FOOD AND DRUG ADMINISTRATION

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

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8:34 a.m.

Thursday, July 19, 2001

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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 committee's
17 input on establishing acceptance limits for microbiological
18 tests that use newly developed technologies. I think this
19 is one of the things we have to grapple with day to day in
20 the FDA, the changing technologies. And as we look at
21 those changes, we have to look at how we're going to change
22 our regulatory processes, or what we need to do differently
23 in our regulatory process to adapt to these changes.
24 Tomorrow the first thing on the agenda is to
25 discuss clinical pharmacology issue on drug transfer into

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

1 time to discuss what direction we're going. However, I
2 want stress the fact that we are definitely interested in
3 the importance of alternative methods for doing
4 bioequivalence, and we're really trying to commit to
5 eliminating or reducing the testing requirements for these
6 products, where possible. We are looking at exploring new
7 alternative methods besides just DPK. So, in November of
8 this year, when the next advisory committee meets, we will
9 bring that topic up again.
10 I know this is a full agenda. I look forward
11 to the committee's discussion and input. I think all of
12 these topics are very important to us in the Office of
13 Pharmaceutical Science, and I know that your input will
14 help us in setting our regulatory direction.
15 Before I end this morning, I do want to
16 recognize that this is Dr. Byrn's last meeting as chairman
17 of this committee. I want to publicly acknowledge how much
18 we in CDER appreciate Dr. Byrn's support and dedication to
19 this committee. He's worked very hard. We've worked with
20 Dr. Byrn in various different settings. He's very
21 dedicated to the whole idea of product quality research and
22 product quality regulation, and we really appreciate all
23 his help. So, I want to publicly announce that FDA really
24 will miss you, Steve. We appreciate everything, and thank
25 you.

1 So, unless there are any questions, I'm going
2 to hand it back to Dr. Byrn. Thank you.
3 DR. BYRN: Thanks very much, Helen. I enjoyed
4 my participation on this committee, even the site-specific
5 stability work.
6 (Laughter.)
7 DR. BYRN: Some of you realize what was
8 involved in that. It was very enjoyable.
9 We're going to move ahead with the
10 subcommittee, and as Helen said, we have two reports of
11 subcommittees. The first one is the Oally Inhaled and
12 Nasal Drug Products Subcommittee, and Dr. Vince Lee will
13 introduce the issues, and then we'll proceed. Thanks very
14 much, Vince.
15 DR. LEE: Thank you, Steve. I didn't realize
16 that this is your last meeting. It could be a long
17 meeting.
18 In any event, I'm here to report to you to set
19 the stage for the presentation to follow. We met about two
20 days ago in this very room to talk about issues concerning
21 the nasal aerosols and nasal sprays. Before I begin, I
22 would like to say that I'm so impressed with how quickly
23 the government got this documentation printed. This was
24 done last evening. Thanks to e-mail, we had the visual
25 material sent here, and then I was impressed to find that

1 it got printed by the government Kinko for us.

2 (Laughter.)

3 DR. LEE: So, the meeting was very interactive.

4 It was meant to last until 5:30 in the afternoon. I'm

5 pleased to report that we finished our business before 4

6 o'clock.

7 The specific issue that we were asked to

8 address was suspension formulations. Helen already talked

9 about that we were there to talk about dose response for

10 these formulations. And the main issue is to see whether

11 or not we can use it as a way to determine the comparable

12 in vivo performance for local delivery. Those of you

13 following the guidance must be aware of the four points

14 above it. You have it and Wally might reiterate it in his

15 presentation.

16 So, by the time we come to this point, we

17 already know the comparability in the actives and

18 inactives, the device, the in vitro performance, and the in

19 vivo performance in regards to systemic exposure.

20 The subcommittee was asked to address two

21 questions, and I highlighted the main points we were asked

22 to consider. The first point was whether or not the

23 placebo-controlled traditional 2-week rhinitis study

24 conducted at the lowest active level would be sufficient to

25 confirm equivalent local delivery of the suspension

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

1 So, this is a very busy slide. It was work of
2 Wally Adams. He asked me to put it up there so that you
3 can all read it to understand the issues. So, the point
4 that we were asked to address that the draft guidance
5 recommends the conduct of a clinical study for allergic
6 rhinitis to confirm equivalent local delivery, and I would
7 like to emphasize that point.
8 So, this is the background for the report this
9 morning, and understand that we have Dr. Meyer and Dr.
10 Chowdhury to teach us so that we can all understand the
11 recommendations of the subcommittee. Wally is going to
12 come up after those two presentations to tell us what the
13 recommendations of the subcommittee were.
14 Thank you.
15 DR. BYRN: Thanks very much, Vince.
16 The next speaker will be Dr. Chowdhury, who
17 will talk about difficulties with showing a dose response
18 with locally acting nasal sprays and aerosols.
19 DR. CHOWDHURY: Good morning.
20 I'll be talking about the point that it is very
21 difficult to show a dose response for locally acting drugs
22 for allergic rhinitis. We had the same discussions in the
23 presentations two days ago. I'll go through the same
24 points again and make the point that for locally acting
25 drugs, which is used for treating allergic rhinitis, it is

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

1 the suspensions.

2 Allergic rhinitis is a pretty common disease.

3 The patients who have allergic rhinitis are sensitized to

4 something in the environment that are called allergens, and

5 when they get exposed to it, they have disease which is

6 typically manifested by a constellation of symptoms, which

7 I'll go through in my second slide as I talk about clinical

8 studies.

9 The clinical studies that are used for looking

10 at these drugs in terms of efficacy for the purpose of

11 approval are of three general types, and they're named as

12 natural exposure study, day-in-the-park study,

13 environmental exposure unit study, or EEU study. I'll go

14 through them one by one.

15 Natural exposure studies are typically done in

16 a season when the patients are exposed to the allergens and

17 are symptomatic. For example, a person who is ragweed

18 sensitive would be studied in ragweed season, which around

19 here is late fall. And the patients for these studies are

20 recruited. They're usually symptomatic, and once

21 recruited, they're taken through a couple of days when they

22 are either given placebo or nothing, to establish the

23 symptoms, and this period is the baseline period.

24 After that, they are put on the drug in

25 question. They are treated for a couple of days, typically

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

1 down they become more pharmacodynamic in nature. For dose
2 response which we're talking about today, typically the
3 natural exposure study and day-in-the-park study are used
4 and we have more experience with. The EEU study is used
5 mostly for questions like pharmacodynamic issues like onset
6 of action, offset of action, and things like that.
7 When I go through my examples, I'll have an
8 example from one day-in-the-park study and the rest will be
9 natural exposure studies.
10 For assessing efficacy, we typically depend on
11 patients' rating of symptoms. They are listed here. The
12 nasal symptoms like itching, sneezing, rhinorrhea, or
13 congestion. Or they can be non-nasal symptoms. As I go
14 through the examples, this will become more clear.
15 The symptoms are more typically scored by the
16 patient and there are various scales used. The one that we
17 use now are typically 0, 1, 2 and 3 scales. However, other
18 scales can be used, as my examples will show.
19 Now, in addition, there are often other
20 measures which potentially may be used. I say potentially
21 because these are more experimental and they are used
22 mainly to study disease pathology or pathogenesis. For
23 example, objective measure like nasal passage patency are
24 markers of inflammation. The point I want to make is,
25 these are very interesting tools. However, they are not

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

1 were used, which will become clear in the next
2 transparency. Drugs were given on a b.i.d. schedule.
3 Since the patients were in the park for 2 days, on the
4 first day they got a drug in the morning, in the afternoon,
5 and the next day they got it again in the morning.
6 Efficacy was instantaneous scoring.
7 Instantaneous means the patients scored the symptoms at the
8 time they were scoring. For example, how do I feel right
9 now? And the six symptoms which were scored are listed
10 here, some nasal symptoms, some eye symptoms. And the
11 scale here was 0 to 5. On the days when the patients were
12 in the park, which was day 1 and day 2, early in the
13 morning, they scored the symptoms very frequently, and then
14 in the evening less frequently. All the scores were summed
15 up and the result that I am going to show will be as major
16 symptoms complex, which is a summation of all the scores.
17 Now, this is the baseline. Throughout my trial
18 presentation, the same format of graphs will be used, the
19 bar graphs, and the bars from left to right will match with
20 the legend from top to bottom. Placebo will be on the left
21 all the time and blue in color.
22 In this study, the three dose levels were one
23 spray b.i.d., two sprays q.d., and two sprays b.i.d. It's
24 a pretty large study with about 50 patients. And the
25 baseline is here, which is pretty close but not exactly the

1 same.

2 Now, this is the result of the study, and I'm

3 expressing the result as mean percentage change from

4 baseline to take care of the baseline differences. We note

5 here the placebo response was about 10 percent. The study

6 had an active control, which is an antihistamine,

7 chlorpheniramine, and the effect size here was about 40

8 percent. So, the difference was about 30 percent here in

9 this study. And if you look at the result, this is the

10 lowest dose, one spray b.i.d., and this is two sprays

11 b.i.d., so this is two-fold higher. This is one spray

12 b.i.d., and this is two-fold higher.

13 If you look at it, perhaps there is a trend of

14 dose response. However, if you look between these two,

15 this is two sprays q.d., and this is two sprays b.i.d..

16 This is higher than this, and the effect goes in the

17 opposite direction. So, the point here is, you don't

18 really see a dose response. It's almost like a random

19 phenomenon. This will become more clear as I go through my

20 other examples.

21 A second example will be the suspension nasal

22 spray, and the first one will be a natural exposure study.

23 This study was conducted in the U.S. a couple of years ago.

24 It was again a natural exposure study, the first one which

25 I talked about. It was conducted in ragweed sensitive

1 seasonal allergic rhinitis patients, ages 6 and above. The
2 study had a 1-week baseline where no drug was given,
3 followed by 4 weeks of treatment in which the experimental
4 drug was given. The treatment was q.d. dosing of four dose
5 levels, and note here the doses were over an eight-fold
6 range. The previous example was just a two-fold range.
7 The efficacy assessment here was 12-hour
8 reflective. The reflective is different than the
9 instantaneous which I said earlier. Reflective means the
10 patients scored their symptoms noting how they feel over
11 the previous 12 hours or so. The symptoms scored here were
12 three nasal symptoms: runny nose, congestion, sneezing.
13 The scale was the typical 0 to 3 scale. The sum of the
14 three scores was used, and we just called it a nasal index
15 score.
16 This is the result. Nasal index score. This
17 is the baseline, treatment, and this is the change, which
18 means the difference between this and this. The baseline
19 here is very similar, so I'm using the raw score. And if
20 you look at the change here, this is the placebo, and the
21 placebo actually had some response, quite a bit of
22 response. And this will come back later on also that for
23 allergic rhinitis, placebo indeed is almost a drug, has
24 some good response.
25 And the dose levels used here were between 32

1 and 256. There's an eight-fold difference, and these are
2 the four bars showing the four dose ranges. The point here
3 is virtually flat. The lowest, 32, and the highest, 256,
4 were very close. So, essentially it cannot really make a
5 difference in the clinical study with this example over an
6 eight-fold range.
7 This study had three symptoms. Just to look at
8 it a bit further, I looked through if these three symptoms
9 looked individually would make any difference or not. And
10 if you look through it, it really did not. Perhaps for
11 congestion there was some trend. However, they were almost
12 flat, and the changes were really, really very small.
13 The next example, in the same study a spray and
14 aerosol was used. The drug substance, drug B, was the
15 same. It was a natural exposure study. It was a Canadian
16 study done in seven centers in 1994. Patients were
17 ragweed-sensitive, seasonal allergic rhinitis patients,
18 ages 12 and above. The design was very similar: 1 week
19 baseline, 3 weeks of treatment, and the dosing was q.d. of
20 three dose levels.
21 Efficacy assessment was the same again:
22 12-hour reflective of three nasal symptoms. And these are
23 the results here. This is the primary efficacy endpoint in
24 this study, which was the nasal symptoms. This is a
25 summation of the scores of rhinorrhea, sneezing, and

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

1 studies before, 12-hour reflective. And eight symptoms
2 were measured here, some nasal and some eye symptoms. They
3 were scored on a 0 to 6 scale.
4 In this particular study, the primary endpoint
5 was on physician-rated symptoms, so that's what I'm showing
6 first. And I'm showing the results over the whole study
7 time period, day 3, day 7, 14, 21, and 28. All the times
8 can be used. I'll just use day 21 to make my point here.
9 The placebo response here as a change from
10 baseline percentage was close to 30 percent. The drug
11 response was 50 to 60 percent, so the separation between
12 drug and placebo was not that large. If you look at it,
13 there was perhaps a dose response, at least numerically
14 trending. However, the separation here between the lowest
15 and the highest, a 16-fold difference, is really less than
16 10 percentage points. Very tiny area to work with.
17 If we look at other times, like day 14, day 28,
18 it really doesn't hold true. Indeed, on day 28 the lowest
19 and the highest dose, 16-fold apart, you really could not
20 pick up a difference between these two.
21 Now, typically we use a patient-rated score in
22 this study which was also done, so we looked at that to see
23 if that would be different. The result is here, and the
24 answer is really no. On day 21, the symptoms that the
25 patients rated were very similar to what the physicians

1 rated.

2 The last example is again the same drug

3 substance. It was one study where aerosol and spray

4 suspensions were used. The study was conducted in 32

5 centers in the U.S. two years ago. It was conducted on

6 seasonal allergic rhinitis patients, ages 12 and above.

7 There was 1-week baseline period followed by 2 weeks of

8 treatment, and the dosing was three dose levels from two

9 devices and over 8-fold range. Again, a pretty large

10 separation.

11 Efficacy was 12-hour reflective of four nasal

12 symptoms, scored on a 0 to 3 scale, and the sum was nasal

13 symptom score.

14 The result is here. The first bar here is the

15 placebo, and the second, third, and fourth bar are with

16 aerosol, and the last three are with the spray. This is

17 mean percentage change from baseline. First week, second

18 week, total, which is week 1 and 2.

19 If you look at it here, again for this drug

20 there is some trend of a dose response at least

21 numerically, but again, we are within 5 percentage points

22 or less. So, a very small difference between the lowest

23 and the highest dose, quite a bit of separation within the

24 two doses.

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

1 very good example here perhaps, the lowest and the highest,
2 you cannot really pick up a difference. If you look at
3 week 2, they're almost flat.
4 So, the point that I made here with all the
5 seasonal allergic rhinitis studies, because typically those
6 were studies that are used for showing dose response, if
7 you look at patients who had perennial allergic rhinitis,
8 the same would hold true.
9 The question comes up, we do not really see a
10 dose response, which is very clear based on the examples,
11 and why we did not see a dose response. Perhaps the
12 clinical studies that we used for looking at efficacy,
13 which is the typical outpatient kind of study, are
14 sensitive enough to pick up a separation from drug and
15 placebo, however, are not discriminative enough perhaps to
16 pick up a dose response, if it existed. They are pretty
17 crude measures. Unfortunately, that's what we have.
18 The second point may be that perhaps for some
19 of these drugs which are already approved, they may already
20 be at the high end of the dose-response curve, so a large
21 separation of dose would not really mean any differences as
22 far as efficacy is concerned.
23 So, that's all I have. If there are any
24 questions.
25 DR. BYRN: Questions for Dr. Chowdhury? Yes,

1 Bill?

2 DR. JUSKO: William Jusko. I think another

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

4 the patients being studied in many of these studies,

5 particularly the first one, did not present with very

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

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

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

9 patients being studied only have very modest disease

10 symptoms.

11 DR. CHOWDHURY: That is true for the first

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

13 patients who are more symptomatic were recruited, and some

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

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

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

17 start off being symptomatic.

18 However, again we're talking about a large

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

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

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

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

23 doesn't really happen.

24 DR. BYRN: Yes, Marvin?

25 DR. MARVIN MEYER: You didn't really mention

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

1 well, a little artificial in that the selection process and
2 the monitoring, et cetera, as opposed to the real world
3 person?
4 DR. CHOWDHURY: The clinical trials try to
5 mimic the real world as much as possible, but again, the
6 study itself is an artificial setting, but as close to the
7 real world, which is a natural exposure study, is better we
8 have a handle of the drug itself and the disease itself.
9 DR. BARR: Did you do repeated measures that
10 would give you an estimate of the intra-subject variability
11 that you're dealing with? Do you have some estimate of
12 that?
13 DR. CHOWDHURY: Not in these presentations, but
14 again, the intra-subject variability is indeed high. I
15 cannot really give numbers right here, but again, the
16 patients who are symptomatic to begin with may change over
17 the time, yes.
18 DR. BARR: What was also surprising is that you
19 are at the top of the dose response curve, that platform
20 for compounds that have different modes of action, which is
21 kind of surprising that you were successful in getting to
22 that upper level in all cases, and it may indicate perhaps
23 more a lack of methodology rather than the drug effect
24 itself.
25 DR. CHOWDHURY: Perhaps true because these are

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

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

1 suspension products.

2 DR. ROBERT MEYER: Thank you very much. Just

3 let me follow up on that last point because I think the

4 belief that we've had, and I think to some degree continue

5 to have, is that although it may be very difficult to show

6 dose response in these studies, clinically there has been a

7 practice and a rationale for having a range of doses

8 available and titrating patients up who would fail to

9 respond to lower doses, as long as the safety profile

10 assures us that those doses are safe. Whether that's been

11 scientifically established or not, that's the rationale.

12 What I'd like to do actually then today is take

13 you through a bit of the presentation that I gave the

14 subcommittee, but I do want to pause on the first slide

15 here to really just recap how we came to have this

16 subcommittee discussion, and how we actually came to have

17 what we had in the draft guidance, which was a

18 recommendation for any one of three potential study

19 designs, with a requirement to show a dose response within

20 those study designs.

21 Back in about 1995, the Division of Pulmonary

22 Drug Products at the time -- the "allergy" has been added

23 since I became director two years ago, but the Division of

24 Pulmonary Drug Products had advised the Office of Generic

25 Drugs that we felt that clinical study really wouldn't be

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

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

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

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

1 pharmacodynamic-type assessments.

2 Other objective endpoints in any of the study

3 designs really, if you will, more true pharmacodynamic

4 endpoints, such as nasal patency through acoustic

5 rhinometry or other measures of air flow or specific

6 markers of inflammation in the nasal mucosa or nasal

7 secretions are regarded as interesting, but they are not

8 clinically validated. I would also point out that they're

9 not really validated as a reliable detector of dose

10 response.

11 Let me just take a slide that Dr. Conner showed

12 the other day, just to remind us why we're focusing on this

13 issue of the clinical study at all for talking about the

14 question that we're taking to it. It really stems from the

15 fact that for a topically acting drug, a nasal suspension

16 or a nasal spray, the therapeutic effect is coming from

17 local delivery and local activity and is not predicted

18 through assessment of pharmacokinetics, although there

19 could be a small contribution of any drug that gets to the

20 blood, either through local absorption or through systemic

21 absorption from the GI tract or any that might come through

22 the lung. There may be contribution to the therapeutic

23 effect, right over here, but in general most of the

24 therapeutic effect comes from the local delivery.

25 On the other hand, the assessment of what gets

1 into the blood, only some of this is coming through nasal
2 absorption, and even for drugs of fairly low
3 bioavailability through the GI tract, if they have low
4 bioavailability through the nasal mucosa, a substantial
5 portion of what does get into the blood will be coming
6 through these other routes, primarily the GI tract.
7 So, to fully get a handle on the therapeutic
8 effect and for bioequivalence, if one really places a lot
9 of concern over any differences in local delivery, one
10 needs to assess more than just the pharmacokinetics. One
11 needs to get some kind of handle on the clinical or
12 pharmacodynamic measurements to accurately reflect the
13 local bioavailability.
14 So, the question as I framed this the other day
15 for the subcommittee is what are we really asking the
16 clinical study to do in the bioequivalence package for a
17 nasal suspension spray. I need to emphasize that I don't
18 want to use these in the regulatory term sense, but just
19 using these in a more casual sense. Are we regarding the
20 clinical study as necessary, but playing a confirmatory
21 role, or are we really looking for it to primarily
22 establish the bioequivalence? That really depends on your
23 interpretation of the unknowns left after you've done a
24 full in vitro assessment and, again, you have Q1 and Q2
25 sameness for the two products and, in fact, your

1 pharmacokinetic assessments as well.

2 For a more confirmatory role, the study would

3 then be necessary to really confirm that given the unknowns

4 that might remain after you've shown sameness in a fairly

5 rigorous in vitro package in pharmacokinetics and Q1 and Q2

6 sameness, that the unknowns left there just require the

7 clinical study to confirm a lack of important clinical

8 differences as a part of this larger bioequivalence

9 package. In a more pivotal sense, then, if you're asking

10 the study to establish the bioequivalence in and of itself,

11 the clinical study would really need to be able to discern

12 differences in dose in quite a sensitive manner, and then

13 to show that no differences exist between the test and

14 reference product.

15 So, again, in a more confirmatory, necessary

16 but confirmatory role, the design would be to broadly

17 assure that no important clinical differences exist. A

18 rigorous showing of dose response and strict equivalence

19 over the dose response between test and reference is not

20 required. The comparison therefore could be on one dose

21 level, such as the lowest dose level, to assure that you're

22 not on any kind of downslope of a curve, for each of the

23 test and reference to show comparable efficacy, safety, and

24 tolerability.

25 If you really look to the study to fully

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

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

1 impossible, through pharmacodynamic equivalence to things
2 like HPA axis assessment for corticosteroids, for instance.
3 So, the main uncertainty left at the point for
4 nasal suspension products that we're talking about is what
5 contribution any differences in particle sizing in the
6 formulation itself might present in terms of clinical
7 efficacy, given everything else being the same. Clearly
8 that's an issue, as I hope I've already conveyed, for the
9 aqueous suspension sprays, and it's more difficult in fact
10 for these sprays than the aerosols perhaps, but even for
11 the aerosols, the MDIs, we don't have a proven, validated
12 way to particle size in the way we do for the orally
13 inhaled, for instance.
14 Given all the difficulties of establishing dose
15 response, but also given a real rethinking of what
16 questions are left at the point that we're discussing or
17 coming to a clinical trial, the FDA presented to the
18 subcommittee that fact that we're now contemplating
19 shifting the question that we're asking of that study in
20 the bioequivalence package. I must emphasize no matter
21 what, however, the clinical study would not trump a lack of
22 equivalence from the prior data set. So, it would have to
23 be Q1/Q2 the same, they would have to be equivalent in the
24 in vitro characteristics, and all the attributes tested, as
25 well as systemic bioavailability.

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

1 Is that correct?

2 DR. ROBERT MEYER: Well, we certainly want the

3 particle sizing of the micronized drug substance

4 characterized and expect that to be done. There is the

5 question that you have, but also the challenge for a

6 generic drug manufacturer, be it that no matter how well

7 they characterize their micronization process, they don't

8 have access to the data of the innovator or the reference

9 product to match that.

10 DR. BOEHLERT: I would agree that that's the

11 case, but the agency, when they review those submissions,

12 would be able to evaluate whether or not they have a

13 meaningful test for particle size.

14 DR. ROBERT MEYER: Oh, absolutely. Absolutely.

15 But I think within certain bounds we also have some

16 uncertainty to what small differences in the micronization

17 in the drug substance might mean in the drug product, so

18 it's both that uncertainty for the innovator and, to some

19 degree, for us, but then any change in the attributes of

20 the particle sizing within the drug formulation would also

21 come into play.

22 DR. BARR: It seems to me that the basic

23 problem is just the inadequate bioassay that we have

24 available to us. The global assessment is extremely

25 insensitive to the point where we can't measure any changes

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

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

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

1 5 percent.

2 That the device should be comparable, either
3 the same device meaning the same metering valve and pump,
4 or one made preferably by the same manufacturer and the
5 same model. If that's not possible, then as close as that
6 can be obtained.

7 In vitro studies and systemic exposure or
8 systemic absorption. The in vitro studies, however, do not
9 assure equivalence of particle size of the suspended drug.
10 Because particle size differences between test and
11 reference products have the potential to alter the rate and
12 extent of delivery of drug to local sites of action, then
13 those differences in clinical effectiveness could result.
14 For this reason, the draft guidance also recommends conduct
15 of a clinical study for allergic rhinitis to confirm
16 equivalent local delivery.

17 Now, what I'd like to do is to skip to a slide
18 that originally I had presented at the subcommittee meeting
19 and I think it is appropriate to present that here. It's
20 not in the packet because I originally wasn't going to
21 present it, but I think it's essential. It's a nice way of
22 explaining what our predicament is.

23 We've indicated that the package of information
24 for bioequivalence for solution and suspension nasal sprays
25 and nasal aerosols is a substantial package, and it's built

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

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

1 this region of the curve with present available
2 methodology. So, we believe that we're up in this region
3 of the curve where the dose response is insensitive.
4 But if we were to conduct a rhinitis study and
5 show that the test and reference products are both equally
6 efficacious, we know then that even at a single dose, that
7 the products would both be working. They'd both be
8 relieving the rhinitis symptoms as long as they're both up
9 here. They would show equivalence. In spite of the fact
10 that a different amount of drug may be getting to the
11 active sites, they would still be showing equivalence.
12 The other concern is that the drug, because of
13 potential differences in particle size distribution, could
14 be delivering different amounts of drug to the systemic
15 circulation, and they could put the test and reference
16 products down here in the region where they may differ on
17 the pharmacodynamic or clinical dose-response curve for
18 safety or for, let's say, adrenal axis suppression. They
19 could differ.
20 Well, we can control that by use of a
21 pharmacokinetic study to show equivalence. Of course, for
22 some of these products in which there's very little drug
23 that reaches the systemic circulation, it may be necessary
24 to do the pharmacodynamic study instead.
25 So, what we would know, then, from this package

1 of information is that the same amount of drug is delivered
2 from the product. The products are equally efficacious,
3 and that they have equivalent systemic exposure or systemic
4 absorption. So, essentially that is the package of
5 information that would be used for these products.
6 Now, to go back to the two questions, does the
7 committee believe that a placebo-controlled traditional 2-
8 week rhinitis study conducted at the lowest active dose is
9 sufficient to confirm equivalent local delivery of these
10 products, and two, does the committee believe that a
11 placebo-controlled park study or EEU study conducted at the
12 lowest active dose is an acceptable option to confirm
13 equivalent local delivery?
14 As we've indicated, two days ago we held a
15 subcommittee meeting to discuss these issues and what I'd
16 like to do is, with four slides, present the outcome of
17 those deliberations. What I'll do is to indicate a summary
18 statement, and then I'd like to try and capture some of the
19 thoughts that were expressed during the meeting on that
20 particular issue.
21 The first conclusion is that based on current
22 technology and methods, demonstration of dose response may
23 not be possible for locally acting drug products for
24 allergic rhinitis. Some of the comments that were made
25 were the limitations of the current study design cannot be

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

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

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

1 That would be the only benefit of doing this study.

2 And lastly, of the three study designs in the

3 draft guidance, the traditional placebo-controlled 2-week

4 rhinitis study is the most appropriate. That is saying

5 that the park study and the EEU study, as pharmacodynamic

6 studies rather than clinical studies, the committee felt

7 were not appropriate, at least at the present time, for the

8 needs for establishing bioequivalence.

9 And a single dose level of test and reference

10 products should be used at the lowest labeled dose. And

11 some of the comments which were made were that an EEU or a

12 park study were not clinically meaningful since there's

13 only 1 to 3 days of exposure of the subjects to this drug,

14 and in fact for full efficacy to take place for the nasal

15 corticosteroids, it can take 2 weeks or even longer to

16 establish that efficacy. So, therefore the traditional 2-

17 week study design is the appropriate one for establishing

18 equivalent efficacy.

19 It said that pharmacodynamic endpoints are not

20 suitable at the present time. We don't know that the onset

21 of action in fact, which can be measured from the EEU and

22 the park studies, is more discriminatory, more sensitive to

23 differences between products than the traditional 2-week

24 study.

25 And the question comes up about should the

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

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

1 Should other classes of drugs, antihistamines,
2 anticholinergic drugs or cromones be developed as
3 suspension products, then the same issues would apply here
4 with regard to the need for a clinical study and a PK
5 study.
6 DR. JUSKO: I'm not really sure that drugs with
7 other mechanisms might require, as indicated, the lengthy
8 period for full onset of effects. That's sort of what my
9 concern is. If they did not require the full 2 weeks for a
10 good effect, then these other test procedures, 1- or 2-day
11 pharmacodynamic assessments, could become highly relevant.
12 DR. ADAMS: I would agree with that. We would
13 deal with that on a drug class basis and work with the
14 Pulmonary Division in terms of the study designs.
15 DR. BYRN: Judy?
16 DR. BOEHLERT: I have a question I guess with
17 your use of terminology. By using the term "equivalent
18 local delivery," are we implying more than you can deliver
19 because you might get equivalent local action or activity
20 or efficacy, but indeed may not have equivalent local
21 delivery because you don't have the same dose-response
22 relationship that you might want. I think I'm being
23 confusing, but if you don't have dose response, then you
24 may not have equivalent delivery of the drug, but you might
25 have equivalent activity.

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

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

1 present at the present time.

2 DR. BYRN: Is the problem in particle size that

3 there are carriers in the suspension that the active is

4 bound to? Is that the problem?

5 DR. ROBERT MEYER: The problem really gets down

6 to there are things like methyl cellulose in these

7 suspensions that in fact are present at pretty high

8 proportions compared to the active drug, which are

9 generally in fairly low concentration. So, it is a matter

10 of interference, I think, as much as any binding --

11 DR. BYRN: But if there were fractionation

12 methods or other approaches developed, there may be ways to

13 do it. As a person that's involved in analysis, I hate to

14 hear somebody say there is no method available. It makes

15 me interested.

16 DR. ROBERT MEYER: I do want to stress the no

17 current method.

18 DR. BYRN: Right.

19 DR. BARR: An alternative approach would be

20 possibly to go into some dissolution because the problem,

21 of course, with the particle size alone is that you have

22 all the other factors that may affect the overall release

23 of drug. So, ultimately there may be some dissolution

24 procedure.

25 DR. ADAMS: That's right. Dissolution is

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

1 well, go ahead and elaborate.

2 DR. JUSKO: I like the phraseology that Dr.
3 Meyer used that this type of test, while it may be
4 advisable to do for reassurance purposes, it in no way
5 provides any confirmation of bioequivalence or clinical
6 equivalence.

7 DR. BYRN: Okay. I guess we're talking about
8 writing a guidance which would use a number of methods.
9 Maybe Dr. Adams can explain what would be in the guidance.
10 I guess this method by itself would not be in the guidance.
11 Is that right?

12 DR. ADAMS: Yes. As Dr. Meyer indicated in his
13 slide, there's a package of information with the
14 formulation/device recommendations and the PK and the
15 rhinitis studies. Furthermore, an acceptable equivalence
16 shown on the rhinitis study does not trump the in vitro
17 data. The in vitro data must show equivalence. We would
18 in no way ask just for the rhinitis study without the other
19 information.

20 DR. BYRN: Does that clarify that, Bill? So,
21 we're talking about a guidance that would have a number of
22 components, including the 2-week study, but the issue is,
23 do we agree that the 2-week study should be included with
24 those components? I guess the choices are more clinical
25 studies or no clinical studies.

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

1 distribution method becomes available, the issue would have
2 to go back to our internal technical committee to discuss
3 whether we would be happy with scientifically feeling that
4 the in vitro data alone would support equivalence. That's
5 a separate issue, should a validated particle size
6 distribution method become available.
7 DR. VENITZ: So, right now if the in vitro
8 package and the PK package and the clinical package all
9 demonstrate bioequivalence, that product is approvable?
10 DR. ADAMS: Yes, it is.
11 DR. VENITZ: If the in vitro package or the PK
12 package show bioinequivalence, regardless of the clinical
13 study, that is not approvable?
14 DR. ADAMS: That's correct.
15 DR. VENITZ: If we had a test for particle
16 sizing, and that was a validated test, and the in vitro
17 package, the particle size package, and the PK package show
18 bioequivalence, a clinical study would still be required?
19 DR. ADAMS: Until we take the issue to the
20 OINDP technical committee and obtain agreement from within
21 the committee and at higher levels of management that that
22 is acceptable to not ask for the rhinitis study.
23 There are various routes you could take. For
24 instance, it might be that a PK study and no rhinitis study
25 might be appropriate as well. So, we would have to discuss

1 what the various options are. That decision has not been
2 made at the present time.
3 DR. VENITZ: Okay.
4 DR. BYRN: Any other comments?
5 (No response.)
6 DR. BYRN: I think we have consensus on topic
7 one.
8 Shall we go to topic two now? Topic two really
9 relates, I think, to the fact that there is not confidence
10 in -- would you summarize what you think topic two relates
11 to, Dr. Adams?
12 DR. ADAMS: I'd be happy to.
13 DR. ROBERT MEYER: I think the upshot of this
14 is that we really brought in some ways two questions to the
15 committee that are somewhat split out. One of them is a
16 bit in the way they were phrased to the committee, and
17 perhaps a bit covert, or not explicit. That is, should a
18 clinical study be done at a single dose, and if so, should
19 it be sort of a traditional clinical study, or are there
20 reasons to allow for or prefer an EEU study or day-in-the-
21 park study, given the question that's being put to that in
22 the clinical study?
23 DR. BYRN: And you're recommending neither an
24 EEU or a day-in-the-park study would be acceptable. Right?
25 DR. ROBERT MEYER: Yes. There was a consensus

1 coming out of the subcommittee that if a study were to be
2 done -- and again, there was not full consensus on the
3 requirement for that -- that it should be the more
4 naturalistic 2-week study at the lowest labeled dose.
5 DR. BYRN: Now, we've already said a study
6 should be done. The whole committee has reached consensus
7 on that.
8 DR. ROBERT MEYER: Right, and in fact, as long
9 as everybody understands this as being explicit rather than
10 implicit, if you've reached consensus on topic one, you may
11 have already reached consensus that topic two is --
12 DR. BYRN: We may have, but I think we should
13 discuss. So, what we're saying now in topic two is saying
14 we're going to do a study. It's going to be 2 weeks.
15 Under this category we were just discussing, we're not
16 going to recommend, at least at this time, a placebo-
17 controlled in-the-park study or an EEU study. We recommend
18 a 2-week study.
19 So, let's have some discussion. Does anybody
20 have a problem with that? Again, this is recommended by
21 the committee.
22 DR. MARVIN MEYER: Just a quick question.
23 Which are the pivotal studies in the NDA review? The
24 natural study?
25 DR. ROBERT MEYER: Yes.

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

1 might need to take that back. But I think it would have to
2 be a change in the universe as it is for these drugs right
3 now.
4 DR. BYRN: Is that okay with you, Dr. Jusko?
5 DR. JUSKO: In part, but I find that first
6 study to be the most flawed, with the baseline being so
7 weak that it would be impossible in that type of study to
8 see real efficacy when you're looking for an improvement
9 from a possible range of 30, when the baseline starts at 10
10 and you look for a score to drop below 10. It's just
11 awfully difficult to see changes.
12 DR. ROBERT MEYER: I guess my point is that if
13 we just simply saw, say, for whatever reason, a suspension
14 antihistamine nasal spray come along and no data from the
15 NDA that we should view that differently in terms of the
16 sensitivity or discriminatory ability of these studies,
17 then I don't think we'd need to rethink the guidance. I
18 think there are a number of things that could change that
19 would lead us to come back to you folks, and we might be
20 talking about new methods of assessing drugs with an
21 ability to better discriminate between doses. It might
22 mean being able to particle size within the suspension.
23 There are things that could change that, and we understand
24 what you're saying but we did write this to be general for
25 what we know now about these drugs.

1 DR. BYRN: So, I think we're reaching consensus
2 on topic two, that we would require a 2-week placebo-
3 controlled study.
4 Go ahead, Wallace.
5 DR. ADAMS: Dr. Byrn, I just wanted to
6 supplement what Bob said. If there were another drug,
7 let's say a suspension antihistamine, to come along, we
8 would intend to use the present paradigm in this guidance
9 for that drug, in terms of what is the universe of drugs
10 that we're talking about here. So, the present paradigm
11 would apply not only to corticosteroids but it would apply
12 to other products, should they be available as suspensions.
13 Yes, we'd have to change some aspects of it in
14 terms of the systemic absorption study. But the basic
15 paradigm would be the PK study and a clinical study
16 conducted for multiple weeks I would presume, a rhinitis
17 study conducted for multiple weeks.
18 DR. MARVIN MEYER: Maybe this relates more to
19 how a guidance works. The draft guidance says the guidance
20 covers studies of prescription corticosteroids,
21 antihistamines, and anticholinergic products. So, if one
22 includes what we are talking about in the framework of that
23 draft guidance, one would assume then that the
24 anticholinergics and antihistamines also require a 2-week
25 natural exposure study, without some specific statement of

1 categorization of the drugs, in line with what Bill's
2 concerns are.
3 DR. ROBERT MEYER: Yes, I think we note the
4 concern is the best way to put it at this point. We'll
5 consider that in the redraft.
6 DR. BYRN: Yes, I think it's appropriate that
7 it's just been noted because the agency would, I'm sure,
8 not apply a guidance unless it was appropriate, unless it
9 had been shown to be appropriate in a submission. So,
10 because it is still just a guidance, if it's not
11 appropriate, some action will be taken.
12 Yes, John.
13 DR. DOULL: I think it might be useful in doing
14 this guidance that the language that says lowest active
15 dose would be a little more precise. Lowest active.
16 You're talking clinical dose. In the dose response slide
17 that you gave, you have a toxicity dose response and you
18 have an efficacy dose response. So, you need to tell us
19 which dose in fact you're looking at. In that case you're
20 looking at --
21 DR. ROBERT MEYER: Yes, it will. And in fact,
22 the subcommittee recommended it be the lowest labeled dose.
23 We, I think somewhat purposely, chose a vague term there
24 because it wasn't clear to us. There are various ways to
25 define the lowest dose. There's the lowest feasible dose,

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

1 DR. BYRN: Opposed?

2 (No response.)

3 DR. ADAMS: Can we have a show of hands on that

4 so we can get a count?

5 DR. BYRN: Okay, all in favor? And I guess

6 we're only voting, official members. I'm not sure who that

7 is.

8 (Laughter.)

9 DR. BYRN: Raise your hand.

10 (A show of hands.)

11 DR. BYRN: Is that 10, Nancy? Eleven? Eleven

12 in favor and none opposed.

13 DR. ADAMS: Eleven to zero then?

14 DR. BYRN: Eleven to zero.

15 And then the second topic, the committee agrees

16 with the OINDP Subcommittee regarding its recommendations

17 that the local study be based on the lowest active dose. I

18 guess that really covers it, doesn't it? Do you want a

19 specific consensus against a day-in-the-park and an EEU, or

20 does that cover it?

21 DR. ROBERT MEYER: I think if the committee's

22 comfortable with the 1 precluding 1, then --

23 DR. BYRN: The way it says it, a traditional 2-

24 week placebo-controlled, I think it covers it.

25 DR. BARR: I would just like to ask a question,

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

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

1 committee would agree with the OINDP Subcommittee
2 recommendation that a day-in-the-park study and an EEU
3 study would not be sufficient. I guess we can just say
4 that. Would not be an option, and maybe that's a better
5 term.
6 Is there any discussion of that, any further
7 discussion?
8 (No response.)
9 DR. BYRN: All in favor, please raise your
10 right or left hand.
11 (A show of hands.)
12 DR. BYRN: Ten in favor.
13 Opposed?
14 (A show of hands.)
15 DR. BYRN: One opposed. So, that is also a
16 consensus.
17 Any other discussion?
18 (No response.)
19 DR. BYRN: Let's take a break. We're running
20 about 10 minutes behind. Let's cut five minutes off the
21 break, if we could. So, we'll come back here at 10:50.
22 (Recess.)
23 DR. BYRN: I think we'll get started. We have
24 three new members up here at the table, but we won't
25 introduce you, if you don't mind, until you're actually

1 speaking because some additional members from the CMC group
2 are coming. So, we'll go ahead and go to the Nonclinical
3 Studis Subcommittee report, and John Doull will introduce
4 the issues.
5 DR. DOULL: Well, I've been asked to introduce
6 this issue. I'll be brief because I know we're all anxious
7 to hear the reports of the working groups.
8 Those of you that have been on this committee
9 for a while will probably recall that our subcommittee, the
10 Nonclinical Studies Subcommittee, was created about two
11 years ago. The charge for this committee was to evaluate
12 the use of nonclinical studies in the development of drugs.
13 In developing the charge to the committee, we really have
14 pushed this a little and we're now more focused on the use
15 of biomarkers to identify both the effects of drugs and
16 also particularly to identify adverse effects, toxicity.
17 We had a second charge, and that second charge
18 was to link nonclinical studies that could be also used in
19 the clinical evaluation of drugs. So, those were our
20 scientific objectives.
21 We were also asked to facilitate the
22 interaction of our subcommittee and Food and Drug with
23 industry, with academia, with other public groups, and
24 we've tried to do that. Yesterday Helen called that
25 leveraging, and I thought about that last night. I'm not

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

1 working group at the present time.

2 Now, the third area that we talked about is the

3 one Dr. Collins talked about yesterday. He talked about

4 the need for biomarkers for liver injury, for cardiac

5 injury, and for vascular injury. We felt that there are a

6 lot of groups that are collaborative groups that are

7 looking at liver injury and that it would be more

8 profitable for our subcommittee to focus more on cardiac

9 toxicity, biomarkers for cardiac effects, and biomarkers

10 for vasculitis. And those are in fact the two committees

11 which we agreed on.

12 We did that last year. By the fall we had sent

13 out notices to the Federal Register, to scientific

14 societies. We asked Food and Drug for suggestions. We

15 asked our members for suggestions, and we got a slew of

16 them. We sorted through all those, and in January we put

17 together two panels, one for cardiac toxicity and the other

18 for vasculitis. I thought, well, gee, we got that all done

19 in January. Perhaps we can meet shortly and start this

20 process. It took an immense amount of effort, and Jim

21 MacGregor really worked long and hard to get through that

22 process. We're learning, and one of the things we've

23 learned is it takes a long time to get these working groups

24 established.

25 But they are now established, and as you can

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

1 introduction. I'm here as a representative of my
2 committee, and this is still work in progress. We have met
3 only one time, and I'm here to provide just an update, a
4 report of what we have done to date.
5 Our committee is composed of members that
6 represent approximately 50 percent from industry and 50
7 percent from academia and the regulatory side. David
8 Essayan is our liaison from the agency representing CBER,
9 and myself and Lester Schwartz are co-chairs of the
10 committee.
11 Following the introduction from Dr. Doull and
12 Dr. MacGregor, we met the first time on May 3-4 of this
13 year, and we tried to interpret our charge, as we
14 understood it. Following that meeting, we understand our
15 charge the following way.
16 One, to first develop a common understanding of
17 exactly what the problem is that we're here to resolve. As
18 you noted from the previous slide, our membership is
19 composed of a wide variety of disciplines, clinical
20 toxicologists, pathologists, pharmacologists,
21 immunologists, and so on. It was clear from our first
22 meeting, within the first hour, that we all did not clearly
23 understand the issue that we were there to discuss, and we
24 did spend a lot of time on the first day trying to zero-
25 base the discussion so that we all understood what we were

1 talking about.

2 The primary reason for that is the term

3 "vasculitis" is confusing to many, especially clinicians.

4 When clinicians think of vasculitis, they usually think of

5 hypersensitivity, drug-induced vasculitis. That is not

6 what we were here to describe within this committee. It's

7 something quite different. So, having clinicians on our

8 team is, A, very important but, B, created some

9 communication problems early on that we had to sort out.

10 Second, we were asked by Dr. Doull to address

11 the criticality of the issue and understand whether or not

12 this was a question that needed to be answered, and that's

13 item 2.

14 And if so, develop an initial list of

15 biomarkers that we might pursue.

16 And following that, then, in the second day we

17 surfaced three or four other issues that will become very

18 important for us to resolve as we move forward.

19 In the process of developing new biomarkers and

20 new assays, the opportunity for intellectual property

21 development is tremendous, and this will become an issue

22 within the committee that we have to deal with as we move

23 forward.

24 Secondly, funding issues are critically

25 important in the research that needs to be done to discover

1 and develop the assays and validate them in the next slide,
2 validate them to the point where they become acceptable as
3 decision making tests within Pharma, as well as within
4 agencies around the world.
5 And lastly, resolving issues of
6 confidentiality, both within the membership and between the
7 membership and the agency. And this is an issue that we
8 have yet to deal with, but one that we will have to come to
9 understand more clearly so that we can all communicate more
10 clearly within the team.
11 So, if we tackle the first issue, understanding
12 the problem, I thought I would present a few slides so that
13 those of you in the audience could understand the problem
14 as we do. So, is this drug-induced vasculitis as we know
15 it in humans, or is this drug-induced vascular injury as we
16 see it in animals?
17 The clinical versus pre-clinical impressions
18 I've already alluded to, but in clinical medicine drug-
19 induced vasculitis is usually associated with
20 hypersensitivity vasculitis, a specific morphological kind
21 of disease that patients usually recover when drug is
22 removed. Sometimes it gets worse, and they redevelop
23 disease when you rechallenge them.
24 Preclinically in animal models, we don't see
25 this syndrome. We see something quite different, and I'm

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

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