which will
5 react with the ATP that you're assaying, as well as oxygen
6 to produce light. And you can measure the light.
7 To do the MicroStar procedure, it's similar to
8 the ChemScan procedure. You filter the sample. In this
9 case, you then replace that membrane onto a solid medium
10 for a brief incubation. This incubation could be 6 to 12
11 hours. It's not as long as if you're looking for total
12 growth. The reason for the incubation is it amplifies the
13 signal by increasing the amount of ATP that's present.
14 You then disrupt the cells to release the ATP.
15 You add the bioluminescence reagent to the membrane. You
16 can then detect the spots of light using a charge-coupled
17 device camera and computer analysis, and then you can
18 analyze the number of light spots you get and count your
19 organisms.
20 The time, again 6 to 12 hours or so for the
21 incubation part, and an hour or so for the analysis.
22 That's all I wanted to say this afternoon, and
23 we'll go to our next speaker.
24 DR. BYRN: Are there any questions?
25 DR. MARVIN MEYER: Steve, the handout listed

1 some advantages and disadvantages to the standard methods.
2 Do you have similar statements for the proposed two new
3 methods?
4 DR. RILEY: I think time is an obvious
5 advantage. As I sort of mentioned, we're looking at
6 probably a larger subset of the viable organisms that are
7 present because you're not looking just at growth on a
8 single medium.
9 DR. MARVIN MEYER: No disadvantages?
10 DR. RILEY: There are probably some
11 disadvantages, but I'm not going to get into a lot of the
12 detail at this point.
13 DR. BARR: Is it likely that this could replace
14 the traditional method?
15 DR. RILEY: It could potentially replace the
16 traditional method, yes.
17 DR. BYRN: Our next speaker is Dr. Kenneth
18 Muhvich, who's going to talk about validation issues.
19 DR. MUHVICH: Being a former FDAer it's a
20 pleasure for me to be here today to talk to you about my
21 views. Since I left the agency, I've worked almost four
22 years in the pharmaceutical industry, and a large part of
23 what I do is audit sterile manufacturers, and I'm always in
24 a micro lab somewhere. So, that's given me a perspective
25 that I want to share with you all. I'm not going to take

1 too much time. I'll really try to give you take-home
2 points on where I think these technologies can be used and
3 their efficacy.
4 I've heard it twice today -- and I use it and a
5 lot of FDA investigators use it -- the common saying that
6 you can't test quality into product, especially for sterile
7 products. That typically refers to a final drug in its
8 final container. Instead, one must use validated
9 sterilization processes and use a proper aseptic technique.
10 That being said, I think that there are a lot
11 of instances and/or points in a manufacturing process where
12 appropriate microbial testing will provide invaluable
13 information and provide a greater sense of control over the
14 manufacturing process. It's not waiting to the end to find
15 out what the quality of your sterile product is like.
16 The bullets on this slide show areas that I
17 think are really ripe, if you will, for use of the new
18 technologies which are really old to me. I used a lot of
19 them as much as 25 years ago. They just haven't been used
20 in this industry and the time is now.
21 Water for formulation; water used for
22 processing, cooling water in autoclaves and washing of
23 stoppers and so forth; raw materials; in-process bulk
24 solution or intermediates. A lot of folks that are making
25 biologics have intermediates sitting on the shelf for

1 months, and they might not be of the same microbiological
2 quality as when they were put up. Microbial limits
3 testing, which Bryan already talked about for a couple
4 minutes. A lot of people use that as an in-process test.
5 I put the final product release testing at the
6 end for a reason. Jeanne Moldenhauer and I had a talk the
7 other day, and I'm going to quote her. I'm not going to
8 take the line for myself. We both think that use of these
9 tests needs to be in some in-process testing areas where we
10 can do some comparison testing and get a real feel for the
11 efficacy of these tests with pharmaceuticals. So, we need
12 to walk a little bit before we're going to run with what
13 everybody really wants them to be used for, which is
14 product release testing.
15 I'll go with a simple definition of validation.
16 It's a process or a test that will, with a high degree of
17 assurance, consistently give the intended results.
18 Now, in the case of one of these type of tests,
19 the validation of a rapid method is going to demonstrate
20 that small numbers of microorganisms -- and I should have
21 put viable there because we can't underscore that enough.
22 These are viable organisms that can grow -- can be detected
23 in the presence of their intended solution. What I mean by
24 that is in the vehicle that they're going to be
25 administered to the patient in, whether that be an in-

1 process solution or the final product solution in the
2 container.
3 Leon Lachman beat me to this one. The key
4 issue in my little talk here is about validation, but the
5 key issue for these is that they need to be validated.
6 Trust me, this is a lot easier than computer validation.
7 It's just work that needs to be done. They need to be
8 validated and used, in my mind, for in-process testing to
9 gain some experience with the testing. We need to know
10 what circumstances are likely to yield a false positive
11 result and that these will be readily recognized. They
12 should only be used for product release when a high level
13 of confidence has been gained with these methods.
14 I want to talk about a couple of case studies.
15 These are real and these are instances that I plucked from
16 my experience both when I was here at the FDA and since
17 that I think are real instances where these types of
18 methods could have been utilized to prevent problems. I'm
19 not doing a Hillary. I'm not saying could have, would
20 have, should have. I'm just pointing out that these are
21 detrimental events that happened that, if technologies like
22 these are explored aggressively, are not likely to be
23 repeated.
24 The first case is a sample from a bulk
25 solution. This is a very high count. It's 10 to the 5th

1 CFUs of Ralstonia pickettii per ml of product. This
2 organism is well recognized that it will go through a
3 sterilizing filter. A lot of people have switched to .1
4 micron filters when they recognize that this organism is in
5 their manufacturing environment.
6 Several hundred thousand units of this sterile
7 product were manufactured before they recognized that this
8 organism had been in their bulk solution. All of this
9 product, which represented a product that was needed on the
10 market and had a value to the manufacturer of the product,
11 was rejected. Then they also had to do quite a cleanup in
12 the facility before they could do any more manufacturing.
13 The second case probably needs no introduction
14 to any long-term FDAer. This is the Copley case, the
15 contamination of the albuterol sulfate solution. The
16 reason that the contamination was undetected is because the
17 microbial limits testing, as was performed for this
18 product, as a release test has a dilution in it. The
19 product had a very low level contamination which escaped
20 the microorganisms' detection during routine release
21 testing. And deaths and serious illnesses occurred in the
22 patients. I feel strongly that if a validated rapid method
23 was available for low level detection, that this type of
24 thing would never happen again.
25 It's well known. People in the FDA have

1 published that they think it's high time that we move on
2 with some of this technology. I would encourage the
3 committee to at least support having a day or so to really
4 take a hard look at what the FDA can do to help the
5 industry in terms of moving this type of testing into the
6 real world of product in-process testing and release.
7 Thank you so much for your time.
8 DR. BYRN: Our next speaker, while we're
9 getting ready, is Dr. Jeanne Moldenhauer, who's going to
10 give an industrial perspective.
11 DR. MOLDENHAUER: I'm probably a little
12 different from most of the folks that work with rapid
13 methods in micro in that I've worked both on the regulatory
14 side and the scientist side. So, I have some different
15 concerns in some cases than what some of the others may
16 have.
17 From an industry perspective, business
18 objectives are really what drive us. Laboratory compliance
19 to FDA requirements is a major concern because our products
20 don't get approved without them. One of the big concerns
21 we have is the ability to understand in advance how
22 investigators are going to look at rapid methods,
23 particularly when there's no guidance from the reviewing
24 division that supports us. When we get in the case
25 studies, I'll tell you about why that became of interest.

1 In fact, it was such a big interest to me, that
2 in one of the companies that I worked at, we brought the
3 FDA in for their drug school to go through some of the
4 rapid methods that were available. They're a fear because
5 they're not familiar with the methods.
6 We have a business objective to be a low cost
7 provider for high quality products. Lost cost providers
8 have to look at the cost in the total process.
9 Microbiological testing causes significant delays in the
10 release of product. That becomes an issue if you look back
11 at when parametric release was approved for the first time
12 by Baxter, and they eliminated a 7-day sterility test and
13 had millions of dollars of annualized savings. Well, that
14 does reflect back into the product cost.
15 Sterile products all require some sort of
16 sterility test. And there's a major reticence on the part
17 of FDA to encourage people to go to other forms of
18 parametric release, and they've documented that in many
19 cases. We're looking for other ways to accomplish the
20 sterility testing and still achieve some of the benefits of
21 reduced inventory hold time. It becomes particularly
22 important in the case of aseptically filled products where
23 you're talking about a 14-day sterility test and there
24 isn't any option for parametric release.
25 Reduced inventory hold time contributes

1 significantly to the total cost of the product, cost in how
2 much warehousing space we need and storage space as well.
3 In the case of parametric release, when they reduce from a
4 7-day hold time down to less than a day, they were able to
5 do just-in-time production with 6 hours from filling to
6 release the product. So, from a business objective point
7 of view, that's a big issue to pharmaceutical
8 manufacturers.
9 We're also looking for expedited product
10 approvals. Here's where the kick comes in looking at rapid
11 methods. On one hand, people want to submit rapid methods
12 and get them approved, but the great fear is that it's
13 going to be the only thing holding up their product
14 approval. So, there's a balance between wanting to use
15 state-of-the-art technology and condemning your product
16 that's in for approval.
17 There are other concerns over rapid methods.
18 One of the biggest ones is that the regulatory expectations
19 are not clear. The reason PDA had the major task force is
20 that everybody wants their new product approved from a
21 vendor point of view. Pharmaceutical manufacturers have a
22 big business objective to want to use those technologies,
23 and no one really knows who is going to approve or not
24 approve them.
25 The cost of the equipment for doing these tests

1 is significantly high. I'm most familiar with the ChemScan
2 technology. That averages somewhere in the vicinity of
3 $300,000 just to buy the piece of equipment. Then by the
4 time you get the accessories and that that you need, that's
5 about another $100,000 and somewhere in the vicinity of
6 twice that cost to validate it. So, when I go in and try
7 to get that approved through my management, they're looking
8 for returns on investment. The return on investment comes
9 from reduced inventory hold times, but there's a perceived
10 high regulatory risk because there's very little guidance
11 on what it will take to get those methods approved.
12 There are compliance issues versus submission
13 issues. If you choose the route of picking a less critical
14 test, if you will, than the final product release test,
15 because you want to ease people into the technology, then
16 you have the issue of convincing compliance to deal with
17 them. I'm going to talk about that exact thing in one of
18 the case studies that we talk about.
19 The other thing is that in terms of regulatory
20 guidance, the thing that we always here is that you can do
21 two methods that are equivalent. Most of these new
22 technologies aren't equivalent because they have superior
23 technology. So, when you go and try to explain that you
24 want to do something, it won't be equivalent, but I'd still
25 like you to get it approved, there are some concerns on

1 that.

2 There are also scientific issues with them on

3 top of everything else that's a regulatory issue that would

4 be useful to obtain some guidance on.

5 The first one I want to talk about -- and these

6 are two real life case stories. Fortunately, I got to

7 participate in both.

8 As a result of the PDA Committee, everyone

9 pretty much agreed that water testing -- and we had several

10 FDA, USP kind of folks on this committee -- was probably

11 not a product release test, and you could probably do this

12 and get it approved as a compliance issue.

13 I'm a daring kind of person, so we went ahead

14 and tried that. We met with the local district, told them

15 we bought this equipment. We wanted to talk about it. We

16 specifically wanted to address in advance the issues of it

17 not being equivalent, as well as how many tests they would

18 buy into or what strategy they would look at for testing.

19 Their first reaction in the first meeting was

20 no way would we even consider it. But we got past that

21 because I went in and explained, did you ever hear of this

22 organism Campylobacter? You won't ever detect it in any of

23 your tests, and by the way, it kills people. Now are you

24 interested in a new technology?

25 They were willing to do that, and they agreed

1 that it would probably raise the bar. Unfortunately, they
2 also told me compliance is not likely to make any quick
3 decision on this and, in fact, they'd get back to me.
4 Well, return on investments, business
5 objectives. I've got to justify why I have a $500,000
6 piece of equipment that's validated that I want to use for
7 a method, and I was starting up a new plant at the time.
8 So, the benefit to me was to be doing all my water testing
9 during the validation when you had thousands of tests to
10 do.
11 Well, six and a half months later, I still
12 didn't even get a follow-up phone call from the meeting,
13 and went back and talked with them some more. The bottom
14 line is no one wanted to make a decision, and we ended up
15 not using the technology for that test method because they
16 couldn't even agree on what it would take to convince them
17 that the technology might be okay to use. And by the way,
18 even if you did use it, don't ever use it as water for a
19 raw material for your product because that wouldn't be
20 okay. And we were talking about making sterile water for
21 injection which, by the way, is grandfathered. So, that
22 was water testing.
23 The next thing that we looked at is, okay,
24 we'll go a different route. The folks in Washington have
25 seen new technologies. Maybe they'd be more agreeable.

1 So, we went to look with developing a test where we could
2 get it approved through Washington, validate it, submit it
3 with a drug. And you know how you do some drugs and you
4 always know that there's going to be a deficiency anyway?
5 Well, we picked one of those to submit it with because we
6 didn't want it to be the only thing holding up the
7 submission. And we also were going to do parallel testing
8 so that if it died, you could just take the new technology
9 out.
10 We had looked at a USP stimuli for revision
11 that talked about one of the new technologies, and it said
12 that the method was suitable for bacteria, fungi, and
13 spores. So, we thought, hey, BIs. That's a really good
14 thing. If we wait 7 to 14 days to qualify the sterilizer,
15 that's still a big inventory hold time. We started to
16 develop the method.
17 We had problems on the very first one with the
18 counts being erratic, had to go back to the vendor,
19 modified the tests multiple times because we were finding
20 counts that were lower than you would expect. Don't
21 forget, I read all these things that it worked great for
22 spores. Well, not really injured spores.
23 So, we eventually were able to modify it, got
24 it to work, we thought. And my counts were 4 logs higher.
25 Well, if you're talking about a sterilization cycle, that

1 becomes a big issue. Does this indict all the
2 sterilization cycles you've been running and is your
3 product really not sterile? Next new problem. Not good.
4 We weren't really sure how we were going to handle that and
5 what to do with the sterilization model.
6 Intuitively I never believed the results. So,
7 we did some follow-up studies and we looked at with
8 controlled kill times were you seeing the kind of
9 logarithmic reduction that you would expect to see with the
10 heat. And we did. It approximated the D-value within a
11 hundredth of the count. So, that made me still believe
12 that counts weren't true.
13 We were eventually able to find out that there
14 was a scientific issue that had to do with clumping, and we
15 were able eventually to get it down to be about a half log
16 difference in counts. But from an industry point of view,
17 there's no guidance that tells me when do I stop the test.
18 What if I had stopped it at the point where it was 4 logs
19 higher? I very easily could have done that because I had
20 data that printed out and routinely told me it was 4 logs
21 higher.
22 So, there are scientific issues that are also
23 needing to be addressed along with the regulatory issues,
24 and the perception out there is I just can't do it. I get
25 routine calls, because I presented a paper on this, that

1 you really would think that FDA might maybe think about
2 considering to approve this. People are frightened to
3 death to do this, and we're being bombarded because these
4 technologies are used in all kinds of other industries.
5 So, the higher management in your company knows that there
6 are technologies out there to resolve our problems, and
7 everybody is scared to death that FDA will not make a
8 decision or will not approve them.
9 DR. BYRN: Thank you very much.
10 Questions?
11 DR. DOULL: In your presentation and in the
12 previous one, you talked a great deal about validation, and
13 you may recall in Dr. Holt's presentation this morning he
14 talked about ICCVAM, which is a multi-agency organization
15 that has undertaken this task of validation. They're
16 concerned primarily with validation of biomarkers, but they
17 have a group that's part of that that's looking at the
18 microbiological and I know the food people at Food and Drug
19 here are, with Listeria and all the ones that they're
20 looking at. Food and Drug is one of the members of ICCVAM,
21 of course, and they're a player and, therefore, are
22 somewhat involved and obligated by where they go and what
23 they decide.
24 So, it seems to me that it's crucial that we
25 have the ability to, in fact, validate these procedures and

1 to get some kind acceptance of that process of validation
2 in order that we can all move ahead in an efficient manner.
3 ICCVAM wouldn't buy into this definition in here of
4 validation because ICCVAM is more pointed towards the
5 argument that validation involves getting the right answer
6 from the test. If you don't have that built in in some
7 way, you're not really validating the procedure.
8 But it would seem to me that because that's an
9 area of concern that's pretty widespread, it would be
10 something that we would all benefit from if we could have
11 some utilization of validation procedures and some
12 agreement as to our ability to accept those once they have
13 been shown to give us the right answer.
14 DR. BYRN: Any other questions or comments?
15 (No response.)
16 DR. BYRN: Should we address the questions that
17 were raised? The first question is not on our sheet. The
18 second question is kind of on our agenda. The first
19 question is, considering the advantages demonstrated by
20 some of the new microbiological testing technologies,
21 should FDA take steps to facilitate the pharmaceutical
22 industry's use of these technologies? I guess translated:
23 help develop validation or be involved in validation or
24 work with people that are doing validation.
25 Does anybody disagree with that?

1 DR. MARVIN MEYER: I don't disagree with it.
2 I'm ignorant of the process. When some new
3 technology becomes available that looks reasonable and
4 people are interested in it, when we say let's get the FDA
5 to buy into it, who are we really talking about at FDA?
6 Does this vary or is there a group that gives final
7 blessing, or how does that work?
8 DR. HUSSONG: One of the problems is FDA is a
9 multi-part organization. So, when you're trying to get FDA
10 to buy into something, it depends on who regulates what.
11 Sometimes that becomes a turf battle.
12 In the example that Dr. Moldenhauer gave to us,
13 a procedure was included in a new drug application and it
14 was part of a validation of another process or if it was a
15 procedure in the application that provided for a finished
16 drug product test, then that would be controlled by the
17 center. If, however, it's just limited to process testing
18 in the line -- the example would be Jeanne's water testing
19 -- that would be done by ORA and the field people. So,
20 when we try to get buy-in, we need buy-in from everyone who
21 would be involved in that method. This is something of a
22 dilemma for us because, obviously, no single buy-in is
23 going to work. It has to be across the board.
24 DR. MARVIN MEYER: I raised the question
25 because that was a recurring theme with both the infrared,

1 as well as this. Maybe it's a matter of some structuring
2 or some group assigned responsibility for final blessing,
3 rather than kind of helter-skelter, depending on who gets
4 to look at it first.
5 DR. SHARGEL: I have sort of a comment about
6 the pharmaceutical industry and it particularly deals in
7 the compliance side. When one manufacturer adds a test or
8 changes a test, then at times the field inspector feels
9 perhaps everybody should do it and raises that bar and buys
10 into it. There is probably in industry a worry if one
11 company starts doing this. Does that mean that everybody
12 should be doing it or would they be held responsible for
13 not doing it? You can word it better, if you understand
14 what I'm getting at.
15 DR. HUSSONG: I understand. It's a
16 philosophical question. Really it boils down to what's the
17 difference between good manufacturing process and best
18 available technology. Certainly in the technologies we're
19 addressing, you can use the most advanced technology, but
20 if you don't apply it to the right circumstances, it's not
21 what you should be doing.
22 Good manufacturing practices are conceptually
23 to me a long way off from using the most cutting edge or
24 best available technology. There is a difference. The
25 situation you're describing has been a serious problem with

1 the perception of regulators. It goes beyond the U.S.
2 regulatory agencies as well.
3 DR. MUHVICH: I'll give you an example. It's
4 not quite technology, but it's something that somebody did
5 that was new. There are only two companies in this whole
6 country that use parametric release for release of
7 pharmaceutical drug products. Other people are able to do
8 this, but they don't put in the effort and get the data
9 that shows that they can do it. The other two companies
10 have a huge number of microbiologists and they took the
11 time and effort to submit the data that would allow the FDA
12 review microbiologists to approve that. But all the other
13 people kind of whine about it and everything, but they need
14 to do the same thing. It's just a matter of effort. It's
15 not a matter of black box technology or anything. It's
16 just that they need to do it. If they want to do it, they
17 should do it. They just need to make a corporate decision
18 as to what they're going to do basically.
19 DR. BYRN: Back on the original question, it
20 seems like there's consensus that we should do this or we
21 should encourage FDA to do it. We just don't know how it
22 can be done. Is that what we're saying?
23 DR. HUSSONG: I'd sure like to know how to do
24 it.
25 DR. BYRN: Yes. Maybe we can just go on record

1 as encouraging FDA. I'm not sure we can tell FDA how to do
2 it. Right?
3 DR. HUSSONG: Well, if you could tell me,
4 please do.
5 (Laughter.)
6 DR. BYRN: I'm pretty sure we can't.
7 DR. BARR: Maybe as a follow-up to Marv's
8 inquiry, to make sure that all the decision making groups
9 are together, to encourage a formation of a committee that
10 would have those people who would ultimately be involved in
11 making the decision.
12 DR. BYRN: Ajaz.
13 DR. HUSSAIN: I had proposed a subcommittee
14 sort of a thing. Maybe this would also be amenable to
15 that, a subcommittee model for this issue also. I was
16 actually tempted to have one larger subcommittee dealing
17 with technology issues altogether. There are enough common
18 things there. A separate committee might be a better
19 approach for that.
20 DR. BYRN: So, what Ajaz is saying is maybe
21 this committee that we already said we would form, we'd
22 just expand the duties of that committee to deal with all
23 new technology and how to validate it. Okay, that sounds
24 great.
25 Any other comments on that question?

1 (No response.)
2 DR. BYRN: The second question is on our
3 agenda. I think I'll just read it. Well, I'll paraphrase
4 it. Most of the guidances and compendia use CFU, use
5 colony counts. Is it appropriate to permit changes to
6 establish acceptance limits that use new technologies
7 rather than colony counts? Can we replace colony counts
8 with new technologies?
9 Maybe this is something else we send to this
10 committee because it's interrelated, but let's see if
11 there's discussion of the committee.
12 DR. SHARGEL: That would strike me almost like
13 finding new impurities at times on an old product. I'm
14 thinking now on an old product that has been out for many
15 years and everybody is happy with it and it has not shown a
16 problem. But using a new technology, you notice new
17 counts. Should the manufacturer, if it's a small product,
18 have to come up to that new bar?
19 DR. MARVIN MEYER: Then kind of following up on
20 a previous comment, if not everyone adopts the new
21 technology, will you then have different limits at
22 different companies?
23 DR. BYRN: I don't know, but now you can think
24 about the USP has parallel tests in certain areas. We're
25 not the USP obviously. I don't know whether the agency has

1 a mechanism to do that or not. I assume it could be done
2 in the USP.
3 DR. BOEHLERT: It certainly allows the use of
4 alternative technology that's equivalent to or better.
5 Under that umbrella, certainly it could be used. But I
6 would agree with Leon, that on old products, if you
7 suddenly start applying a new standard, you don't want to
8 go putting them off the market if they've been acceptable
9 for many years. And that applies to a lot of changes in
10 technology and limits.
11 DR. BYRN: In the USP, couldn't you have an
12 entry that would have this test or that test?
13 DR. BOEHLERT: Its limits for that test. But
14 the old test with its limits would still be acceptable.
15 DR. BYRN: That's one way to deal with it.
16 DR. BOEHLERT: But right now USP, I don't
17 think, very often has alternative tests to measure the same
18 parameters. They have alternative tests where the endpoint
19 is different.
20 DR. BYRN: Well, they have different
21 dissolution media. They have a couple of these famous
22 ones.
23 DR. BOEHLERT: It's too bad Roger is not here.
24 DR. BYRN: Jeanne has been wanting to say
25 something.

1 DR. MOLDENHAUER: I had two things.
2 One was, first off, in the case of
3 microbiology, these new technologies are no different than
4 doing an endotoxin test versus pyrogen test where you had
5 different limits. So, that existed already.
6 In addition, in the case of microbiology, many
7 of our tests are not product release tests, but they have
8 limits and those limits are different from company to
9 company anyway in the case of things like environmental
10 monitoring and that. So, I think you're adding in
11 commentary that really is not as relevant in the case of
12 microbiology.
13 DR. MUHVICH: I'll make a comment about that.
14 As microbiology with the regulatory authorities that exist
15 today, right now you're not rejecting batches on in-process
16 bioburden limits. However, your sister agency, CBER, is
17 coming to that, and they're coming to it fast. They want
18 reject limits for product in process, bulk. So, I don't
19 know where that's going to leave us all, but I just wanted
20 to let you know that.
21 DR. BARR: I think this is a very important
22 area and I think it's something that requires very careful
23 study. I certainly don't feel qualified to make a judgment
24 if I had to make a vote on this, but I would hope that we
25 would move this to a committee that would be more qualified

1 and would have the time to consider it to make a wise
2 decision on it.
3 DR. BYRN: It seems to me that this committee
4 could handle these issues and maybe get some consultants
5 that could deal with some of these nuances and handle the
6 new technology in a general way.
7 DR. HUSSAIN: Steve, there are many common
8 elements I think. The committee I had in mind probably
9 would cover the common elements of validation, who does
10 what. But there are technical issues which are very
11 specific issues to microbiology. So, you probably would
12 need a separate group for that.
13 DR. BYRN: I'm sorry, Ajaz. Are you thinking
14 now about a separate group or a subcommittee of the
15 subcommittee?
16 DR. HUSSAIN: No, a separate group might be a
17 better approach.
18 DR. BYRN: A separate committee. So, we'd have
19 two committees.
20 DR. HUSSAIN: Just for microbiology, right.
21 DR. BYRN: One would be microbiology, but they
22 would have sort of a similar general charge. I think
23 however the agency would like to structure it -- well,
24 let's see what other people think is fine with us. Is
25 there any comment on that? I don't think it makes a

1 difference whether it's two separate committees or one
2 committee. That's up to you I think. We're just saying we
3 like the idea of having committees that study these areas.
4 (Laughter.)
5 DR. DOULL: But I don't think it should be
6 limited to microbiology because the issue is once you
7 validate a procedure and show that it's more predictive
8 than what we were using before, then that technique or
9 procedure needs to have some ability to be incorporated
10 into the regulatory process. And that's not just for
11 micro; it's for a whole bunch of areas. It's a very
12 important issue. Whether that's a working group or a
13 subcommittee or a committee or whatever, it clearly is, as
14 you said, Bill, an area that needs to be addressed.
15 DR. BYRN: Vince?
16 DR. LEE: Yes, I think I might be repeating
17 what John said, that it looks like that we have on the
18 horizon a number of new technologies, and it seems to me
19 that somewhere, sometime soon that we need to come to grips
20 with what to do with them. In addition to that, we have
21 two specific technologies on the plate. So, it seems to me
22 it is very important for us to take a look at how to deal
23 with new technologies.
24 DR. BARR: I don't know how the structure of
25 this works, but it seems if there are places for outside

1 experts or consultants to be on these committees, that it
2 probably would be worthwhile to have one or two of the
3 members of this committee, at least somebody there that
4 would be sitting in on that that could come back and give
5 us some of the details of the interactions.
6 MS. WINKLE: You're right. Actually every
7 subcommittee has to have two members of the advisory
8 committee as members of the subcommittee. So, you guessed
9 it right. So, that's what we'll plan on doing. Whether we
10 have two different subcommittees or one subcommittee that's
11 going to handle both of these issues, we will actually ask
12 members of this committee to be on that.
13 DR. BYRN: I think this committee could perform
14 a tremendous service if we were involved in dealing with
15 new technologies and how regulatory changes could
16 accommodate those technologies. Maybe we'd have
17 presentations like we've had today and then decisions would
18 be made, it goes to this existing committee or another new
19 committee is set up. Since it's hard to predict new
20 technologies, it may be better just to let everything come
21 to this committee and then a decision be made whether it
22 goes to one of the existing committees or another new
23 committee is formed. But anything like this I think will
24 be tremendous for the industry and the agency.
25 Any other comments?

1 (No response.)
2 DR. BYRN: I think we turned over the issue of
3 the different counts to this committee indirectly. We had
4 some input on that, but I think we deferred that issue,
5 unless somebody else wants to comment. We deferred the
6 issue of the differences in CFU and the other data that are
7 given to this new committee. Is that what everybody
8 understands?
9 Any other questions or comments? Yes, Gloria.
10 DR. ANDERSON: Mr. Chair, it seems to me like
11 there's a fundamental issue here that maybe the committee
12 might want to think about making a recommendation related
13 to, and that is whether or not in fact the FDA, as a matter
14 of policy -- and I don't know enough about FDA to know
15 where this goes. But from what I've heard this afternoon,
16 it seems to me like there's apparently some resistance, for
17 whatever reason, to move into the 21st century with the new
18 technology.
19 I would just like to see us explore the
20 possibility, if it's within whatever it is this committee
21 has to do, to go on record as supporting any explorations
22 of new technology that would improve the regulatory
23 process, to the extent that this committee is empowered, so
24 that we don't limit it to NIR or one particular thing.
25 That would form the basis for any future applications.

1 DR. BYRN: Gloria, I'm just informed that the
2 best mechanism would be to use subcommittees. I don't know
3 whether we need a motion or we can just take this as part
4 of our charge, but I think what Gloria is saying and what
5 everybody is saying is this committee will become involved
6 in new technology development.
7 So, do we think we need a motion or can we just
8 take it as our charge, Helen, just directly?
9 MS. WINKLE: I think you can take it as your
10 charge directly.
11 DR. BYRN: Okay.
12 Any other comments or questions?
13 (No response.)
14 DR. BYRN: Then we'll adjourn until 8:30
15 tomorrow in this room.
16 (Whereupon, at 5:02 p.m., the committee was
17 recessed, to reconvene at 8:30 a.m., Friday, July 20,
18 2001.)
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