

FOOD AND DRUG ADMINISTRATION
ORALLY INHALED AND NASAL DRUG PRODUCTS SUBCOMMITTEE
OF THE
ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

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8:34 a.m.

Tuesday, July 17, 2001

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

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C O N T E N T S

AGENDA ITEM	PAGE
CONFLICT OF INTEREST STATEMENT by Dr. Nancy Chamberlin	6
INTRODUCTION AND OBJECTIVES by Ms. Helen Winkle	10
BIOEQUIVALENCE CONSIDERATIONS FOR LOCALLY ACTING NASAL DRUGS by Dr. Dale Conner	15
THE JUNE 1999 DRAFT NASAL BA/BE GUIDANCE: HISTORY, RECOMMENDATIONS OF THE DRAFT GUIDANCE, LOCAL DELIVERY EQUIVALENCE, CONTRIBUTION OF DOSE-RESPONSE by Dr. Wallace Adams	35
DIFFICULTIES WITH SHOWING A DOSE- RESPONSE WITH LOCALLY ACTING NASAL SPRAY AND AEROSOLS FOR ALLERGIC RHINITIS by Dr. Badrul Chowdhury	51
CLINICAL STUDY OPTIONS FOR LOCALLY ACTING NASAL SUSPENSION PRODUCTS: CLINICAL AND PHARMACODYNAMIC STUDIES by Dr. Robert J. Meyer	69
SUBCOMMITTEE DISCUSSION	88
OPEN PUBLIC HEARING PRESENTATIONS: by Dr. Cynthia Flynn	105
by Dr. Joel Sequeira	112
by Dr. Piyush Patel	117
SUBCOMMITTEE DISCUSSION	127

P R O C E E D I N G S

(8:34 a.m.)

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2
3 DR. LEE: Good morning. I'm Vincent Lee. I'm
4 the chair of the subcommittee, and I welcome you to this
5 subcommittee meeting.

6 Before we start, I would like to turn it over
7 to Nancy.

8 DR. CHAMBERLIN: Welcome.

9 The following announcement addresses the
10 conflict of interest with regard to this meeting and is
11 made a part of the record to preclude even the appearance
12 of such at this 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 an entire class 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 the FDA's invited guests, Dr.

1 Leon Shargel, Dr. Walter W. Hauck, and Dr. Izabela J. Roman
2 have reported interests which we believe should be made
3 public to allow the participants to objectively evaluate
4 their comments.

5 Dr. Shargel would like to disclose that he is
6 employed by Eon Labs Manufacturing Company.

7 Dr. Hauck would like to disclose ownership of
8 stock in Bristol-Myers Squibb. Also, his employer, Thomas
9 Jefferson University, has contracted to perform
10 biostatistical services for various pharmaceutical
11 companies. Additionally, Dr. Hauck has numerous consulting
12 agreements with the pharmaceutical industry related to
13 bioequivalence, bioassay, and content uniformity.

14 Finally, we would like to disclose that Dr.
15 Roman is medical director and co-founder of Target Research
16 Associates.

17 In the event that the discussions involve any
18 other products or firms not already on the agenda for which
19 an FDA participant has a financial interest, the
20 participants are aware of the need to exclude themselves
21 from such involvement and their exclusion will be noted for
22 the record.

23 With respect to all other participants, we ask
24 in the interest of fairness that they address any current
25 or previous financial involvement with any firm whose

1 products they may wish to comment upon.

2 Thank you.

3 DR. LEE: Thank you, Nancy.

4 I think it would be useful to go around the
5 table and everybody introduce herself or himself, and who
6 they're with and why they're here.

7 Dr. Roman?

8 DR. ROMAN: Good morning. My name is Izabela
9 Roman. I am a medical director and principal of a CRO,
10 Target Research Associates, and I am here as an invited
11 industry guest.

12 DR. LEE: Thank you.

13 DR. HAUCK: I'm Walter Hauck. I'm a professor
14 and head of biostatistics at Thomas Jefferson University.

15 DR. SHARGEL: Good morning. I'm Leon Shargel,
16 vice president of biopharmaceutics for Eon Labs, a generic
17 manufacturing company, and I'm an invited industry
18 participant.

19 DR. ADAMS: Good morning. My name's Wallace
20 Adams. I'm in FDA's Office of Pharmaceutical Science in
21 CDER and am involved in the nasal BA/BE guidance drafting
22 that we're discussing this morning.

23 DR. MEYER: Dr. Bob Meyer. I'm the director of
24 the Division of Pulmonary and Allergy Drug Products in
25 CDER, and I've also been involved with the drafting of the

1 | guidance.

2 | DR. CHOWDHURY: I'm Badrul Chowdhury. I'm a
3 | medical team leader in the Division of Pulmonary and
4 | Allergy Drugs.

5 | DR. CONNER: I'm Dale Conner. I'm director of
6 | the Division of Bioequivalence in the Office of Generic
7 | Drugs, FDA, and I'm a speaker today.

8 | DR. CHAMBERLIN: I'm Nancy Chamberlin. I'm the
9 | exec sec.

10 | DR. LEE: I'm Vincent Lee, the acting chair.

11 | DR. ANDERSON: I'm Gloria Anderson, Callaway
12 | Professor of Chemistry at Morris Brown College, Atlanta.

13 | DR. AHRENS: Richard Ahrens. I'm on the
14 | faculty of the University of Iowa in the Division of
15 | Pediatric Allergy and Pulmonary Disease.

16 | DR. OWNBY: Dennis Ownby. I'm professor of
17 | pediatrics and medicine in the Medical College of Georgia
18 | and head of the section of allergy and immunology.

19 | DR. DYKEWICZ: Mark Dykewicz. I'm associate
20 | professor of internal medicine and director of the training
21 | program in allergy and immunology at Saint Louis University
22 | School of Medicine.

23 | DR. HENDELES: I'm Leslie Hendeles. I'm a
24 | professor of pharmacy and pediatrics at the University of
25 | Florida in Gainesville.

1 DR. LEE: Thank you very much.

2 Anybody else?

3 (No response.)

4 DR. LEE: Well, I guess that concludes the
5 introduction, and I would like to invite Helen Winkle, the
6 acting director of the Office of Pharmaceutical Science, to
7 give us our marching orders.

8 MS. WINKLE: Good morning, everyone.

9 Unfortunately for today, my slides got
10 misplaced, but it's understandable. I think many of you
11 will know this is only the first of four days of advisory
12 committee sessions that are going on this week. So, if
13 mine are the only slides that are misplaced for four days,
14 I think we're going to be real fortunate. It's been a lot
15 of work.

16 I want to start off by welcoming everybody
17 here. I'm really happy that the members of the
18 subcommittee could join us to talk about this very
19 important issue, and I especially want to thank Wally
20 Adams, who put this subcommittee meeting together. He's
21 worked long and hard to make sure that we're focused on the
22 right issues that we need to address here today.

23 I also want to thank Dr. Meyer and Dr.
24 Chowdhury for joining us from the Pulmonary Division. I
25 think their input will be very helpful.

1 I wanted to talk a little bit about the
2 background of the subcommittee, just so everyone here is
3 aware of why this subcommittee exists, but before I do
4 that, I just wanted to mention the fact that this is sort
5 of an ad hoc subcommittee arm, basically, of the Advisory
6 Committee for Pharmaceutical Science. In this ad hoc type
7 of situation, we bring in experts in the field of nasal and
8 orally inhaled drugs, depending upon what topics we're
9 going to discuss.

10 So, today, basically the people that are here
11 as members of this subcommittee or to participate with the
12 subcommittee are people who have clinical backgrounds,
13 since basically we're going to be talking about how to
14 handle clinical issues, basically dose response and the
15 merits of three-study design. So, the people that are here
16 are basically those people who can best give us their
17 expertise in these areas.

18 This subcommittee actually started as an expert
19 panel back in 1999. It met to discuss issues relating to
20 various guidances having to do with nasal sprays and
21 aerosols and orally inhaled products. In 2000 we decided
22 that probably it would be advantageous for us to start a
23 subcommittee to address these issues, and therefore we
24 formed the Advisory Committee for Pharmaceutical Science's
25 Subcommittee on Orally Inhaled and Nasal Drug Products, or

1 OINDP, which is a lot easier for us to relate to.

2 The purpose of this subcommittee is basically
3 to address some of the issues that we have to do in order
4 to have good regulatory decisions in these product areas,
5 and these are somewhat complicated in many cases. So,
6 although we're looking at a variety of products in CDER, we
7 have certain products that are more complicated, have a lot
8 more issues that have to be addressed, and this is one of
9 the areas where we feel that we really need some expert
10 advice from outside of the agency to help us in addressing
11 these regulatory issues.

12 When the panel was formed, under the Advisory
13 Committee Act, in order to form a subcommittee, you have to
14 take two members from the advisory committee, and we asked
15 Dr. Lee and Dr. Anderson if they would join us on this
16 subcommittee, and Dr. Lee agreed to chair it. So, those
17 are the two members from the advisory committee. They
18 report back to the advisory committee on the
19 recommendations of this subcommittee.

20 The first time this subcommittee met, which was
21 April 26th of 2000, they addressed a variety of issues
22 having to do with the four guidances that we are developing
23 in this area, and these are guidances we've been working on
24 currently. These are on metered dose inhalers, the CMC
25 requirements, and nasal sprays and inhalation solutions,

1 the suspension CMC, and both of those have been issued in
2 draft and we're working on the draft, and as we're
3 developing the draft, of course, we have questions.

4 We also have two other guidelines on BA and BE.
5 They're BA and BE studies for nasal aerosols and nasal
6 sprays for local action and BA and BE studies for orally
7 inhaled MDIs, DPIs, and inhalation solutions for local
8 action, and that particular guidance is in preparation
9 form.

10 Today we're only going to be dealing with the
11 draft guidance for nasal BA and BE. We're focused
12 specifically on questions on local delivery for nasal
13 sprays and aerosols, and basically we're looking at this
14 issue in order that we can better determine bioequivalence
15 of the suspension form for nasal aerosols and sprays for
16 allergic rhinitis. One of the requirements is for in vitro
17 studies. However, in doing these in vitro studies, it's
18 very difficult to assure equivalence of the particle size
19 of the suspended drug, and because particle sizes differ
20 between the test and reference product, the potential to
21 alter the rate and extent of delivery of the drugs to the
22 local sites really can have some difference in clinical
23 effectiveness.

24 So, basically we've put together some questions
25 that we would like to have answered today in order to

1 | determine how best to ask for these studies to determine
2 | bioequivalence. The specific questions we have -- and
3 | Wally will again go over these questions as we move forward
4 | in his presentation today -- is, is a placebo-controlled
5 | traditional two-week rhinitis study conducted at the lowest
6 | active dose sufficient to confirm equivalent local delivery
7 | of suspension formulation nasal sprays and nasal aerosols
8 | for allergic rhinitis? And the second question we have, is
9 | a placebo-controlled park study or an EEU study conducted
10 | at the lowest active dose an acceptable option to confirm
11 | equivalent local delivery of suspended formulation nasal
12 | sprays and nasal aerosols for allergic rhinitis? We feel,
13 | with some direction from you on these particular questions,
14 | we can then move forward and make recommendations to the
15 | advisory committee.

16 | Now, the advisory committee is meeting on July
17 | 19th, which is Thursday. It's actually meeting July 19th
18 | and 20th. So, the recommendations that come out of this
19 | group will go directly to the advisory committee on
20 | Thursday, and Wally and Dr. Meyer and Dr. Chowdhury will
21 | again present to that advisory committee and will present
22 | the recommendations from this.

23 | So, basically, today this subcommittee is here
24 | to address the questions related to equivalent local
25 | delivery for in vitro BA and BE data and to provide

1 | recommendations to that committee.

2 | I want to personally thank all of you for
3 | taking the time. Again, I think your expertise is very
4 | valuable to us at FDA in helping to address these very
5 | important regulatory decisions.

6 | Thank you very much.

7 | DR. LEE: Thank you very much, Helen. You've
8 | done extremely well without slides, and I'm beginning to
9 | worry about when will those slides turn up.

10 | But let me reiterate two things that Helen
11 | said. Number one is that we're here to address two
12 | questions. There were specific questions. The rest of the
13 | morning will be devoted to the background information to
14 | arrive at some kind of recommendations. I'd like to remind
15 | the subcommittee that we're not here to vote. We're here
16 | to develop a consensus.

17 | Without further ado, I'm going to call on Dr.
18 | Conner to tell us something about bioequivalence
19 | considerations for locally acting nasal drugs.

20 | DR. CONNER: Good morning. I am leading off on
21 | this because I think it was felt that some introduction or
22 | setting the stage for a bioequivalence discussion is really
23 | kind of necessary in this topic.

24 | Usually when I give this talk, even my
25 | simplified explanation of bioequivalence runs at least for

1 an hour to an hour and a half, and that's really cutting it
2 quite short. So, I'm really pressed for time here.
3 Hopefully, I'm going to cut to the chase to a few issues
4 that really need to be considered to set the stage for
5 speaking about bioequivalence, because as you'll see within
6 the next few slides, I believe that sometimes committees
7 like this, and even we within the FDA, become quite
8 confused between strictly bioequivalence questions and
9 perhaps other peripheral or distantly related questions.

10 First off, there are many definitions of
11 bioequivalence. I've picked only one of them, and as
12 you'll see, I have several kind of definition or
13 explanation slides in the next few, all trying to make the
14 point or drive home what we're talking about here in
15 general terms. First off, the first thing you have to
16 understand is, and certainly when we approve generic drugs
17 and we refer to bioequivalence, we're talking about
18 pharmaceutical equivalents. So, that's the first point
19 that you have to realize, and the point that often is
20 confused by many clinicians in the outside world is when we
21 talk about a generic drug, it's a pharmaceutical
22 equivalent.

23 What do we mean by that? Pharmaceutical
24 equivalents have the exact same drug substance. So, it
25 isn't a question of therapeutic substitution, where you're

1 substituting yet a totally different drug. It's in the
2 same form. For example, a pharmaceutical equivalent of an
3 immediate release tablet would be an immediate release
4 tablet containing the exact same drug substance, or a
5 solution nasal spray from a pump, the pharmaceutical
6 equivalent would be a solution nasal spray from a pump, not
7 a suspension nasal spray, and so forth. So, we're talking
8 about the exact same dosage form and dosage form type
9 containing the exact same drug substance, and furthermore,
10 the labeling and the intended uses of that product are the
11 same. There are some other similarities, but those are the
12 critical parts. The first thing not to be confused about
13 is we're not talking about different drug substances.
14 We're talking about the exact same drug substance in the
15 exact same form for the exact same use when we talk about
16 bioequivalence in its application to the approval of
17 generic drugs.

18 So, my definition is pharmaceutical equivalence
19 is rate and extent of absorption are not statistically
20 different when administered to patients or subjects at the
21 same molar dose under similar experimental conditions. So,
22 this would be the first definition.

23 But I've expanded on that to say, well, that's
24 fine to look at the definition, but what is our endpoint?
25 And I'm speaking specifically about generic drug approval,

1 but this could also apply to certain aspects of NDA
2 formulation testing, especially when a set of clinical
3 trials that go to approve an NDA are carried on in one
4 formulation, a clinical trials formulation, and then either
5 the scale-up or the change in the eventual marketed
6 formulation requires some additional connection to those
7 clinical trials, and often it's a very similar case that
8 that new changed or scaled-up NDA formulation has to be
9 tied back to the formulation that was used in the clinical
10 trial. So, that's an analogous situation to perhaps
11 approving a generic drug, although not exactly so.

12 So, the main endpoint or what we're trying to
13 achieve when we look at bioequivalence of these
14 pharmaceutically equivalent dosage forms is at the end
15 we're trying to achieve therapeutic equivalence, and it's
16 important to note that when I say therapeutic equivalence,
17 I mean equivalence of both safety and efficacy of these two
18 products. You have to really remember because that
19 division becomes important, as you'll see later on when we
20 talk about nasal sprays or other topical or local delivery
21 drug products.

22 This is my own definition, that bioequivalence
23 products can be substituted for each other without any
24 adjustment in dose or other additional therapeutic
25 monitoring. This is an official statement that's come out

1 for other purposes when we talked about drugs like warfarin
2 or other controversial generic drug approvals, that when
3 bioequivalent generic products are switched for each other,
4 that no additional monitoring over and above what would
5 ordinarily be done for that patient for that disease, given
6 that drug, should be needed when a bioequivalent product is
7 switched.

8 I will state that the most efficient method of
9 assuring therapeutic equivalence is to assure that the
10 formulations perform in an equivalent manner, and probably
11 some explanation of what I mean by performance of the
12 formulation -- I mean, obviously we have a drug substance
13 that comes in a product. Sometimes that drug substance is
14 in solution, sometimes it's in a solid form, but certainly
15 I think we would all agree that whether it's an oral tablet
16 or a nasal spray or any other drug product that we give,
17 the drug substance must leave the formulation and enter the
18 patient or interact with the patient in some way.

19 So, that critical step is the drug substance
20 coming out of the formulation, and as you'll see, I have a
21 schematic of that later, but that is the critical step
22 we're trying to measure. How does that relate to
23 formulations? How does the drug substance actually leave
24 the formulation and become available to the patient? And
25 for bioequivalent products, that process or that step

1 should be equivalent between two comparable or equivalent
2 dosage forms.

3 Now, another thing that I've seen at committees
4 and many internal FDA meetings where we have discussions
5 like this, one of the critical things that is often
6 confused is the difference between bioequivalence and
7 bioavailability. The two have some similarities, but the
8 purpose that they're done for and what's actually what we
9 do in the types of studies to determine bioavailability,
10 say, of a new chemical entity for a new drug product in an
11 NDA are quite a bit different and the endpoints of what
12 we're trying to achieve are quite a bit different than a
13 bioequivalence test.

14 With a bioavailability test, it's very
15 descriptive. You're interested in the characteristics of
16 both the formulation, but also the drug substance. You're
17 trying to study how that drug substance is absorbed into
18 the body from various forms and how it interacts with the
19 formulations that you put it in. So, it's both involved in
20 formulation development to find out a proper formulation
21 for that drug substance, as well as to describe the basic
22 characteristics of the drug substance and how it's
23 absorbed.

24 So, that's very important. It's descriptive.
25 Most of the time, it's not necessarily comparative but is

1 simply trying to figure out the important characteristics
2 of that drug substance and perhaps how it interacts with a
3 particular formulation.

4 On the other hand, bioequivalence is entirely
5 comparative, and not only comparative, but it is
6 specifically referring to the formulation.

7 Now, if you go out of here repeating this
8 mantra to yourself, bioequivalence is all about the
9 formulation. Presumably, by the time you get to do a
10 bioequivalence study, you already know, through the
11 bioavailability and other studies, what the characteristics
12 of the drug substance are, and the drug substance is the
13 same in the same form in two or more products that you're
14 doing bioequivalence testing on. So, that is more or less
15 taken out of the equation, and the only question is, are
16 these formulations performing or releasing their drug
17 substance in an equivalent manner or are they not?

18 So, if you go out repeating to yourself
19 bioequivalence is all about the formulation or a test of
20 comparative formulation performance, then you'll have
21 gained quite a lot from my talk and I'll go away happy, if
22 no one else does.

23 But additional definitions or explanations of
24 bioequivalence. The question is, are the two
25 pharmaceutically equivalent formulations equivalent in

1 | their in vivo performance, leading to therapeutic
2 | equivalence? Again, that's just kind of a rehash of what
3 | I've said before, and again I've already defined
4 | performance as the release of the drug substance from the
5 | drug product.

6 | First off, I'd like to set the stage for nasal
7 | sprays by discussing a somewhat simpler case. Now, first,
8 | to start off, to put things in perspective, I'm displaying
9 | a simple case, which is, fortunately for us, most of the
10 | drug products that we look at, probably 70 or 80 percent,
11 | fall into this category. They're some type of oral dosage
12 | form, usually solid oral dosage forms, and fortunately for
13 | us, we see this simple process.

14 | Now, for my schematic, I've oversimplified the
15 | process quite a lot, but I wanted to display the critical
16 | steps in going from a dosage form or a comparison of two
17 | dosage forms to our eventual outcome, which is hopefully a
18 | therapeutic or some therapeutic effects, and to do this
19 | process in a comparative manner on two dosage forms of the
20 | same drug product. So, we see that when we start out at
21 | the left, we end up with the dosage form.

22 | Now, in a manner of speaking, those of you from
23 | the pharmaceutical industry know that this dosage form and
24 | how it's made, and therefore how it performs in the body,
25 | is the only thing in this whole process we really have

1 control of. The rest of it, beyond that first step where
2 the drug leaves the dosage form, which depends on how it's
3 made and formulated, is really pretty much up to the
4 patient or the subject, if you're looking at an normal
5 volunteer study, and we have very little control over all
6 the rest of the steps.

7 So, this first step is the only thing we as
8 formulators or as manufacturers of the dosage form have
9 really any control over. The rest of it beyond here -- the
10 gut wall, appearance in the blood, appearance at the site
11 of activity, and eventual therapeutic effect -- are mainly
12 characteristics of the patient or patients or normal
13 volunteers.

14 So, the question is, this is the process that
15 we are trying to make equivalent. So, when, say, a generic
16 drug manufacturer formulates their product, they try and do
17 the best they can to make sure that this particular step,
18 which is the dosage form performance where the drug
19 actually leaves the dosage form and becomes available to
20 the patient, that that step is the same between their
21 product and the brand name or reference product.

22 Again, as I said, fortunately for us, this is a
23 relatively simple process. You could put a couple of boxes
24 in between here if you really wanted to go into a lot of
25 detail, but as I said, I've simplified it. The drug,

1 usually in solid form, has to leave the dosage form and go
2 into solution. That's one of the beliefs that we have that
3 a drug is available for absorption through the GI tract
4 when it's in solution, and that's true not only in the GI
5 tract, but a lot of other areas.

6 Some oral drugs are already in solution, so in
7 a way we skipped this step, and the regulations that we
8 operate under allow us to assume that for a drug in
9 solution, the bioequivalence, when you've left that part
10 out, is self-evident. So, the regulations allow us to
11 waive in vivo bioequivalence testing for many oral drugs
12 that are in solution.

13 So, once you get to that point, you go through
14 a variety of steps. The drug in solution passes across the
15 gut wall into the blood, and eventually the blood carries
16 it to the site of activity, and when the drug appears at
17 its site or sites of activity, we get a pharmacodynamic or
18 clinical effect, be it a desirable one or an undesirable
19 one.

20 This is a relatively simple process. We've
21 chosen, I think -- and I could go into a long explanation
22 of why, but to me it seemed perfectly logical -- to measure
23 this process and to assess this step back here through the
24 blood. Because of a variety of characteristics of blood,
25 it's easily measured. For most drugs, not all, it's a

1 fairly linear process. If I give a greater dose or I see a
2 greater amount delivered from one formulation versus
3 another, it's reflected on a linear scale here, so it's
4 easy to relate differences in dosage form performance or
5 relative bioavailability or bioequivalence in the blood.
6 It's very easy to do, and the variability is quite low
7 compared to going through a few other steps.

8 It's important to point out that every one of
9 these steps adds variability as I go along. So, by the
10 time I get to site of activity and therapeutic effect, my
11 variability of these effects is quite high. So, again,
12 that increases the difficulty of doing a study.

13 The other is sometimes, as you'll see for the
14 nasal sprays, we really can't do this effectively. Either
15 it's not valid to assess therapeutic effect or perhaps
16 there might be other technical problems where we aren't
17 able to do it in blood, and therefore we have no choice but
18 to do either a pharmacodynamic or a clinical test of the
19 eventual therapeutic effect to make sure that those
20 products are therapeutically equivalent.

21 As you'll see, part of the whole thrust of this
22 discussion about dose response is that the therapeutic
23 effects or pharmacodynamic effects don't fall on a nice
24 straight line. As most of us remember from our
25 pharmacology textbooks, if you display it on the right type

1 of graph, they usually have a sigmoidal or dose-response
2 type of curve, and where you are on the dose-response curve
3 really determines how good your measurement is. I have
4 some blowups of these here to more characterize the
5 difficulties of doing it on this particular graph, which is
6 one of the questions that we have to deal with today.

7 So, now, I showed you a very simple case, one
8 that we're all familiar with and fortunately we deal with
9 most of the time. However, now we see a simplified
10 schematic of what I've done to describe what happens with a
11 nasal spray. There are somewhat similar things that you
12 could draw very similar schematics for what happens with,
13 say, an inhaler or perhaps other locally acting drug
14 products.

15 This one is specifically for nasal sprays, and
16 again it's oversimplified. Those of you who really know
17 this process and deal with it with patients or in
18 developing products know that there are a lot more steps
19 here, but I did this schematic to show that, number one, we
20 again have this critical step here, which is again the only
21 one we really have any control of. We as U.S.
22 manufacturers or formulators and we as regulators can
23 control how this dosage form performs, how it releases its
24 drug substance to the patient.

25 However, it then goes through a variety of

1 processes, and as you'll see, there are branch points here
2 that are not necessarily there in an oral product. For
3 example, what we're really trying to achieve with most
4 nasal sprays is a local administration to or very close to
5 the site of activity.

6 So, on the top, it shows that particular
7 process. The drug -- say it's from a suspension nasal
8 spray -- first has to go into solution, then cross the
9 nasal membrane to its site of activity, and you'll note
10 here that there's no blood in between there. It simply
11 passes across a membrane and achieves in very close
12 proximity the site of activity, and eventually achieves a
13 therapeutic effect. That's essentially what we're trying
14 to achieve.

15 Unfortunately, knowing the characteristics of
16 this dosage form and the way that the nose and the body
17 handles this, this is not the only process that we have to
18 deal with. When you give a drug from a nasal spray, or an
19 inhaler, for that matter, but certainly from a nasal spray,
20 a certain percentage of the dose usually is swallowed. So,
21 perhaps not even the majority ends up in this pathway, but
22 down in this pathway. It's swallowed. It goes into the GI
23 tract. It can also, as another pathway, be inhaled into
24 the lung.

25 Again, these could be considered undesirable,

1 but effects that we simply probably can't get around. I
2 mean, they do happen, and sometimes they happen when a
3 major part of each nasal spray may go into the GI tract or
4 the lung.

5 Now, the importance of this is those pathways
6 also end up in absorption into the bloodstream. As I said,
7 the nasal spray itself goes through the site of activity.
8 Also, a portion or perhaps even all of the drug that's in
9 the nasal membranes goes into the blood as well, and that
10 blood concentration then carries it to distant sites of
11 activity, which can result in usually toxic effects, but it
12 can result in some therapeutic efficacy as well from
13 systemic effects. So, we have here a much more complicated
14 picture than what I originally outlined for an oral drug.

15 The advantage of an oral drug for doing blood
16 concentrations determined by equivalence is we have one
17 test, and through that one test we can determine both
18 safety and efficacy equivalence. So, the entire package of
19 therapeutic equivalence is all wrapped together very nicely
20 and conveniently in one single test.

21 If we were to take the exact same rationale
22 here and simply try and measure blood, we wouldn't really
23 be covering all the bases. We would not be adequately
24 assessing the therapeutic effect part, the therapy that
25 we're trying to achieve. We probably would be correctly

1 | assessing the systemic toxicity. So, this is definitely
2 | not to say that a blood concentration test of equivalence
3 | is not useful. It simply is not a single test that
4 | encompasses or answers all of our questions.

5 | The other question, and perhaps equally if not
6 | more important, is how much drug comes out of this
7 | formulation to reach its site of activity in the nose, and
8 | therefore create the desirable therapeutic effects.

9 | So, we're left with a point of having no single
10 | test that can answer all our questions about therapeutic
11 | equivalence. This blood certainly doesn't answer the
12 | question about equivalence of this, but it does perhaps
13 | give us the other half about equivalence of toxic systemic
14 | effects. So, what we're left with is probably doing at
15 | least two separate bioequivalence tests to be able to
16 | answer our question, which is overall therapeutic
17 | equivalence of two pharmaceutically equivalent nasal spray
18 | dosage forms.

19 | Now, just to finish up and discuss some of the
20 | problems, as I said, blood concentration is usually very
21 | nicely behaved, and even when we have a nonlinear drug, we
22 | can deal with that effectively. But you'll see that this
23 | dose-response PD or clinical dose-response curve does give
24 | a few problems that we have to deal with.

25 | Now, I've drawn it on a log scale, so it has a

1 nice sigmoidal appearance. If you don't do it on a log
2 scale, it more or less rises and comes to a plateau, but
3 this is the way that most pharmacology books or
4 pharmacologists like to display it. It adequately
5 represents the fact that this test and where I conduct the
6 test on this curve really turns out to be quite critical.
7 If I wanted to use this as a single test of bioequivalence
8 and make a strong bioequivalence statement, the portion of
9 this dose that I study it at is quite critical, and I'll
10 explain why.

11 If I study it at a fairly high dose -- and you
12 must remember that for nasal sprays, often the minimum dose
13 that you can possibly give is probably somewhere around up
14 here. Simply, the characteristics of many drugs available
15 in nasal sprays, and that's part of what you'll be
16 discussing today.

17 The problem that must be overcome or dealt with
18 is the fact that if I'm up on top of this plateau, I can
19 have two products that are quite different in their
20 delivery of the drug substance. Well, to state an extreme,
21 I could have several hundred percent difference, as long as
22 I was up in this region, and the clinical effect I'd get
23 from those two products would be virtually identical,
24 simply because I'm up on top of a plateau and no matter how
25 much I work my way out on this and how much difference I

1 have between these two products, both of which are at the
2 dose up at that plateau, the effect that I'm trying to
3 measure, which in this case is either a clinical effect or
4 a pharmacodynamic one, is not going to show any difference
5 at all. So, studied in this range, the comparative test
6 considerably lacks sensitivity.

7 However, if I had enough knowledge of these
8 products and I had enough flexibility to give the products
9 at whatever dose I wanted, which obviously is not true for
10 a nasal spray, I would pick a dose to do my study down in
11 here, and we have a relatively steep part of this dose-
12 response curve, and even a tiny difference shows quite a
13 significant difference in effect.

14 Granted, I've drawn this dose-response curve in
15 a very extreme manner to be very steep. We might see a
16 variety of different forms of this, from a very shallow to
17 a very steep dose-response curve, but the best chance that
18 we have of doing a good, sensitive test is to somehow
19 establish our testing range or our dose of testing down in
20 here.

21 As we all know, with a nasal spray, you can
22 give one spray, two sprays, three sprays, and if that one
23 spray is already up here, you have a problem. You really
24 don't have the flexibility you might have with some other
25 drugs of working yourself down and picking an exact dose

1 that's ideal, even if you were able to determine what that
2 dose is.

3 So, this is the problem with many nasal sprays,
4 that even at the minimum dose, we're already up here.
5 That's part of what we come to you today about, is dealing
6 with this in an effective manner and putting together a
7 package of studies that will still be convincing as far as
8 bioequivalence of these products.

9 This is simply an illustration of what I said
10 about the blood. If we have a drug with linear
11 pharmacokinetics, it really doesn't matter what the dose
12 is. As long as I have a good assay and can measure that
13 dose, the same difference -- say these are two products,
14 the blue product and the black. If I have a nice linear
15 response and the products are this much different as far as
16 their delivered dose, if I study it at this dose versus
17 this dose, I'm still going to get the same response, which
18 in this case the response is the plasma concentration
19 difference. So, that's one of the many advantages of blood
20 concentration monitoring for equivalence purposes, and
21 that's why for oral products, when we can do it, we
22 virtually always go with blood concentration monitoring to
23 show equivalence.

24 In this case, as I said before, to reiterate,
25 the blood only shows us a portion of what we want to know.

1 | It's not a single test that can answer all of our questions
2 | about nasal sprays.

3 | That's it.

4 | DR. LEE: Thank you very much.

5 | We have time for maybe one question if there is
6 | any. Yes, Les?

7 | DR. HENDELES: What is the evidence that a drug
8 | inhaled into the nose gets into the airways?

9 | DR. CONNER: Well, I listed that as a
10 | possibility. I think Wally has some papers. Mainly, that
11 | particular route depends on particle size. It's not one of
12 | the things we're discussing today, but if you're aware of
13 | the in vitro tests we do, there's quite an effort to
14 | determine particle size and to try and make sure that the
15 | amount or the percent of fines, which are the things that
16 | presumably will get down into the lung, are the same
17 | between two products.

18 | If you were using those same techniques to
19 | develop a new product, you'd probably want to reduce or
20 | eliminate that particular range of particle size, but part
21 | of the in vitro testing we do is try and make sure that if
22 | a reference product has that particular characteristic,
23 | that the test product also has it.

24 | But I think, Wally, if you want to answer that?

25 | DR. ADAMS: Some of the evidence for that, Les,

1 | is sinographic evidence. The University of Maryland has
2 | done some studies in which they've looked at nebulizers, a
3 | nasal nebulizer with a very fine, slow spray and effect.
4 | In that case, where the mass median aerodynamic diameter is
5 | down in the few micron range, they did find a substantial
6 | amount of drug getting into the lungs.

7 | But for properly formulated nasal sprays and
8 | MDIs and DPIs, we would not expect for there to be much
9 | pulmonary deposition at all and, as Dale has indicated, we
10 | do have in vitro testing that helps protect against that.

11 | DR. LEE: I think that we have to move on. I
12 | think Dale has done a very good job in setting the stage,
13 | and I would like to remind everybody to pay attention to
14 | the top slide on page 4, which will be reiterated by Drs.
15 | Chowdhury and Meyer later on.

16 | The next item on the agenda is the presentation
17 | by the architect of the draft nasal BA/BE guidance, Wally
18 | Adams, and he's going to give us some history and not take
19 | too much time, but he's going to tell exactly why they
20 | posed those two questions before the subcommittee.

21 | While we have some dead time, let me remind the
22 | subcommittee that I do have an electronic gavel. I have a
23 | button that can cut you off.

24 | (Laughter.)

25 | DR. LEE: And I hope I won't have to use it.

1 DR. ADAMS: Well, good morning, everyone.
2 Thank you for coming. I'd like to thank the subcommittee
3 for participating in today's activity.

4 Also, I'd like to thank Helen Winkle for her
5 opening presentation with regard to the objectives of
6 today's meeting, and for Dr. Conner for laying a very
7 strong background for the bioequivalence issues that we're
8 talking about today.

9 The title of this talk refers to the nasal
10 bioavailability/bioequivalence guidance, and I'd like to
11 talk about the history, recommendations, and local delivery
12 issues, and this will lead up to presentations by Dr.
13 Chowdhury and Dr. Meyer.

14 I would like to emphasize what Ms. Winkle had
15 indicated, that today's discussion will be centering solely
16 on nasal aerosols and nasal sprays and does not involve the
17 orally inhaled products whatsoever.

18 The guidance covers four groups of drugs for
19 local action -- corticosteroids, anticholinergics,
20 antihistamines, and cromones -- and in three of those
21 groups all of the presently marketed drugs are solution
22 formulations. Only the corticosteroids exist either as
23 solution or suspension formulations. We have a different
24 path for solution formulation bioequivalence than we do for
25 the suspension formulations, and I'll mention that later

1 on. The topic today is restricted to the suspension
2 formulations.

3 The outline and history of guidance
4 recommendations for bioequivalence and local delivery
5 bioequivalence issues. I have three slides on the history
6 of this.

7 I wanted to emphasize that the issue of
8 establishing bioequivalence for nasal sprays goes back for
9 many years. In fact, Beconase AQ, a Glaxo SmithKline
10 product, went off exclusivity back in July of 1990, and at
11 the present time, 11 years later, there is still no generic
12 product for this innovator product. So, we are still
13 struggling with issues with regard to establishing
14 bioequivalence for such products.

15 In September of 1993, the Generic Drugs
16 Advisory Committee, with Pulmonary and Allergy Drugs
17 Advisory Committee representation, meeting was held, and at
18 that meeting it was determined that bioequivalence for
19 nasal solution formulations may be established with in
20 vitro testing only. That recommendation is reflected in
21 our June '99 draft nasal BA/BE guidance.

22 In April of 1995, there was a CDER internal
23 memo which made the recommendation for bioequivalence of
24 generic formulation aqueous suspension nasal sprays,
25 providing that the generic version would be qualitatively

1 and quantitatively the same, that there were comparative in
2 vitro data which were acceptable to the Office of Generic
3 Drugs, and a multiple-dose PK study, and that that
4 information establish bioequivalence. You'll notice what's
5 not in that list is a clinical study for local delivery or
6 rhinitis.

7 The second slide on the history. In December
8 1996, there was a letter which was received by FDA from the
9 innovator industry. It said that OGD requirements for
10 bioequivalence of aqueous suspension nasal sprays do not
11 require data on drug particle size distribution. We did
12 ask for information on droplet size distribution, but not
13 for the particle size or particle size distribution of the
14 active pharmaceutical ingredient, and therefore this letter
15 contended that the requirements from OGD were not adequate
16 to assure bioequivalence.

17 They made an argument, which in fact is
18 plausible, that drug particle size distribution can affect
19 both the rate and extent of dissolution and absorption from
20 the aqueous suspension nasal sprays to sites of action. It
21 is plausible. It's an argument which we took very
22 seriously. However, that letter had no accompanying data
23 to support the claim. It was rather a theoretical or
24 pharmaceutically-based scientific argument in the absence
25 of data. But we did take the issue seriously.

1 In May of 1997, the Orally Inhaled and Nasal
2 Drug Products Technical Committee was organized, and then
3 in June of 1999, the draft nasal BA/BE guidance, which came
4 out of that organization of the technical committee, was
5 issued. It's been somewhat over two years now, and it
6 immediately preceded an AAPS workshop, which many of you
7 may have attended, which talked about in vitro and in vivo
8 issues, CMC issues, compendial issues, and in vitro and in
9 vivo BA and BE. It was a long two-day meeting which had
10 much valuable information in it.

11 The last history slide. In November of 1999,
12 the OINDP Expert Panel was organized, as Ms. Winkle has
13 indicated, and that was subsequently changed into a public
14 subcommittee format, of which this is the second meeting.
15 April 26 of 2000 was the first meeting. That was a very
16 ambitious meeting, and we took in vitro and in vivo CMC and
17 BA/BE issues and questions to that subcommittee meeting. A
18 report of that subcommittee was then made to the full
19 Advisory Committee for Pharmaceutical Science in November
20 of 2000. That takes us up to date, then, as to where we
21 are today.

22 What I'd like to do now is to talk about some
23 regulatory issues with regard to establishing
24 bioequivalence, and to indicate that, according to the CFR,
25 there are four basic methods for establishing

1 bioequivalence, and they are: pharmacokinetic studies,
2 which is the first bullet; pharmacodynamic studies, the
3 second bullet; comparative clinical trials, the third
4 bullet; and comparative in vitro studies, the fourth
5 bullet.

6 That list in the CFR is in descending order of
7 accuracy, sensitivity, and reproducibility, so therefore
8 that says, according to our regulations, that we'd prefer
9 to establish bioequivalence based upon pharmacokinetic data
10 when and if that is appropriate. As Dr. Conner has
11 indicated, for locally acting drugs delivered to the nose,
12 there are issues with regard to efficacy and issues with
13 regard to safety, and those issues for the suspension
14 formulations cannot be answered with a single study. So,
15 in fact, the approach that's in our nasal BA/BE guidance
16 uses several of these bullets in order to completely
17 establish bioequivalence.

18 Bioequivalence can play a role for NDAs. It
19 could ask questions about a to-be-marketed product. Is it
20 comparable to the clinical trial product? For ANDAs, is a
21 generic product bioequivalent to the innovator product?
22 For NDAs and ANDAs, it could be used for certain post-
23 approval changes where appropriate.

24 Now, the bioequivalence recommendations in the
25 guidance are as follows, and as Dale has indicated, we are

1 asking for in this guidance a package of information, and
2 I'm going to go through that now.

3 Qualitative sameness, Q1, identical active and
4 inactive ingredients as in the reference listed drug, and
5 that is a key aspect of the recommendations which we make
6 for bioequivalence because we're aware that different
7 inactive ingredients can alter the absorption and the
8 efficacy of a particular product. So, if an excipient or
9 inactive ingredient is present in the reference listed
10 drug, these recommendations say it must be present in the
11 test product. If an ingredient is not present in the
12 reference listed drug, it may not be present in the test
13 product.

14 That's the recommendation. There could be some
15 exceptions with regard to establishing safety and efficacy,
16 but these are our recommendations.

17 A quantitative sameness, what we call Q2. Our
18 recommendation is that each of these inactive ingredients
19 be present within plus or minus 5 percent of the
20 concentration in the reference listed drug. We recognize
21 that while the labeling for the product indicates the
22 inactive ingredient composition, it does not provide the
23 concentrations of those ingredients, and that does require
24 some analytical work on the part of the generic applicant
25 in order to determine what is the concentration of each of

1 the inactive ingredients. And that is a doable
2 recommendation.

3 The guidance makes recommendations with regard
4 to device. "Assurance of equivalence," and I'm quoting,
5 "is greatest when the test product uses the same brand and
6 model (particularly the metering valve or pump and
7 actuator) as used in the reference listed drug."

8 If that's not feasible, we recommend that the
9 metering valve or pump, the pump spray device, and the
10 actuator designs should be as close as possible in all
11 critical dimensions. Those would include such things as
12 metering chamber volume, actuator orifice diameter, and
13 nominal spray angle of the actuator insert.

14 Now, comparable in vitro performance. We have
15 six tests that are asked for to assure equivalence in terms
16 of in vitro performance.

17 The first, dose content uniformity through
18 container life, our working group has recommended that we
19 change that to unit spray content because in fact that is
20 not a content uniformity test. It's not meeting a
21 nonparametric test as recommended either by FDA's CMC
22 guidance or the USP, but rather it's an equivalence issue.
23 Is the test product delivering out of the actuator the same
24 amount of drug as the reference listed drug? We have
25 statistical criteria for that, and so we would have

1 confidence, then, that through this first bullet, the unit
2 spray content, that test and reference products are
3 delivering the same amount of active drug from the
4 actuator.

5 Droplet and particle size distribution is
6 another attribute which we ask for. I'm going to come back
7 to the particle size distribution in a moment, but first
8 I'll flip to the next slide.

9 We ask for spray pattern, plume geometry,
10 priming and repriming, and tailoff characteristics as well,
11 all of these being comparative. The droplet size
12 distribution, the spray pattern, and the plume geometry all
13 impact where the drug is going to be deposited in the nose.
14 So, if the droplet size distribution, the spray pattern,
15 and the plume geometry are the same, then we believe that
16 the test and reference products will deposit in the same
17 regions of the nose.

18 However, particle size distribution, as Ms.
19 Winkle indicated, is the problem that we're dealing with
20 which brings us to this meeting today, and that is that the
21 center is unaware of any validated method for determining
22 particle size distribution of the drug in the nasal spray
23 or, for that matter, nasal aerosol products. In the case
24 of the nasal spray products, in addition to the drug, the
25 product contains inactive ingredients, and there's an issue

1 | about determining the drug from the inactive ingredient.

2 | I should say, too, with regard to particle size
3 | distribution that a generic firm, in order to match the
4 | particle size distribution, which can affect the rate and
5 | extent of absorption to sites of action, if the generic
6 | firm had access to the bulk drug of the innovator, then it
7 | would be an easier issue of being able to match that
8 | product before it went into the formulation. That, of
9 | course, is not the case. The generic firm has only access
10 | to the marketed product, and therefore it's a question of
11 | determining the particle size distribution of the drug in
12 | the marketed product, and that's the challenge, because
13 | this validated methodology is not available.

14 | As Dale has indicated, differences in particle
15 | size distribution can affect rate and extent of dissolution
16 | and rate and extent of reaching the sites of action,
17 | whether it be the local sites for efficacy or systemic
18 | sites leading to toxicity, and consequently when particle
19 | size and particle size distribution cannot be determined,
20 | there are issues with regard to efficacy and safety.
21 | That's why, therefore, for these suspension products we ask
22 | for additional in vivo studies.

23 | The guidance asks for dose response to document
24 | sensitivity, and it talks about for the local delivery
25 | three types of study designs, which Dr. Chowdhury will

1 describe and discuss in some detail.

2 It also asks for a systemic exposure study, a
3 pharmacokinetic study, and I won't go through all the
4 bullet points here, but that study is a single- or
5 multiple-dose study. Multiple actuations per dose to
6 achieve measurable plasma concentrations, if necessary.
7 These products, of course, are not intended to deliver drug
8 systemically. The levels are very low, and therefore the
9 PK study would be a high-dose study. We would look at AUC
10 and Cmax measures and apply a statistical criteria to it
11 for equivalence.

12 In the event that pharmacokinetics is not
13 possible -- and we know that it is for a number of these
14 nasal sprays, but for some it may not be possible -- when
15 that's the case, since we're talking about corticosteroids,
16 we recommend an adrenal axis suppression study, and the
17 endpoint there would either be 24-hour urinary free
18 cortisol or 24-hour serum cortisol.

19 So, the package of information, then, that
20 we're talking about for establishing bioequivalence of
21 these products is Q1 and Q2 sameness, device
22 recommendations for comparability or equivalence,
23 comparable in vitro performance, and for solution
24 formulations those consist of our complete recommendations
25 for bioequivalence.

1 For the suspension formulations which are on
2 the table today, as I've mentioned, we go on to ask for in
3 vivo studies for local delivery and systemic exposure, so
4 there's a comparable in vivo performance for local delivery
5 for suspension formulation products and comparable in vivo
6 performance for systemic exposure or absorption for the
7 suspension formulations.

8 Now, the guidance indicates, for the topic of
9 local delivery issues, that a clinical study may be crucial
10 to establish bioequivalence for local delivery. What it's
11 getting at there is the issue of unknown or unvalidated
12 particle size distribution between test and reference
13 products. There are issues with regard to equivalence of
14 local delivery.

15 Regarding dose-response relationship, it says
16 that it may not be possible to show this or that it may not
17 be consistently reproducible. So, those are some
18 substantial challenges with regard to dose-response
19 relationship.

20 It says that the clinical study should document
21 sensitivity between different doses, that doses may differ
22 by two- to four-fold, and it also says that that two- to
23 four-fold range of the two active doses, that the low dose
24 in fact may be below the minimum labeled dose, and that's
25 consistent, then, with a recognition, however, that the

1 | minimum dose could be not less than one spray per nostril
2 | daily.

3 | Part of that's what Dale was getting at with
4 | regard to these products. You can't arbitrarily lower the
5 | dose lower than what the product can deliver. It delivers
6 | a particular amount of dose in a spray. There's one spray
7 | per nostril for these products, or more, and you can't get
8 | lower on daily dosing than one spray per nostril. So, it
9 | limits how far down you could get on a dose-response curve,
10 | if in fact there were a substantial dose-response curve.

11 | Well, I put this slide in. I didn't want to be
12 | outdone by Dale's slide.

13 | (Laughter.)

14 | DR. ADAMS: I liked his slide so much, but let
15 | me try and comment additionally on this.

16 | First off, let me describe this. This is a
17 | dose-response slide with a dose on the x axis and percent
18 | maximum response on the y axis, and I've shown dose-
19 | response curves both for efficacy -- that is, the local
20 | activity -- and also for a safety curve where, as you go up
21 | the safety curve, you're getting increased concerns about
22 | the safety. That could be, for instance, for the
23 | corticosteroids, adrenal axis suppression.

24 | Further, if we were on the rapidly rising
25 | portion of the efficacy curve, then clearly we would have a

1 | more sensitive means of distinguishing a test and a
2 | reference product. We would know that they're delivering
3 | different doses. But as indicated for the nasal sprays, it
4 | may very well be that we're up on the plateau of response
5 | and we cannot conduct a study in the more sensitive region
6 | where we would desire.

7 | Now, recall from the in vitro studies, which
8 | all of these products must provide, we know that the test
9 | and reference products are delivering the same amount of
10 | drug X actuator, they're delivering the drug to the same
11 | regions of the nose, based upon the spray pattern, plume
12 | geometry, and droplet size distribution.

13 | What we don't know, however, is that because
14 | the particle size distribution may differ, the amount of
15 | drug reaching the active sites in fact may be different
16 | between these products, even though the drug X actuator is
17 | the same and the distribution to the various regions of the
18 | nose is the same. The particle size is an issue, and
19 | consequently the position of test and reference products up
20 | on the plateau could differ, and we do not have a sensitive
21 | methodology for distinguishing where we are on that
22 | plateau.

23 | But we would propose putting a bioequivalence
24 | criterion on the test-to-reference ratio, so that there is
25 | an equivalence criterion, and we know therefore that the

1 test and reference products are both equally efficacious.
2 They could be tested only at one dose, but they're both up
3 on the plateau and they both would demonstrate equal
4 efficacy, even though the amount of drug reaching the sites
5 of action may be somewhat different as a result of these
6 potential particle size differences.

7 Well, just as a different amount of drug could
8 be reaching the active sites because of particle size
9 differences, similarly systemic absorption could be
10 different between the test and the reference products, and
11 that puts us down onto the safety curve. We could have a
12 situation where if these differences caused a difference in
13 systemic delivery, that it could put us in a different
14 place on the safety curve.

15 That is why we have to ask for a systemic
16 exposure or systemic absorption study, preferably a
17 systemic exposure study. By that, I mean a comparative
18 pharmacokinetic study, because any of the adverse effects
19 which are systemically mediated would be covered by
20 pharmacokinetic equivalence, and so we would prefer to use
21 a PK study, rather than an adrenal axis study, in order to
22 assure equivalent systemic exposure.

23 But as I've mentioned, there are some drugs,
24 some of the more recently developed corticosteroids, where
25 the systemic absorption may be so low that the levels just

1 | can't be realistically measured in the plasma. In that
2 | case, we would ask for an adrenal axis study and assure
3 | ourselves through those studies that the test and reference
4 | products are equivalent.

5 | So, the proposal for a bioequivalence study,
6 | then, for the nasal suspension aerosols and sprays is this.
7 | Formulation recommendations. That's the Q1 and Q2. Device
8 | recommendations. That's saying we want for the devices to
9 | be the same or as close as an applicant can get it. In
10 | vitro studies which assure us delivery is equivalent and
11 | that distribution to the various regions of the nose is
12 | equivalent.

13 | Then for the suspension products, in vivo
14 | studies. One, to assure equivalent local delivery. That's
15 | the rhinitis study, and two, a pharmacokinetic study to
16 | assure equivalent systemic exposure. The rhinitis study,
17 | we're recommending a low dose in order to try and put us
18 | down onto the more sensitive region of the curve to the
19 | extent that that can be done, and the pharmacokinetic
20 | study, in order to get measurable levels, would be a high-
21 | dose study. The alternate to that would be a
22 | pharmacodynamic study. So, that is the proposal that we
23 | are making today.

24 | Now, I'd like to acknowledge the participation
25 | in this development of the nasal BA/BE draft guidance of a

1 large number of individuals within the Food and Drug
2 Administration, within the center and OPS, and that would
3 be our OINDP Technical Committee, and I have a subsequent
4 slide to show that; Helen Winkle and Ajaz Hussain, both of
5 whom strongly supported the development and the continued
6 development of this guidance as it's dealt with a number of
7 issues, each one of which has had to be discussed by our
8 working groups; and Roger Williams, who initially made the
9 suggestions for and saw the need for a guidance to provide
10 industry with bioequivalence approaches for these locally
11 acting products.

12 This last slide shows our working groups.
13 There are six working groups which look at various aspects
14 of the guidance, both in vitro and in vivo, CMC, and so on.
15 Each of the individuals on here has participated in the
16 development of this guidance and the further refinement of
17 this guidance.

18 So, I'd like to stop there. Thank you.

19 DR. LEE: Is it really the end?

20 DR. ADAMS: That's the end.

21 DR. LEE: Thank you, Wally. You left a couple
22 of minutes for some burning questions.

23 (No response.)

24 DR. LEE: Well, if not, I think that Wally did
25 impress upon us what needs to be done in his slide 19, and

1 | also he stressed the difficulties that we should anticipate
2 | encountering with a PD study.

3 | So, Dr. Chowdhury is going to tell us whether
4 | it is really difficult, or the difficulties with showing a
5 | dose response with locally acting nasal sprays.

6 | DR. CHOWDHURY: Good morning. I'm going to
7 | talk about the dose response that we have been talking
8 | about for so long, and for the next half an hour or so I'll
9 | show some data about which I'll try to explain why showing
10 | a dose response with these locally acting drugs such as
11 | nasal sprays and aerosols are so difficult in allergic
12 | rhinitis.

13 | Before I go into the specific data where I will
14 | talk about dose response and the difficulty in showing
15 | those, I would like to talk with you briefly about nasal
16 | sprays and aerosols in general using one slide, and then
17 | I'll talk about allergic rhinitis, specifically the study
18 | design aspects, so that when I go into the data, those will
19 | be more clear.

20 | Now, as we heard, the nasal sprays and aerosols
21 | are in different chemical forms, and the ones we're talking
22 | about today are the suspensions. However, the nasal sprays
23 | are solutions also, which is not really the big issue, and
24 | the nasal aerosols are also suspensions. Just to make the
25 | point, the nasal aerosols are the ones which have some

1 | propellant in it like CFC, and the nasal spray solutions
2 | and suspensions are usually aqueous formulations.

3 | Throughout my talk, I'll be referring to them as solution
4 | nasal sprays, suspension nasal sprays, and nasal aerosols.

5 | Some examples of these. The nasal sprays which
6 | are solutions, examples are the antihistamine azelastine,
7 | the anticholinergics, cromolyn sodium, and some steroids.
8 | The suspension nasal sprays are all steroids and the
9 | aerosols are, again, all steroids. Again, the focus is on
10 | the suspensions for my talk and today's discussion.

11 | Now, on to allergic rhinitis. Allergic
12 | rhinitis studies can be done in different ways, and the way
13 | that we look at it, mainly the sponsors do it to gain
14 | approval of drugs. Typically, there are three kinds of
15 | rhinitis studies and I'll walk you through those. We just
16 | call them a natural exposure study, a day-in-the-park
17 | study, or an environmental exposure unit study, or an EEU
18 | study.

19 | The natural exposure studies are typically done
20 | as an outpatient setting in the natural environment of the
21 | patients where they're exposed to the allergens in the
22 | natural setting. Typically, these are parallel-group
23 | studies. The patients are recruited and they're treated
24 | for an initial time period with no drug or perhaps a
25 | placebo, and we have a placebo run-in period where the

1 patients score their symptoms or some of the efficacy
2 measures, and we get a baseline.

3 Then the patients are put on drug or controls,
4 and they're again treated for a duration, and again the
5 same measures are recorded again, and we get a treatment
6 effect. The difference of the baseline and treatment is
7 the drug effect or the drug efficacy.

8 The duration of studies typically for a
9 seasonal allergic rhinitis study are 2 weeks. The
10 perennial allergic rhinitis studies are 4 weeks. However,
11 there are some exceptions to that.

12 The next study design that we usually see is
13 the day-in-the-park study, which is again a natural
14 exposure study. The patients who are allergic to some
15 environmental agents are taken to a park and at the time
16 they're taken, presumably the allergen exposure is very
17 high, and they're given the drug, and again they score
18 symptoms. These studies last for a day, 2 days, or 3 days,
19 and the symptom scores here are done very, very frequently.
20 Again, these are usually parallel-group studies.

21 The third kind, the EEU kind, is an artificial
22 setting. The patients are usually studied out of season,
23 which means they're not exposed to the usual allergens.
24 They're brought into the allergy unit, the EEU unit.
25 They're exposed to the allergen to sensitize them, and once

1 | they're sensitized, they're brought back and given the drug
2 | or the placebo, either in a parallel fashion or in a
3 | crossover fashion, and then the effect of the drug is
4 | studied.

5 | Now, when we go from the natural exposure to
6 | the EEU, we're actually migrating from a natural study more
7 | to a pharmacodynamic study, the EEU being a classically
8 | pharmacodynamic study. The EEU studies are typically used
9 | to look for pharmacodynamic questions, such as onset of
10 | action.

11 | The common studies that we see are typically
12 | natural exposure studies. During drug development,
13 | sponsors and companies usually do a dose-ranging study to
14 | pick an effective or therapeutic dose, and they are
15 | typically done in the natural exposure setting.

16 | Now, the second point I want to cover are the
17 | endpoints, and as I said, there can be varieties of
18 | endpoints one can look at. The ones that we typically use
19 | and the ones that are validated are based on patient
20 | scoring of symptoms. Depending on the drug, they can be
21 | nasal symptoms or non-nasal symptoms, and a scoring scale
22 | can be done in a variety of ways. Typically now, more and
23 | more people are using the 0-3 scale. When I show you
24 | examples, I'll show these scales. Maybe in some studies
25 | different scales were used.

1 The symptoms typically for a nasal drug would
2 include nasal symptoms, such as itching, sneezing,
3 rhinorrhea, and congestion.

4 Now, there are potentially other objective
5 pharmacodynamic measures. For example, measuring nasal
6 passage patency or inflammatory markers, such as cytokines,
7 chemokines, cells, and nitric oxide. At this current time,
8 they are a pretty useful experimental scientific tool.
9 However, they are not validated to the extent that it can
10 be used in clinical trials. Therefore, they are not
11 typically used for drug approval.

12 Now, on to my examples, and I will use three
13 drugs or drug substances to show why and how it is
14 significant to show dose response. Some of the data I will
15 show are proprietary. Therefore, I'll be using made-up
16 names, A, B, and C. However, some of these, actually the
17 results are published or available in the public domain.

18 Just to make a point that these problems with
19 dose response are not something unique to the suspension.
20 I will show an example with a solution also.

21 The studies that I will show are pretty large
22 studies. I'll have five clinical trials that I will run
23 through. For the solution, it will be a day-in-the-park
24 study. If you remember, this is more of a pharmacodynamic
25 kind, short duration of exposure. For the drug B and drug

1 C, I will show one natural exposure dose-ranging study for
2 B and for C, and then I'll also show a study where actually
3 a suspension spray formulation was compared with an aerosol
4 formulation. So, a lot of data. I'll go through the five
5 clinical trials that are described one by one.

6 The first one, this is a solution nasal spray.
7 I'll call it drug A and this is a day-in-the-park dose-
8 ranging study.

9 Now, this study was conducted in two U.S.
10 centers about 11 years ago and they were conducted on
11 seasonal allergic rhinitis patients, ages 12 and older.
12 The patients were in the park for 2 days and the drug here
13 was used on a b.i.d schedule, which means on day 1, they
14 got a dose in the morning and in the evening. On day 2,
15 they got a dose in the morning. The three dose levels will
16 be clear when I show the results.

17 The efficacy measured here was instantaneous
18 scoring. By instantaneous, it is meant how the patient is
19 feeling at the time when he is scoring, like how do I feel
20 now?

21 In this particular study, they used six
22 symptoms, which are listed here, mostly the nasal symptoms.
23 There were also eye symptoms. The scale here was not 0 to
24 3, but is 0 to 5, which was used at that time, and the
25 symptoms were scored hourly when the patients were in the

1 park in the morning of day 1 and day 2, and when they went
2 home they were scored less frequently. To show the
3 results, they were all summed up, and this sum of scores
4 that I'm going to use is called major symptoms complex.

5 This is the baseline that I'll show first. For
6 this slide, and throughout the presentation, the legends
7 here from top to bottom will follow the bars which are from
8 left to right. So, left-most will be the top, and again
9 throughout my presentation, the placebo will be the top or
10 the left, and the color will be blue.

11 In this particular study, there was an active
12 control, which was chlorpheniramine, and as I was talking
13 about earlier, there were three dose levels and these are
14 the three dose levels. This is one spray b.i.d., two
15 sprays q.d., and two sprays b.i.d. The number of patients
16 were approximately 50 in each group, a pretty large study.

17 This is the mean score, so they were not really
18 very comparable. However, they were pretty close, between
19 9.5 to about 10.5.

20 Now, this is the result on treatment. Since
21 the baselines were not really very much the same, I'm
22 expressing the results here as mean percentage change from
23 baseline. If you see the result here, between placebo and
24 active drug, there's approximately a 30 percent difference.
25 We are working in a 30 percent range to show an efficacy

1 and we are actually trying to show a dose response here.

2 These are the three active drugs, and if you
3 look through, it is very difficult to pick up a dose
4 response. If you see, for example, the yellow bar, which
5 is one spray b.i.d., and then the dark red, two sprays
6 b.i.d., you perhaps see a dose response. However, if you
7 look at this, which is two sprays q.d. once a day and two
8 sprays b.i.d., the two sprays once a day appears to be more
9 efficacious than two sprays b.i.d., which goes against it.

10 So, really, this is almost like a random
11 phenomenon, and I'll show more examples, because here one
12 can argue the separation of the doses were not that large.
13 One spray, two sprays, just two-fold difference.

14 Let me show another example. This I'm calling
15 drug B, and again there will be two trials I'll show. The
16 first one will be a natural exposure dose-ranging trial and
17 the second one is going to be a comparative study.

18 Now, this is the dose-ranging study, and as I
19 said before, this was a natural exposure study, which means
20 long duration. It was done in 14 centers in the U.S. about
21 seven years ago. The patients were ragweed-sensitive
22 seasonal allergic rhinitis patients ages six and above.
23 There was a 1-week baseline period for the baseline scoring
24 and there was a 4-week treatment for the drug effect.

25 The treatment here was q.d. There were four

1 doses used and, as I will show you in the results, the
2 separation of the doses here were actually over an eight-
3 fold range, pretty large.

4 Efficacy here was 12-hour reflective, and the
5 reflective means how the patients are feeling or had been
6 feeling for the last 12 hours, almost like an area under
7 the curve for efficacy.

8 They measured here three nasal symptoms --
9 runny nose, nasal congestion, and sneezing -- on the
10 typical 0-3 scale. They were all summed and the total sum
11 is called the nasal index score.

12 This is the total result and this is the nasal
13 index score. This is the baseline treatment and the
14 change, which is the difference between treatment and
15 baseline. The baselines are very comparable. I'm showing
16 raw data here. The point to look at really is the change,
17 because this is the difference between baseline and
18 treatment, and the doses here are between 32 and 256,
19 eight-fold, and the placebo response size here is about
20 less than 1. If you look at all four, it's basically a
21 flat curve. The lowest and the highest dose, virtually
22 there is no difference.

23 I tried to look to see if looking at individual
24 symptoms that this composite is made up of would show
25 anything, and it actually did not, and here it is.

1 Rhinorrhea score, sneezing score, congestion scores. If
2 you look at any of these, if there were any hints, perhaps
3 it was for congestion, but again the lowest dose was more
4 effective than the higher dose. Really, it's almost like
5 random for almost all the doses.

6 Well, this is another study with the same
7 active drug substance, drug B, and there are two
8 formulations in the same study. One is a suspension,
9 aqueous, and the second one is an aerosol.

10 The design, this was a natural exposure, seven-
11 center Canadian study. Patients were ragweed-sensitive
12 seasonal allergic rhinitis, ages 12 and above. It had a
13 1-week baseline period, followed by 3 weeks double-blind
14 treatment.

15 The three dose levels, again the same drug,
16 q.d. dosing. The efficacy here was the same: 12-hour
17 reflective, three nasal symptoms, and the scale is 0 to 3.

18 If you look at the results, it's really the
19 same story. These are three nasal symptoms: rhinorrhea,
20 sneezing, congestion. This is the sum of these three, and
21 this is eye symptoms.

22 Let's just pick up this one and look at it,
23 because they all are the same. This particular second bar
24 here, the dark red, is 256 q.d. This is spraying. The
25 second one is 400 q.d., again the spraying. So, this is

1 | the lower dose and this is the higher dose. It goes in the
2 | opposite direction.

3 | This one is 400 q.d. spraying. This one, 200
4 | b.i.d., which is equal to 400 q.d. total dosing. This is
5 | an aerosol. If you look at it, the same dose virtually.
6 | You see some separation. So, bottom line, this is all
7 | almost waving around the baseline.

8 | Let me go to my last example, which is drug C.
9 | I picked up these examples because I looked through almost
10 | all the drugs which are approved in the country and picked
11 | up three just to make the point. The first one I picked up
12 | was a solution. The second one I picked up was a classic
13 | case representative of almost most of the drugs. The third
14 | one I picked up because this particular drug moiety perhaps
15 | has a hint as to what is a dose response, so this may be
16 | the best case scenario. And let me show you two studies
17 | with this drug.

18 | This was a natural exposure study done in 15
19 | centers in 1992, pretty large. SAR patients, 18 and above.
20 | There was a 1-week baseline period, followed by 4 weeks of
21 | treatment. Q.d. dosing and the four dose levels. And the
22 | range here is higher, 16-fold, so there's a wide spectrum
23 | of dose ranges covered here.

24 | The efficacy was almost like before, 12-hour
25 | reflective. Here they looked at eight symptoms, runny

1 | nose, congestion, sneezing, itching, and a couple of eye
2 | symptoms, and they were scored on a 0-6 scale every
3 | morning.

4 | This is the result. The primary efficacy
5 | measurement here in this particular study was done by
6 | physicians. Typically, we would like patients to rate
7 | because patients know the symptoms better, and the others
8 | which I showed earlier were all patient recording. This
9 | one was physician recording, although the study also had
10 | patient recording and I'll show that later on. The primary
11 | was physician, so let me show that first.

12 | The results are mean change from baseline, and
13 | I'm showing it sliced on different days, day 3 through day
14 | 28. The points are almost all the same. I'll just pick up
15 | on day 21 and show the results.

16 | This is the change with placebo, and the effect
17 | size for placebo is about 30 percent, which we have seen
18 | typically with the nasal placebo spray because they are
19 | really also active.

20 | Here, as I said before, this is a drug that has
21 | got some hints of a dose response. However, they are
22 | within approximately 7, 8, or 9 percentage points, so it's
23 | a very tight range. And if you look at other days -- for
24 | example, day 14 and day 28 -- it is not that consistent
25 | anymore. So, again, it is almost at the top of the dose-

1 response curve, and what one is seeing is almost a
2 fluctuation around that, and even if this really had a dose
3 response, the margin between the lowest dose and the
4 highest dose, and the difference being 16-fold, are so
5 close that one would not be able to pick a difference
6 between these two extremes of doses.

7 As I said, I'll also show the patient scoring,
8 because they were done, and the point is here again the
9 same. If you look at day 21, for example, there is a hint,
10 but again it is within a very tight range, within perhaps
11 about 10 percent or so.

12 The last study that I will show is another
13 dose-ranging study where a suspension and spray were used.
14 It's a pretty recent study done about two years ago, a very
15 large study done in 32 centers. It was again a natural
16 exposure study. Patients were seasonal allergic rhinitis,
17 ages 12 and above. The study had a 1-week baseline,
18 followed by 2 weeks double-blind treatment.

19 It was q.d. dosing of three dose levels from
20 two devices. Again, a pretty wide spectrum, eight-fold
21 range.

22 Efficacy was the same as before, 12-hour
23 reflective. However, they only measured four nasal
24 symptoms -- rhinorrhea, congestion, sneezing, and itching
25 -- on a 0-3 scale.

1 This is the result. I'm showing this result as
2 mean percentage change from baseline, and the primary was
3 day 1 to 15. The first week and the second week is also
4 shown here. Let me just go through this, which is day 1
5 through 15.

6 The first bar here is placebo, and there are
7 two formulations here, so three of these would make a pair.
8 Second, third, fourth, and fifth, sixth, and seventh.
9 These are two. These three are with the aerosol and these
10 three are with the spray.

11 If you look at it, the placebo response was
12 again in this study about 15 to 20 percent, and if you look
13 at the day 1 to 15, there is again a hint towards a dose
14 response. However, we are again working within perhaps
15 even 4 percentage points here. So, virtually, if you do
16 statistics on that, I don't think one would ever be able to
17 pick a difference between the lowest and the highest dose,
18 and chances are that if the study was done again, it may
19 come another way. And if you look at the second week, day
20 9 to 15, it does not really hold up. So, for an eight-fold
21 difference, there is no dose response.

22 So, the bottom line here is for these nasal
23 sprays, either solutions or suspensions or aerosols, there
24 is perhaps no dose-response relationship, and if it exists
25 it is very difficult to show, irrespective of what study

1 design you pick up. I showed a natural exposure study
2 because that's what we have data on. I showed one day-in-
3 the-park study where one could not see a dose response.

4 The question comes up really why we don't or we
5 fail to show a dose response. The reasons may be perhaps
6 that the symptom score that we have at this time for
7 assessment of efficacy for these drugs is not a sensitive
8 enough measure to show a dose response. For now, that's
9 all we have, because the other measures which I talked
10 about earlier -- for example, the mediators or other PD
11 measures -- are not validated to be used to assess dose
12 response.

13 The second, which was touched upon earlier, is
14 for many of these drugs, perhaps we are working at a high
15 flat portion of the dose-response curve, and Dr. Conner
16 showed towards the end of his talk the flat portion, and
17 perhaps we're working there. So, it doesn't matter if you
18 make a difference between the drugs 10-fold which I showed
19 here, they are the same. I believe even if it was not the
20 case, the assay that we have is perhaps not sensitive
21 enough.

22 That's all I had, and thanks for your
23 attention.

24 DR. LEE: Well, thank you very much.

25 Les?

1 DR. HENDELES: I have two quick questions.
2 What is the impact of the pollen count? Does that change
3 the dose-response relationship? And then also, is there a
4 frequency-response relationship? I recall early data with
5 beclomethasone showing that three times a day was better
6 than once a day.

7 DR. CHOWDHURY: First of all, the pollen count
8 on these studies were looked at, and of course the pollen
9 count results come after the fact, and the pollen counts
10 indeed were high in most of the studies. The day-in-the-
11 park studies, typically pollen counts were high that day.
12 So, pollen counts typically do not have any impact on this.
13 However, if you move to an EEU setting, that may be a
14 different question.

15 The frequency I do not think has an effect
16 either, because we are on the flat portion, so it doesn't
17 matter, and the formulation itself limits how much really
18 you can go down.

19 DR. LEE: Other questions? Yes, Dr. Roman?

20 DR. ROMAN: Actually, Leslie, in one of the
21 studies on drug B, there was q.d. versus b.i.d. and there
22 was no difference. So, even the presented studies showed
23 that frequency really doesn't mean anything.

24 I just want to make one point, and I know we
25 will be discussing it later, so not to belabor it. One of

1 | the conclusions you made is that potentially we're on the
2 | flat curve part of the curve for dose response and we do
3 | not study the lowest effective dose. One of the
4 | limitations of what we define as the lowest effective dose
5 | is a dose which separates statistically from placebo, and
6 | throughout all your presentation we see that effectiveness
7 | is here, at the best, 10-20 percent or twice the placebo or
8 | less, and the lowest dose, if we go lower, will just simply
9 | not separate from placebo. So, I think it's a method
10 | problem, rather than the dose selection problem.

11 | DR. CHOWDHURY: That is correct. That is
12 | correct, and perhaps with the drug C which I showed, I
13 | mean, there is a hint towards a numeric dose response, but
14 | again, if you go down in the dose, you'll be hitting
15 | placebo. Your point is actually well-taken, but for
16 | perhaps some of the older drugs which have been in the
17 | market perhaps for a longer time and the safety was not
18 | that much appreciated, it is an open question where they
19 | are on the dose-response curve.

20 | DR. ROMAN: Exactly, and also I assume that
21 | whenever you said no difference, you mean of course no
22 | statistical difference, and whenever you said difference
23 | means statistically significantly different.

24 | DR. CHOWDHURY: That's absolutely correct.

25 | DR. ROMAN: Not that I think that "statistical"

1 is the only way of believing that that works, but it's our
2 way.

3 The last quick statement is also that the
4 pollen counts you said several times were measured and they
5 were not really different.

6 DR. LEE: I just noticed that Walt was
7 motioning to say something.

8 DR. HAUCK: Just a quick question, actually.
9 This might be more for Wally. Since you did have placebo
10 in all these studies, I couldn't tell, looking through your
11 notes, Wally, as to whether placebo is going to be
12 recommended in your clinical studies in fact.

13 DR. CHOWDHURY: Yes.

14 DR. LEE: Very well. I think we do have time
15 set aside for discussion at 11 o'clock, and I think now I
16 was told that we have to take a break. Is that right? So,
17 would you please come back at 10:30 and we will hear a
18 presentation with Dr. Meyer on the study design.

19 (Recess.)

20 DR. LEE: Will the subcommittee members please
21 take a seat?

22 I think that Dr. Meyer is very interested to
23 get going. He is ready. He is going to tell us about
24 study design and the topic he will address is clinical
25 study options for locally acting nasal suspension products,

1 | clinical studies and pharmacodynamic studies.

2 | DR. MEYER: While that's being done, while they
3 | get my slides actually to show, I just wanted to basically
4 | recap and set the stage for what I'd like to talk about.

5 | If you recall from Wally Adams' slide about the
6 | history of how we came to be here today, in about 1995 my
7 | division, which was then the Division of Pulmonary Drug
8 | Products, sent a memo of advice on what we would consider
9 | sufficient to establish bioequivalence for the nasal
10 | sprays, given the relative short distance the drug product
11 | had to travel and the less complex anatomy than, say, the
12 | upper airways and in fact the lower airways, and the other
13 | characteristics of the nasal sprays. We had felt at that
14 | point that even for the suspension nasal spray products,
15 | that a package consisting of in vitro sameness,
16 | pharmacokinetic sameness, and Q and Q sameness, and so on
17 | was sufficient to establish bioequivalence and did not feel
18 | a clinical study was necessary.

19 | However, with the concern raised about the
20 | possibility of particle size distribution in the
21 | formulation itself making a difference in terms of
22 | efficacy, we had shifted to working with the OGD folks to
23 | argue that perhaps if that is the case, that if one wanted
24 | to convincingly establish bioequivalence, one must do an in
25 | vivo study. And if you're doing that to establish the

1 bioequivalence, you have to do it in a manner that
2 demonstrates the study itself was sensitive to dose
3 response, and in fact the response for the test and the
4 reference were the same, given the sensitive study design.

5 However, at the same time that we said that and
6 the same time we put that in our guidance, we were also
7 cognizant of the fact that showing dose response with
8 clinical studies, as Dr. Chowdhury has reminded us all in
9 his talk, is extremely challenging.

10 Now, one could argue that if you looked at the
11 data that Dr. Chowdhury showed, that if in fact an eight-
12 fold dose really doesn't make much difference, why are we
13 all that concerned about the possible impact of particle
14 size distribution in a nasal spray suspension? And the
15 fact of the matter is that I think everybody in my division
16 and elsewhere is concerned that although on the mean dose
17 doesn't seem to make much difference, individual patients
18 are likely sensitive to dose. So, even if you can't easily
19 show a dose response in a large study on mean, that does
20 not negate the fact that dose may matter to individual
21 patients.

22 So, that's just kind of setting the stage for
23 how we came to be here today, and following on to the talks
24 given this morning, I'd like to touch on four basic areas
25 in my talk today.

1 I wanted to talk about what the options are for
2 a "clinical" study. And you'll notice that I have that
3 almost in parentheses there, or certainly in quotations,
4 because largely what I'm talking about will be study
5 designs with clinical endpoints, but two of the study
6 designs that we in the division consider more, in some
7 ways, pharmacodynamic in characteristic because they're
8 more controlled, less natural, less generalizable. Then I
9 will talk a little bit about the details of the clinical
10 studies we normally see.

11 After I've done that, I'd like to really
12 address this bullet, which is what is the question that
13 you're expecting these studies to answer. Because clearly
14 the study design that you choose will be critically
15 dependent on the question that you're putting to that
16 study. What answer are you expecting to get out of the
17 study? Once you clarify the question, then what is the
18 best study design to accomplish the end result that you're
19 looking for? And then I'll close with some observations
20 and come back to the recommendation that Wally Adams had
21 shown earlier.

22 Well, in terms of what are the options for
23 study design, the disease in question here is allergic
24 rhinitis, as you've already heard, and that disease is
25 primarily experienced and assessed subjectively, although

1 | there are ways of assessing airway patency or perhaps
2 | disruption of the nasal mucosa in terms of scoring allergic
3 | rhinitis. Primarily, again, as patients experience it, it
4 | is a symptomatic disease and that is how we have
5 | historically assessed it and how we are most comfortable.
6 | In essence, the most clinically validated pathway for
7 | assessing allergic rhinitis is through subjective measures.

8 | The basis of approval has been, then, with
9 | clinical studies with subjective symptom scoring, and Dr.
10 | Chowdhury took us through that earlier, but typically these
11 | would include a total nasal symptom score where you have
12 | component scores for runny nose, for congestion or nasal
13 | blockage, sneezing, and nasal pruritus.

14 | Pharmacodynamic questions, such as things like
15 | onset of action or the appropriate dose or the dosing
16 | interval, frequently, although they may still be addressed
17 | through a clinical endpoint, are addressed with differing
18 | designs in our applications. But even if we do have some
19 | day-in-the-park studies or some EEU studies, we really
20 | expect the basis of approval to come through the natural
21 | clinical study because this really integrates safety,
22 | efficacy, and a more generalized setting.

23 | As Dr. Chowdhury had said earlier, these are
24 | generally short-term studies. Two weeks is typical for
25 | seasonal allergic rhinitis; four to six weeks for perennial

1 allergic rhinitis, often parallel group and looking at
2 comparative changes in total nasal symptom score over the
3 treated period. In other words, change from baseline for
4 active versus the placebo.

5 Patients are enrolled prior to or at the start
6 of their season, they go through a baseline period to
7 establish their symptoms, and then are randomized.

8 As I said, this really allows for the
9 assessment of efficacy, but really fully, for a season
10 anyway, it would allow a reasonable assessment of safety
11 and tolerability. Perhaps not fully elaborating on
12 systemic safety, but certainly on local safety and
13 tolerability.

14 The EEU study uses a clinical endpoint, but in
15 some ways we regard this more as a pharmacodynamic tool and
16 not as a firm basis of approval, because it does not fully
17 integrate the clinical response and is not perhaps as
18 generalizable, but a useful tool nonetheless. As Dr.
19 Chowdhury had previously conveyed, this is typically done
20 out of season and exposes patients with known sensitivity
21 to an allergen to high levels of a specific pollen, where
22 everyone is exposed in a chamber at the same time to the
23 same high level of pollen, and then symptoms are assessed
24 over a very short-term period, typically over a period of
25 hours following their exposure within the chamber.

1 These are often used for assessing onset of
2 effect in dose finding. However, I would say that I'm sure
3 that we have very firm data to establish that this study
4 design is much more sensitive to dose response than is the
5 typical natural study.

6 Then somewhere in between the two studies, in
7 terms of generalizability and intent, is the day-in-the-
8 park study, where a cohort of patients with known allergen
9 sensitivity, but typically a fairly low level of symptoms,
10 are taken to an outdoor setting where they're all exposed,
11 because they're all in the same place, to the same pollen
12 counts. But this is in essence a natural short-term
13 exposure and it does allow for some short-term efficacy and
14 safety. Again, typically in our packages, although it sort
15 of crosses between a true clinical study and a more
16 pharmacodynamic study, it is used more for pharmacodynamic-
17 type questions, such as onset of effect and assessing dose
18 response and duration of effects.

19 So, from our divisional standpoint, from the
20 Division of Pulmonary and Allergy Drug Products -- and
21 actually, in the intervening time since the guidance that
22 we're discussing today was published, we have published a
23 draft guidance on the evaluation of products for allergic
24 rhinitis -- we regard the natural clinical study as most
25 informative for approval purposes. Again, we regard these,

1 | even though they use clinical endpoints, as more
2 | pharmacodynamic in nature, and to date we've not approved
3 | new drugs solely on the basis of things like EEU, although
4 | those kind of studies are often in the NDA packages.

5 | Other objective endpoints in any of the study
6 | design, be it the natural study or one of the shorter-term
7 | studies -- and those would be assessments of nasal patency,
8 | such as acoustic rhinometry or markers of inflammation --
9 | we would regard as interesting, but not clinically
10 | validated. And I would say that I'm not aware of data that
11 | would establish these as being particularly more sensitive
12 | to dose response than our clinical study either.

13 | So, let's turn to the question that we're
14 | bringing to the clinical study for bioequivalence. I think
15 | the way to really look at this, although I don't want to
16 | perhaps hang my hat too firmly on these terms, is are we
17 | looking at the study to really confirm a data package that
18 | has otherwise established pharmaceutical equivalence and
19 | bioequivalence, or are we looking at this as the primary
20 | means for establishing bioequivalence, and everything else
21 | is sort of background, but viewed as less important. So,
22 | really that depends on one's interpretation of the in vitro
23 | and BE comparisons.

24 | But if one takes the pathway that the clinical
25 | study is confirmatory, then your question that you take

1 | into the clinical study is you want it to confirm a lack of
2 | important clinical difference from any of the unknowns that
3 | might remain after you've fully assessed through in vitro
4 | and PK comparisons.

5 | If you look at it more as pivotal in
6 | establishing bioequivalence, then you really have to have a
7 | study that can do that, and I'll get to what I mean by that
8 | in a second.

9 | So, for the confirmatory role, we could really
10 | look to a design that broadly assures no important clinical
11 | differences, given an already established background of
12 | pharmaceutical equivalence and systemic pharmacokinetic
13 | sameness.

14 | If you were looking at a confirmatory setting,
15 | then, you really would not have to show a rigorous dose
16 | response or show sensitivity to dose of the test so much,
17 | because you're not going to be looking at the test and
18 | reference in such a discriminating manner. So, therefore,
19 | the comparisons could be done at a low-dose level in
20 | looking for comparable efficacy, safety, and tolerability
21 | in that study, taken on the background of everything else
22 | that has been done to date to establish equivalence.

23 | If the intent taken to the clinical study,
24 | however, is to establish bioequivalence, then you really
25 | must show that the study design could discriminate between

1 rather small differences in doses. In some of the studies
2 that Dr. Chowdhury showed, we were looking at eight-fold
3 differences in dose with very little change in clinical
4 response. Clearly, a drug product that was being developed
5 would have to be very, very different from the reference
6 product to show up in these clinical study designs as being
7 different. So, when you go to wanting the clinical study
8 to establish bioequivalence, really where we're hanging up
9 is coming up with a design that has sufficient sensitivity
10 to assess differences in dose.

11 Now, of course, even in this scenario, a
12 clinical study would still compare some relative safety and
13 tolerability, but in essence the difference in the question
14 you're bringing to the clinical study critically changes
15 the design that would be expected or the outcome that would
16 be expected.

17 Again, as Dr. Chowdhury I think showed from his
18 survey of studies, and we have many, many others,
19 bioequivalence would be very difficult to establish with
20 standard designs and endpoints. So, the task set out in
21 the draft guidance of two years ago of using the clinical
22 study really to establish bioequivalence, because of this
23 concern about the particle size distribution within the
24 drug formulation, is very daunting indeed, and in fact in
25 our experience may prove to be impossible.

1 Now, we did allow in the draft guidance for the
2 possibility of using either EEU or day-in-the-park-type
3 studies to look at this, but I must emphasize that we don't
4 really have data to say that they are much more sensitive
5 to dose effect. So, it's not entirely clear. They may be
6 a better approach to establishing bioequivalence, but it's
7 really somewhat of an unknown. But clearly, they could
8 have a role in a confirmatory setting, just as a natural
9 exposure clinical study would.

10 Now, we have had some comments to the draft
11 guidance about the possibility of using a true
12 pharmacodynamic-type endpoint, such as markers of nasal
13 inflammation or measures of nasal patency. But as I've
14 said before, these are really unproven in sensitivity to
15 dose response and/or they're not clinically validated, so
16 any differences detected in those may or may not be
17 informative about the clinical differences we're concerned
18 about.

19 Other potential endpoints in standard trials,
20 such as well-validated and constructed health-related
21 quality of life instruments, could be potentially useful,
22 and this was again a comment raised to the docket, but I
23 think that they're unproven as superior in sensitivity to
24 dose response.

25 So, really the question that we're bringing to

1 | the subcommittee today is that we have a concern raised by
2 | comment from industry that the uncertainty about particle
3 | size within the suspension formulation for nasal sprays
4 | could impact on the local bioavailability of the
5 | formulation, but as Wally Adams pointed out, that
6 | contention was made without supportive data to show that
7 | particle size within such a suspension nasal spray would,
8 | in fact, lead to clinical differences. But it is at least
9 | a scientific concern and one that we've taken very
10 | seriously in our draft guidance.

11 | However, given the difficulties of establishing
12 | dose response within clinical studies and using the
13 | clinical study in this package to actually establish
14 | bioequivalence, and given the fact that we're not entirely
15 | certain that this concern is in fact clinically important,
16 | we're now contemplating shifting the question of the
17 | clinical study in the BE package.

18 | I must say, however, that no matter how one
19 | regards the clinical study, it would not trump the lack of
20 | equivalence from in vitro or systemic bioavailability. In
21 | other words, if the sponsor of the test product couldn't
22 | show that they had similar or reasonably comparable in
23 | vitro characteristics to define the drug as being the same,
24 | and they were not able to show comparable systemic
25 | activity, then they wouldn't even get to the point of doing

1 a clinical study in either of the paradigms that we've
2 discussed, either in the draft guidance, where we're asking
3 for dose response, or in the paradigm that we're presenting
4 today.

5 I did also want to stop and make one other
6 point that follows on to Dr. Conner's presentation earlier,
7 or perhaps this is actually from Wally, but what we're
8 asking for in this draft guidance is Q and Q sameness. Dr.
9 Conner was very careful in his talk to talk about having
10 the same drug substance, same route of administration, same
11 dosage form. We're actually going a step beyond what is
12 required for oral products, for instance, where the
13 excipients can differ. We're saying the excipients have to
14 be the same, and in fact they have to be very close in
15 their proportion in the drug formulation. So, we're
16 already going a step beyond that in terms of Q and Q
17 sameness, and then asking for characterization of the in
18 vitro characteristics of the device itself, since that's
19 critically important in how the drug is delivered to the
20 patient and released, and then looking at systemic
21 exposure.

22 If all of that gets you to comparability or
23 sameness, then what we're saying is perhaps we could look
24 at the clinical study as being confirmatory in nature, and
25 if one wanted to do that, given the dose-response curves

1 that Wally had shown us earlier, one could examine the
2 lowest dose of the test versus the reference and do a
3 statistical comparison between this lowest dose, as they
4 relate to placebo, ensure therefore that the test or the
5 new product is not meaningfully different in this clinical
6 study from the reference product, and given that, with all
7 this background, one could say that one has equivalence.

8 Now, if we went forward with this paradigm, one
9 of the questions, or actually the heart of the questions
10 presented, is what then would be the best way to do that?
11 Would it be through a clinical study, an EEU study, a day-
12 in-the-park study, or perhaps some other study design?

13 So, that is a summation of how we got here and
14 the background to the questions that we're presenting
15 today, and I'm happy to entertain a few minutes of
16 questions, I guess, if anybody has any.

17 DR. LEE: Well, thank you very much, Dr. Meyer.

18 I think that the conclusion I can draw from
19 this morning is that the PowerPoint presentation really
20 keeps everybody on time, ahead of schedule.

21 I see that Les is ready for some questions.

22 DR. HENDELES: Is there any evidence that nasal
23 challenge studies produce a dose response? I personally
24 haven't seen that data. I was wondering if you have. Any
25 form of nasal challenge.

1 DR. MEYER: I'm not really aware of data that
2 has really established that, number one, and number two, I
3 guess, depending on the particular challenge that you're
4 talking about -- frequently we're talking about sort of Q-
5 tips dipped in allergen and applied topically -- I think
6 we'd still have the question of clinical validity of that,
7 too. So, to me, it sort of has two strikes against it
8 right now, not to say that it couldn't be useful in the
9 future, but I'm not sure how well it's been related to
10 clinical differences and I'm not aware of data that firmly
11 establish that could easily show dose response either.

12 DR. OWNBY: I've got a question. If you've got
13 Q and Q identity between the reference and the test product
14 and you've got a device that's substantially the same, if
15 not identical, is there any evidence to say you could then
16 generate an aerosol that would be substantially different?

17 DR. MEYER: The question that really brings us
18 here is not so much about the aerosol itself, but about the
19 particle size within the droplets, and if those were to be
20 substantially different, you wouldn't detect that through
21 any of the testing we do because in the suspension
22 products, for instance, the excipients, such as methyl
23 cellulose, really interfere with your ability to assess in
24 a validated manner the particle sizing of the drug
25 substance.

1 The concern, then, isn't that the aerosol is
2 different or that the deposition is different. It's that
3 when the particles get to where they're going, because they
4 might be different sizes, they might have different rates
5 of an extent of absorption.

6 But our concern isn't, given Q and Q sameness,
7 and in an ideal situation even the same metering pump and
8 so on, that we would suspect the aerosol itself will be
9 different.

10 DR. LEE: Dr. Roman?

11 DR. ROMAN: Yes. I would like to sort of
12 organize my understanding and thoughts after your
13 presentation, and if you can help me with this.

14 So, I understand that you believe that there
15 are two reasons why the company would do clinical studies,
16 one which you say is confirmatory and one when you do not
17 have any previous bioequivalence based on the blood sort of
18 measurements. And if there isn't any previous
19 bioequivalence established by blood measurements, then you
20 are suggesting that clinical studies of nasal allergy will
21 include dose response.

22 DR. MEYER: Not exactly. What I'm saying is
23 that we in the draft guidance have said that everything
24 else has to be the same, the in vitro package and the
25 systemic bioavailability, either directly measured by the

1 blood, preferably, when that's possible, or established
2 through HPA axis or some other measures of systemic effect
3 in a pharmacodynamic study. So, that is given in anything
4 that I said. So, if one were to fail to show sameness to
5 any of those, to the in vitro package or to the systemic
6 bioavailability, you're not equivalent and you couldn't go
7 the generic route under this paradigm.

8 So, the main thing is the question that you're
9 putting to the clinical study, and that really gets to the
10 uncertainty that's remaining after you do everything else.
11 If you feel like there's a lot of uncertainty, then you
12 really need the clinical study to establish bioequivalence,
13 and therefore you need a very sensitive study design that
14 can clearly separate small differences in dose and then
15 show sameness.

16 If one takes the remaining questions after
17 you've looked at all the in vitro package and the
18 pharmacokinetics are very few, then you're just looking to
19 any clinical study to just make sure there aren't any
20 important signals that we've missed in everything else
21 we've assessed, because clearly, although what Wally Adams
22 has presented is a very comprehensive package that we're
23 expecting from folks, including Q and Q the sameness all
24 the way down, there are always going to be some remaining
25 uncertainties.

1 So, the question really is what are you
2 expecting the clinical study to do? If you're only
3 expecting it to really kind of put the products into
4 comparison where you're looking for just any important
5 signals of difference, you're really expecting much less of
6 the data than where you're having to establish sensitivity
7 to dose response and then critically look at that dose
8 relationship.

9 Now, I do want to emphasize, we're still
10 talking about statistical comparisons of this lowest dose
11 in what we're asking about today, but it's really kind of a
12 shift in what you're asking the clinical study to
13 demonstrate.

14 DR. ROMAN: Okay, because one of the obviously
15 reasons of the design -- and if you don't mind, I will
16 concentrate on the natural exposure, because I agree with
17 you that potentially the EEU and the park study, it's more
18 of a pharmacodynamic in terms of questions you ask.
19 However, since we are talking about products which are
20 mostly taking some time to act, such as steroids, a single
21 dose or very few doses which you can deliver during the
22 park study really excludes the study designs for any
23 meaningful clinical study with steroids, because even in
24 the data presented previously, you can see that there is an
25 increase in effect with time. So, indeed, the natural

1 exposure of 2 weeks for steroids is probably the minimum
2 which we can use for establishing efficacy, not to mention
3 differences in doses.

4 But one of the major reasons we have a problem
5 with dose response is that this nice sort of S-shaped dose
6 response which we would all like to see does not work with
7 intranasal delivery systems, and one of the reasons
8 actually is that placebo is an effective treatment. A
9 nonclassical way of treating nasal allergy is by washing
10 the nose with water or with saline, and that is an
11 effective, nonmedical, if you wish, treatment. So,
12 delivering vehicle really acts almost as an active
13 treatment. Therefore, on an S-shaped dose response, the
14 placebo will be around 20 or 30 percent of the maximum
15 response with an active drug. So, we can never get into
16 the lower levels of concentration of the active formulation
17 because we have an active treatment, which is placebo.

18 DR. MEYER: By and large, I agree with that. I
19 think the interesting thing to me in that is that if you
20 think back to the first study that Dr. Chowdhury showed,
21 the placebo in that was vehicle. Correct?

22 DR. CHOWDHURY: Yes.

23 DR. MEYER: And actually, there was a pretty
24 good separation between placebo and chlorpheniramine in
25 that study. So, I think certainly the installation of the

1 | vehicle can wash away some allergen and be sort of an
2 | emollient in effect. I'm not sure that that's the whole
3 | answer to why we're not able to show a difference. That
4 | study would suggest that the placebo response, or actually
5 | the effective placebo, is not as huge a factor as one might
6 | suspect.

7 | DR. ROMAN: Actually, if I recall, this was the
8 | product A, which Dr. Chowdhury presented, and since they
9 | used chlorpheniramine as an active comparison, I would
10 | suspect that it was antihistamines which they were studying
11 | and it was in a park study.

12 | DR. MEYER: It was.

13 | DR. ROMAN: So, indeed, in a park study with a
14 | single dose, you have sort of an enlarged response with an
15 | active.

16 | DR. MEYER: Right. It gets you into a paradox
17 | with the nasal steroids because the longer you go, perhaps
18 | the more the placebo actually acts as a true therapy.

19 | DR. ROMAN: Exactly.

20 | Now, what I am discussing actually here is how
21 | to do the sort of well-designed clinical studies for
22 | bioequivalence with steroids, specifically. Again, I agree
23 | with you that we have to characterize them as well as we
24 | can, but there are limitations of methodology which we sort
25 | of cannot overcome with the subjective nature of an

1 endpoint.

2 DR. LEE: All right. I think that we should
3 give Dr. Meyer a break. Thank you very much.

4 Let me summarize what we heard this morning.
5 We began this morning with a charge from Helen Winkle about
6 why we are here, and then we went into the background to
7 address two questions in relation to the development of the
8 draft guidance on nasal BA/BE. Wally Adams gave a very
9 comprehensive history about that, and also we had
10 presentations by FDA scientists and clinicians about the
11 background information.

12 So, now we're moving into the session on the
13 agenda which is committee discussion, and the purpose of
14 this is primarily to clarify any questions from any of the
15 presentations made this morning. Then we're going to open
16 up the floor to the public hearing, and then we adjourn for
17 lunch. So, basically, this is an opportunity for the
18 subcommittee members around the table to pose questions to
19 the presenters.

20 And may I suggest that you identify yourself
21 when you speak for the minutes takers, and also, just
22 because you do not have a microphone in front of you,
23 doesn't mean that you cannot speak. All right?

24 DR. SHARGEL: Hi. I'm Leon Shargel, Eon Labs.
25 In general, bioequivalence studies, the in vivo

1 bioequivalence studies, have not been clinical studies. As
2 Dr. Conner mentioned, they were very often for oral dosage
3 forms, blood level kinds of studies. And in terms of those
4 studies, generic manufacturers do not do confirmatory
5 clinical studies or look at clinical differences between
6 the test and reference product, even though my brand-name
7 counterparts feel that it should be done.

8 In this particular case, we have been talking
9 about using confirmatory clinical studies. However, in the
10 case of pharmacodynamic endpoints, they're often
11 unsuitable, and again, if we did pharmacodynamic endpoints,
12 we wouldn't see the need in previous type products to do
13 confirmatory studies. It's usually assumed, such as in a
14 blood level time curve.

15 My question really is, in looking at a slide of
16 Dr. Meyer, I noticed that the environmental exposure under
17 one of the slides says, "Often used for assessing onset of
18 effect and dose finding." Is that a better endpoint and
19 more objective than a clinical study?

20 DR. MEYER: I think at this point we really
21 don't have enough data to look at whether differences in
22 formulation -- I would say from the innovator perspective,
23 we don't have enough data to say that that study design
24 would be discriminating in terms of differences in
25 formulation or other aspects of the drug product.

1 I think it is conceivable. Certainly as we've
2 wrestled with this, it is conceivable that such attributes
3 as onset of effect or offset of effect, in fact, might be
4 more informative or more sensitive to dose than some of the
5 other things we've traditionally looked at, but we really
6 don't have a lot of data to strongly state that that is the
7 case at this point.

8 DR. LEE: Yes, Dr. Ahrens?

9 DR. AHRENS: Dick Ahrens. I've got a couple of
10 questions for Dr. Meyer, again to follow up on the talk.
11 One is you noted that there would be statistical
12 comparisons between the lowest dose of test and reference
13 versus placebo to assure that there is not a meaningful
14 difference of test from reference. Is it possible to give
15 any idea of how "meaningful" is going to be defined and
16 what kind of comparison is going to be made there? Is it
17 simply failure to show a statistically significant
18 difference or will there be criteria in terms of showing
19 sameness? You get what I'm after here, I think.

20 DR. ADAMS: Dr. Ahrens, Wallace Adams speaking.
21 I think we'd have to look at that issue in more detail, but
22 at the present time, we have been discussing in our working
23 group about a statistically significant difference between
24 the low dose and the placebo as showing that there is
25 sensitivity to the study.

1 The difference between the test and the
2 reference?

3 DR. AHRENS: Yes, that's what I was interested
4 in.

5 DR. ADAMS: How would we assure equivalence for
6 that?

7 DR. AHRENS: Yes.

8 DR. ADAMS: I presume that would be a standard
9 two one-sided test procedure equivalence study looking at
10 the test-over-reference ratio.

11 DR. AHRENS: With the equivalence criteria yet
12 to be determined.

13 DR. ADAMS: Yes, that's correct. As Dale has
14 indicated, in the past the default criteria for that is 80
15 to 125, and so we most likely in our guidance would not
16 include an equivalence criterion or limits for that 90
17 percent confidence interval to meet, but we would have to
18 look clearly at that issue. You raise an important point.

19 DR. AHRENS: And one more question, if I might.

20 DR. LEE: Sure.

21 DR. AHRENS: And that relates to, if you look
22 at inhaled steroids as used in the treatment of asthma, it
23 seems to be clear now that one of the reasons it's so
24 difficult to show dose-response relationships there is
25 because most of the studies that have been done as parallel

1 studies in the past, and the between-subject noise, just
2 difference in asthma from one subject to the next, appears
3 to bury the very real dose-response relationships that are
4 seen, at least in some subjects, that can be identified
5 when crossover studies are done.

6 So, my question here is are you aware of any
7 data looking at nasal steroids where that issue has been
8 looked at where there are crossover, as opposed to
9 parallel, studies? I realize it would probably have to be
10 something like an exposure unit study.

11 DR. MEYER: I'm not aware of any data. I don't
12 know whether any of my colleagues from the FDA are, but I'm
13 not aware of any such data. Even given an EEU study
14 design, I think it would be still quite complex because of
15 the issues of priming and so on. There would be, I would
16 suspect, a significant period effect in such a trial that
17 would have to be dealt with.

18 DR. DYKEWICZ: Mark Dykewicz. A question about
19 I guess the efficacy versus safety assessments in terms of
20 comparing the test versus the reference drugs. The
21 proposal is that for assessing efficacy, you would look at
22 a single dose of the test versus reference drug, and am I
23 understanding correctly that in terms of assessing safety,
24 you'd look at a single dose of the test versus reference
25 drug, but using a dose that was the highest labeled dose or

1 | even beyond that? What I'm thinking of is that in actual
2 | use, there may be some patients who are using more than the
3 | labeled use of the drug, and so there might some additional
4 | safety issues about the labeling.

5 | DR. MEYER: According to the draft guidance
6 | currently, and we're not, I don't think, contemplating any
7 | particular change to this component, the systemic safety
8 | would be approached through pharmacokinetics measures at a
9 | high dose, and whether that would have to be within the
10 | label range or whether there might in fact be mechanisms
11 | where you might have to go higher than label, I think we're
12 | cognizant of, but I'm not sure that the draft guidance
13 | really is very clear on that, the reason being that as one
14 | gets beyond the labeled dose, you get into issues about if
15 | you were to do, say, eight sprays of a product in very
16 | close succession, one would be concerned that you might be
17 | swallowing a larger proportion of the dose than you would
18 | be otherwise. Now, there may be ways to get around that
19 | where you wait 20 minutes in between sprays and so on.

20 | But the upshot is that we're aware that you're
21 | probably going to have to look at a higher dose than you
22 | would be for efficacy, for instance. So, it really gets to
23 | wanting a dose that could be properly characterized through
24 | pharmacokinetics, ideally.

25 | I would also add, though, that if one does a 2-

1 week clinical study, you also get some important local
2 safety information from there, although presumably, with a
3 product that is Q and Q the same to a reference product,
4 that shouldn't be much of an issue, but it's there
5 nonetheless.

6 DR. LEE: Dr. Ownby?

7 DR. OWNBY: Dennis Ownby. Following up on
8 that, if you were talking about the typical 2-week study
9 and you talk about local safety, what kind of parameters
10 would you look at in terms of local safety that you think
11 would be meaningful?

12 DR. MEYER: What actually typically is done is
13 the patients have daily diaries that they record adverse
14 events in, including things like epistaxis and so on, and
15 then it's not unusual for the clinical studies to include
16 local observation by the clinician, just basically looking
17 at the mucosa. We're not talking about biopsies or
18 anything more elaborate, but basically a clinician
19 assessment of the nasal mucosa, along with patient adverse
20 event reporting.

21 DR. LEE: Of course, a question from Les.

22 DR. HENDELES: I'd like to pose this to Dale.
23 If you had a drug that had 99 percent first-pass
24 metabolism, why wouldn't you be able to use a
25 pharmacokinetic approach to document bioequivalence, since

1 | the drug in the blood has to come from the nose?

2 | DR. CONNER: Well, unfortunately, we don't have
3 | many that are -- I can think of one that I personally
4 | worked on when I was in Bob's division, which is
5 | fluticasone. If you've looked at the clinical information
6 | and the labeling of that drug, if we can use that as an
7 | example, the oral availability I think, if I'm remembering
8 | the labeling correctly, is less than 1 percent. So, if you
9 | simply give orally the whole dose, you do not get very much
10 | of the parent compound absorbed. So, that would be the
11 | type of drug that you're talking about.

12 | In theory, you might say, well, I could then
13 | assume that the blood concentration that I see is primarily
14 | from the nose. I'm not really sure you would be entirely
15 | firm on that because, as I said, there are other possible
16 | -- although in your other question, we said that it's
17 | unlikely, but still possible -- that there are other routes
18 | other swallowing.

19 | That's the first point. So, I can't be 100
20 | percent certain that all of the drug you see in the blood
21 | simply went into the nasal mucosa and entered the blood,
22 | and all that I see is through that route.

23 | The second is really a much more fundamental
24 | question about locally acting products, and I was talking
25 | to someone during the break about if you look at perhaps a

1 more simple case, such as absorption through the skin,
2 where there are no really peripheral routes of entry into
3 the blood, the blood still ends up being a point or event,
4 if you will, that's after the site of activity, and in many
5 cases appearance in the blood is actually an undesirable
6 phenomenon. You'd like to supply just enough drug to the
7 local area to create the effect you want and minimize that
8 absorption. So, it actually is, in most cases, undesirable
9 and it's actually an event that happens after the event
10 that you're really interested in, which is appearance at
11 the local site of activity.

12 Some would argue and have argued that that
13 still may contain enough information to make inference
14 backward, but it isn't as clear cut as in oral product,
15 where that's the intervening compartment, and you assume
16 that there is an equilibrium between that compartment and
17 what you're interested in, which are sites of activity.

18 So, there are some more technical problems
19 before we ever accepted that for local products in general.
20 It is an interesting question, but it's not something we're
21 ready to necessarily assume at the current time.

22 DR. HENDELES: It seems that even for those
23 drugs that have larger oral bioavailability, you could
24 artifactually change that situation by giving a dose of
25 activated charcoal along with a test dose and have

1 | essentially produced the same thing you have with
2 | fluticasone.

3 | DR. LEE: Dale, do you have a response?

4 | DR. CONNER: The activated charcoal blockade is
5 | brought up, and I think you and others have done work on
6 | that. I'm not totally convinced that that's a pure and
7 | effective way of totally blocking drug input and it doesn't
8 | otherwise affect the pharmacokinetics or disposition of the
9 | drug over and above what's blocked from getting in.
10 | Perhaps I'm not up to date on this and you know more about
11 | it. I think your early work with theophylline and some
12 | other drugs showed that even if you put the charcoal down,
13 | it tended to enhance the clearance over and above the
14 | prevention of absorption. So, I would worry about at least
15 | the theoretical aspect of that happening.

16 | DR. HENDELES: That was a multiple-dose
17 | phenomenon. A single dose of charcoal blocks the
18 | absorption without altering the metabolism of that
19 | particular drug, but it would be really easy to show. You
20 | could give a drug orally with charcoal and without and see
21 | what you get.

22 | DR. LEE: Wally, you want to comment?

23 | DR. ADAMS: Yes. I wanted to respond to that
24 | also. In addition to what Dale said, Les, is that the PK
25 | data would not tell you necessarily anything about the

1 | site-specific delivery of the product to the particular
2 | regions of the nose. I believe you could get comparable PK
3 | plasma concentration versus time curves, and yet the two
4 | products may have delivered the drug to different regions
5 | of the nose, and so it wouldn't tell you anything about
6 | that, even if you were to use charcoal block and prevent
7 | the drug coming in from the gut.

8 | We certainly know that various products can
9 | deliver differently to different regions of the nose,
10 | depending upon whether it's a nasal spray or an MDI, for
11 | instance, or depending upon a spray angle of the actuator.
12 | So, we would have that comfort or that confidence. Of
13 | course, our in vitro data helps us with that issue.

14 | DR. CONNER: Another theoretical example that
15 | might be slightly closer to this is, if you look at
16 | systemic absorption from the lung and say we'll have a
17 | hypothetical case where drug only gets into the lung and
18 | it's only absorbed from the lung, still the lung is a very
19 | large area with different segments, and your aim may be to
20 | deposit drug or a sufficient amount of drug in certain
21 | areas of the lung and you do not want to do it in others.
22 | So, two products could perform very differently in that
23 | case. You might in theory see the same systemic
24 | absorption, and the systemic absorption doesn't necessarily
25 | feed back and say I've gotten the exact amount of drug from

1 | these two products into the exact same part of the lung
2 | that I'm trying to do. It doesn't necessarily prove that.

3 | The same thing, in certain respects, with the
4 | nose. I could have absorption from the nose as a whole,
5 | but it might not necessarily be from the areas that I want
6 | it to be absorbed from or to reach.

7 | DR. HENDELES: Is there any evidence that you
8 | have to apply the reference product to a certain part of
9 | the nose?

10 | DR. CONNER: To gain efficacy? Well, that's
11 | what we're assuming here.

12 | DR. HENDELES: We're dealing with a disease
13 | that is relatively benign, although uncomfortable. But it
14 | certainly doesn't result in emergency room visits,
15 | hospitalizations, or deaths, so it's very different from
16 | asthma.

17 | On top of that, you have patients who are very
18 | poorly adherent on average. The adherence to this
19 | formulation, to an intranasal steroid, for example, is
20 | dramatically less than it is to an oral inhaled steroid.
21 | So, you're talking about people not taking it consistently.
22 | You're talking about a relatively benign disease, and
23 | you're talking about, at least from what I've seen, you
24 | don't have the ability to distinguish between a huge
25 | difference in dose.

1 So, yes, it's confirmatory, but why do you need
2 to confirm it? If you have a good bioavailability study,
3 where you've taken into all the accounts and you can
4 reproduce something like the fluticasone situation, I just
5 think that that's all you really should need and everything
6 else is overkill, in my opinion.

7 DR. LEE: Are you moving for adjournment?

8 (Laughter.)

9 DR. ADAMS: Les, just for clarity, you said
10 that you would need what in your opinion? You wouldn't
11 need the clinical study.

12 DR. HENDELES: I think if you were able to do a
13 well-controlled bioavailability study -- pharmacokinetic,
14 blood level -- if you could do that and address all of the
15 concerns, and there was a real tight relationship between
16 the two products in terms of AUC and Cmax, et cetera, I
17 think that anything more than that would be overkill.

18 DR. ADAMS: You're talking about with the
19 charcoal block?

20 DR. HENDELES: It depends on the drug, but if
21 you were talking about triamcinolone, you would need to do
22 that, and maybe one step before that would be to prove in a
23 first study that the charcoal block really blocks, that you
24 couldn't get any drug into the blood if you took it with
25 charcoal.