

1 DR. LEE: Bob?

2 DR. MEYER: I just wanted to maybe press a  
3 couple of questions or points with you and have you  
4 respond. Would you want to look at the concentration-time  
5 curve? You mentioned the metrics of Cmax and AUC, but one  
6 of the issues that was raised by the letter about the  
7 particle size distribution within the formulation was rate  
8 of absorption, not just extent. The metrics you mentioned  
9 may or may not get to rate of absorption. They really  
10 focus more on extent of absorption. So, would you want  
11 similar curves as well as metrics for Cmax and AUC?

12 DR. HENDELES: Yes. I think you would have to  
13 include Tmax as well. If you had differences in Tmax, then  
14 there may be a reason to then require a clinical study,  
15 because that would probably reflect differences in release  
16 of the drug or particle distribution.

17 But I think if you had really solid Tmax, Cmax,  
18 AUC, and of course the appropriate design -- if it was a  
19 drug that had an accumulation factor, you may need to do a  
20 steady state instead of a single dose. I mean, you'd take  
21 that into account, but if you did a quality study and you  
22 could not show a difference, including Tmax, then I think  
23 that that proves bioequivalence to me.

24 DR. MEYER: Then let me press a second point.  
25 If one were to take a drug that is reasonably orally

1 bioavailable -- triamcinolone, or beclomethasone -- has  
2 some oral bioavailability and you do a charcoal block, are  
3 you then properly assuring the bioequivalence for the  
4 systemic safety if the information you're focusing on is  
5 the pharmacokinetic characteristics of what's getting in  
6 through the nose?

7 DR. HENDELES: That's an interesting question,  
8 and maybe you'd have to do it with and without the charcoal  
9 block to answer that question or you'd have to do a second  
10 study at the higher dose range. Maybe you could combine  
11 them both in one study, but you'd have to have a third arm  
12 or an arm where you did it with and without the charcoal  
13 block.

14 DR. LEE: Leon, you have a follow-up question?

15 DR. SHARGEL: I just had a follow-up, more or  
16 less, comment. I agree with Dr. Hendeles about the idea of  
17 doing systemic blood levels. However, I disagree about  
18 measuring Tmax. If we do that kind of approach, we'd do  
19 the same as we do for oral drug products. Rate is  
20 generally done by Cmax, even though it may not be the best  
21 metric for rate, but it has generally been the acceptable  
22 metric, as well as AUC for extent. There's no particular  
23 reason to be different for these products if we're just  
24 talking about a blood level time curve comparison. In oral  
25 drug products, we do see occasionally differences in

1 | particle size, but we can see superimposable blood levels  
2 | within statistical values. So, I would leave the criteria  
3 | the same. I wouldn't try to be anything novel, since this  
4 | is rather tried and true.

5 | I also agree we do not need necessarily  
6 | confirmatory clinical studies if we have an objective  
7 | bioequivalence study.

8 | DR. LEE: I would like to change -- okay.

9 | DR. DYKEWICZ: Just one last comment.

10 | DR. LEE: Identify yourself.

11 | DR. DYKEWICZ: Mark Dykewicz again. One of the  
12 | concerns that I have is that we're looking at the prospect  
13 | of having drugs which may not have a great deal of systemic  
14 | absorption, and so if we're talking about maybe some of the  
15 | traditional nasal steroids, we can do all these nice  
16 | pharmacokinetic studies, but that may not be the case as we  
17 | get further into some new drugs, and in there I really do  
18 | think it is going to be more important to have the clinical  
19 | studies available for confirmation of the relative efficacy  
20 | between the test and the reference drug.

21 | DR. HENDELES: What kind of drugs did you have  
22 | in mind?

23 | DR. DYKEWICZ: The question from my colleague  
24 | was what type of drug class did I have in mind? Well, for  
25 | instance, in terms of the systemic absorption from nasal

1 cromolyn, that's relatively minor. I think some of the  
2 newer nasal steroids also are having very little evidence  
3 that you can pick up blood levels with that. If I'm wrong  
4 on this, please let me know, but I think we are looking at  
5 the prospect of this type of scenario where we're not going  
6 to be able to have the information coming from systemic  
7 bioavailability studies to enter into the fray, so to  
8 speak.

9 DR. LEE: In the last five minutes, I would  
10 like to make sure that every speaker will have a chance to  
11 be questioned. Wally Adams has not been asked any  
12 questions, although he responded to several.

13 (Laughter.)

14 DR. LEE: Are there any questions for Wally?

15 (No response.)

16 DR. LEE: No questions for Wally. So, maybe  
17 save that for the afternoon.

18 Any questions for Dr. Chowdhury?

19 (No response.)

20 DR. LEE: No questions.

21 Yes?

22 DR. ROMAN: Izabela Roman. Actually, I think  
23 that I would like an official statement. Dr. Chowdhury, do  
24 you believe that with existing methodology we can measure  
25 dose response in intranasally delivered drugs?

1 DR. CHOWDHURY: With the existing  
2 methodologies, I do not believe that one can, and by that I  
3 mean the traditional outpatient 2-week study using the  
4 symptom scores, and looking through the completed studies  
5 that have been done for the NDAs, we don't see that. With  
6 that experience, I don't believe with some new drugs you  
7 would be able to see that.

8 DR. ROMAN: Thank you very much.

9 DR. LEE: Any other questions for anyone?

10 (No response.)

11 DR. LEE: Hearing none, we're going to move  
12 into the next item on the agenda, and that is the open  
13 public hearing. As you know, or you might not know, but  
14 there are three individuals who have expressed interest to  
15 speak, and the first two represent the Inhalation  
16 Technology Focus Group of the AAPS and the IPAC-RS.  
17 Cynthia Flynn is going to be talking about review of the  
18 CMC OINDP issues addressed by her group. She has six  
19 minutes and the timer has started.

20 (Laughter.)

21 DR. FLYNN: Good morning. My name is Cindy  
22 Flynn and I will be speaking on behalf of the ITFG/IPAC-RS  
23 Collaboration.

24 ITFG is an organization which is a subset of  
25 the American Association of Pharmaceutical Scientists.

1 IPAC-RS is an industry association. These two groups have  
2 formed a collaboration in 2000 to address the various CMC  
3 and BA/BE issues which are contained in the FDA draft  
4 guidances. The technical teams had previously presented  
5 their concerns to this subcommittee in April of 2000,  
6 concerning the issues which are contained in the draft  
7 guidance.

8 My objective today is to provide the  
9 subcommittee with an update on the work and proposals that  
10 have been completed to date by the CMC technical teams. In  
11 addition, my colleague, Dr. Joel Sequeira, will be  
12 presenting the views of the BA/BE technical teams on dose-  
13 response studies.

14 As has been mentioned by Dr. Lee, I am limiting  
15 my time, so I would like to mention that additional  
16 information is contained in our written statements, which  
17 have been submitted to the FDA and the committee, and those  
18 statements are on the table in the back. Actually, outside  
19 the back door.

20 There are four critical CMC issues which I'd  
21 like to discuss with you today. The first issue is that of  
22 dose content uniformity. The collaboration has collected  
23 and analyzed a dose content uniformity database and we have  
24 found that 68 percent of the products analyzed do not  
25 comply with the FDA test requirements.

1           Subsequent to this finding, we have then met  
2 with the FDA twice to discuss the findings and to plan the  
3 work for the future. The outcome of these meetings has  
4 been that we have decided to develop an improved dose  
5 content uniformity test.

6           This improved test is based on a parametric  
7 tolerance interval approach, which is very similar to the  
8 approach presented by Dr. Walter Hauck at the subcommittee  
9 meeting last April of 2000. Our approach also uses test  
10 design concepts which are very similar to those proposed by  
11 the ICH. Our improved test uses quality standards which  
12 are superior to the current test that is contained in the  
13 FDA draft guidances, and we have developed our test keeping  
14 in mind the consideration and capabilities of modern  
15 inhalation technology.

16           The parametric tolerance interval test that we  
17 have designed allows for increased efficiency in the use of  
18 sample information. In addition, it provides improved  
19 consumer protection as compared to the current test listed  
20 in the draft guidances. It also provides improved producer  
21 protection.

22           In our test, we have defined quality in terms  
23 of the proportion of doses within a batch that will fall  
24 within a given target interval. We ensure this quality by  
25 having instituted three acceptance criteria. Those

1 acceptance criteria have been established for the sample  
2 mean, the sample standard deviation, as well as a term  
3 called the "acceptance value." These three criteria ensure  
4 that the dose that will be delivered by the product will be  
5 very close to the label claim, that the variability of the  
6 dose within a batch will be very minimal, and that the  
7 frequency of outliers will be limited.

8 Our test provides for a consistent quality  
9 standard, regardless of the type of product tested. So, it  
10 doesn't matter if it's an MDI or a DPI, single dose, or  
11 multiple dose.

12 The test does have flexibility, though, with  
13 regards to the testing schedule that can be used by a  
14 producer. Our test, as designed, requires only a single  
15 test to look at both the within-unit and between-unit  
16 variability of a product. The current draft guidance  
17 actually requires two separate, independent tests.

18 Of course, I've just mentioned to you that we  
19 feel that there's quite a lot of advantages with our test,  
20 but there's always a tradeoff, and that tradeoff with  
21 regards to our test is that the sample size, on average, is  
22 increased as compared to the current guidance.

23 We anticipate that we will be providing a  
24 report that fully explains this test to the FDA in the  
25 fall, and we anticipate meeting with them to discuss this

1 new test. We would like to very strongly recommend that  
2 this new test replace the one that is currently listed in  
3 the draft guidance.

4 The next issue which I'd like to discuss is  
5 that of particle size distribution. The current guidance  
6 has a requirement that the mass balance must be within 85  
7 to 115 percent of the label claim. We feel that this is  
8 not appropriate as a drug product specification. Rather,  
9 we feel that the label claim of a product should be  
10 controlled by the emitted dose test. It might be  
11 appropriate to use the mass balance criteria as a system  
12 suitability test, but then, through validation studies, the  
13 exact limits on the mass balance must be established.

14 We have come to these conclusions following  
15 analysis of a database that we have collected, which showed  
16 that in general compliance with this requirement was not  
17 feasible. In fact, only 11 percent of the products within  
18 our database would meet this requirement.

19 A second particle size issue that I'd like to  
20 discuss very briefly is that of in vitro bioequivalency  
21 tests. The current guidance requires that a test and  
22 reference product be compared using the chi-square test,  
23 and this recommendation has been made, to the best of our  
24 understanding, based on analysis of a single product --  
25 that is, albuterol -- using a single test method. We feel

1 that to generalize this conclusion to all product types and  
2 using all different types of testing equipment is not  
3 appropriate at this time. Rather, we are recommending that  
4 additional investigations into alternative tests, in  
5 addition to the chi-square, be carried out to determine  
6 which is the most appropriate test for comparing in vitro  
7 bioequivalence.

8           The third CMC issue that I'd like to discuss,  
9 then, is that of tests and methods contained in the draft  
10 guidances. The current guidances require that the exact  
11 same battery of QC tests be performed for all products. We  
12 are recommending, by contrast, that only appropriate QC  
13 tests be selected, based on the development database.

14           We had provided a report to the FDA in May and  
15 this report contains recommendations concerning the eight  
16 tests that are listed on this slide.

17           Lastly, before my six minutes is over, I'd like  
18 to just discuss the last point, which is leachables and  
19 extractables. The key concern with regard to leachables  
20 and extractables is that the current guidance does not  
21 contain a reporting, ID, and qualification threshold for  
22 leachables and extractables. In addition, there is not a  
23 very clear and precise definition of two very important  
24 terms. That is, a "correlation" and a "critical  
25 component." We have submitted a report to the agency just

1 | this past March in which we highlight various points to  
2 | consider, and I'd like to just review some of those with  
3 | you.

4 |           First of all, in our paper, we are recommending  
5 | that toxicological qualification be performed only on  
6 | leachables. We also in our paper recommend specific  
7 | reporting and qualification thresholds for leachables, and  
8 | we have provided justification for our selection of those  
9 | values. We have developed a process for the qualification  
10 | of leachables. Our strong recommendation with regards to  
11 | this point is that the guidances need to be updated to  
12 | incorporate a leachables qualification program, and that  
13 | reporting and toxicological qualification thresholds for  
14 | leachables need to be included in the guidances.

15 |           I'd like to thank you all very much for your  
16 | attention, for listening to these very critical issues for  
17 | the CMC team, and we are confident that if we work together  
18 | with PQRI, the subcommittee, as well as the agency, that we  
19 | will be able to resolve these.

20 |           Thank you.

21 |           DR. LEE: Thank you, Cindy.

22 |           Any questions? Just one or two?

23 |           (No response.)

24 |           DR. LEE: No questions. Thank you very much.

25 |           We move on to Joel Sequeira, who's going to be

1 | talking about BA/BE team work and their comments on the  
2 | issue of dose response.

3 |           DR. SEQUEIRA: Good afternoon. As mentioned by  
4 | Dr. Flynn and by Dr. Lee, I'm speaking here as a  
5 | representative of the BA/BE technical team of ITFG and  
6 | IPAC-RS.

7 |           In our one-and-a-half-year history, the BA/BE  
8 | team has been very productive and has worked constructively  
9 | on this very difficult issue of bioequivalence of locally  
10 | acting nasal drug products.

11 |           As you can see listed on this slide, there were  
12 | three face-to-face meetings, one with the OINDP  
13 | subcommittee, the Advisory Committee for Pharmaceutical  
14 | Science, and the agency. The BA/BE team has also prepared  
15 | three reports which were submitted to the FDA on this  
16 | topic.

17 |           After review of the current literature,  
18 | scientific literature and medical literature, in this area,  
19 | a task which has been taken over the year and a half, we do  
20 | not have any substantive new approaches on dose response  
21 | for efficacy, but feel that risk assessment and risk  
22 | management must be done first to put this whole issue of  
23 | nasal drugs into proper perspective, as discussed later in  
24 | my presentation.

25 |           In vitro study designs in draft BA/BE guidances

1 are useful for determining comparability of products, but  
2 unproven in value for establishing clinical equivalence and  
3 substitutability. \

4 We support inclusion of at least two doses of  
5 the reference and test product in the clinical dose-ranging  
6 study, and at least one of these doses should be  
7 representative of the currently approved dosage regimen for  
8 the reference product. .

9 At this point in time, we agree that the  
10 traditional treatment study offers the most appropriate  
11 study design for assessing nasal drug products intended for  
12 local delivery. We agree that the 2-week duration for the  
13 study is appropriate.

14 However, there is a need for the draft BA/BE  
15 guidance to further develop the statistical requirements  
16 for this study if it is to be used for equivalence testing,  
17 so as to appropriately link to the guidance on allergic  
18 rhinitis without confusing the issues of equivalency and  
19 comparability. As most of you know, weaknesses of this  
20 design include dependence on seasons and a measurable  
21 placebo effect.

22 Since the last advisory committee meeting, the  
23 BA/BE team has sought additional information to answer the  
24 questions posed in connection with dose-response studies,  
25 in vivo study waivers for locally acting nasal products,

1 and test metrics for in vitro as well as in vivo  
2 comparisons. This effort continues to reinforce the  
3 earlier findings that the development of robust clinical  
4 protocols, the availability of reliable metrics, and the  
5 establishment of relevant in vitro test platforms are in  
6 fact lagging behind present regulatory needs.

7 In my next slide, we put forth an example which  
8 highlights the need for additional work in this area. This  
9 is a study published in the Annals of Allergy, Asthma, and  
10 Immunology in 1999, and it's by Casale, Azzam, and  
11 coworkers on the demonstration of therapeutic equivalence  
12 of generic and innovator beclomethasone in SAR.

13 On reviewing this paper, we see three issues  
14 with this kind of a study. The first is that, as stated by  
15 the authors, the primary objective of the study was to  
16 compare two doses of the test product -- in this case, the  
17 generic -- versus the placebo. It was a secondary  
18 objective of this study to compare the reference product --  
19 that is, the innovator product -- against the test product.  
20 We think that in this case a reversed hierarchy is more  
21 appropriate, in that it should have been the primary  
22 objective to compare the reference versus the test product.

23 The second issue is one of sample size. The  
24 study was designed as a study to study differences and not  
25 equivalence. The sample size was adequate to distinguish

1 between active and placebo, but inadequate to distinguish  
2 between either type of BDP preparation or between the two  
3 doses of BDP, had there actually been a difference.

4           Whereas the study detected differences between  
5 active and placebo, it failed to statistically  
6 differentiate between the different actives. Failure to  
7 differentiate in this case does not mean that a difference  
8 does not exist, had the design been more appropriate in  
9 order to detect one.

10           The third issue with this was the dose of  
11 administration. The administration of active was followed  
12 by a placebo, and the treatments were not randomized. This  
13 brings up the issue of bias, in that the placebo could have  
14 a washout effect on the drug treatment.

15           I mention this paper not to reiterate or  
16 critique this particular paper, but only to use it as an  
17 example of the need for further work in this area.

18           This leads me to the key issues to confirming a  
19 correct study design, which are summarized on this slide.  
20 Firstly, the draft guidance must address the issue of  
21 substitutability and not confuse this with comparability,  
22 and secondly, we need to develop statistical requirements  
23 for this study design for use in equivalence testing.

24           Now, one way to deal with open questions in  
25 bioequivalence study design is to use risk management to

1 focus scientific investigation on those critical elements  
2 whose uncertainties should be given priority as the  
3 development of guidances progresses.

4 Three risk areas that are present with locally  
5 acting nasal sprays in the context of dose response and  
6 clinical equivalence include the primary local effect, the  
7 local side effects, and systemic side effects resulting  
8 from absorption of a fraction of the applied dose.

9 While the first two risk areas can possibly be  
10 grouped together and dealt with in a single trial, the  
11 third must be treated independently. In fact, the types of  
12 clinical trials needed to address each risk area may be  
13 very different in nature and construction. It cannot,  
14 therefore, be presumed that an in vitro test that correctly  
15 correlates with the local actions will also be predictive  
16 of the systemic exposure.

17 In conclusion, the BA/BE team agrees that  
18 development and validation of an appropriate model for  
19 assessing dose response as a model for in vivo equivalence  
20 is an important element in the development of equivalence  
21 standards for this group of products.

22 The BA/BE team also believes that a high-risk  
23 area in the establishment of product equivalence is the  
24 systemic absorption component. We suggest the design of  
25 studies to assess systemic availability and equivalence

1 | between nasal solutions for local actions deserves  
2 | appropriate attention.

3 |           Thank you for allowing us the time to present  
4 | the views of the committee to this distinguished group and  
5 | the FDA experts who are leading this guidance.

6 |           Thank you.

7 |           DR. LEE: Thank you, Joel.

8 |           Any questions for Joel?

9 |           (No response.)

10 |           DR. LEE: If not, thank you, Joel.

11 |           The last one for this morning is Dr. Patel, and  
12 | he's going to talk about an environmental exposure chamber  
13 | and the design of a pilot study to determine dose response  
14 | and response variability with topical nasal steroids.

15 |           DR. PATEL: Thank you very much.

16 |           My name is Dr. Piyush Patel. I'm the medical  
17 | director at Allied Clinical Research. We're a CRO in  
18 | Toronto. We have a lot of experience in doing allergy and  
19 | asthma studies. In fact, that's what we specialize in.  
20 | We've done over 350 studies and about 15 or so rhinitis  
21 | studies in the last four or five years.

22 |           What I wanted to do today was to discuss the  
23 | functionality of the exposure chamber that we've just  
24 | developed over the last couple of years, and share with you  
25 | the thoughts of a pilot study that we've designed for this

1 chamber that we're going to be doing this coming fall.

2 This has already been discussed today, but  
3 obviously there are limitations of doing studies in the  
4 traditional way or in the park setting related to the  
5 unpredictable nature of pollen exposure. Typically, pollen  
6 counts are very, very variable depending on the weather and  
7 pollen exposure is submaximal. Symptom scores are not the  
8 maximum that you would get. As the symptom scores are  
9 smaller, the degree of sensitivity of the assay isn't very  
10 good.

11 There are also issues of patient compliance,  
12 the issue of not being able to do the study in a timely  
13 manner in terms of seasonal dependence, and also the need  
14 for multiple sites.

15 To give you an idea of the variability of the  
16 pollen counts, this is the pollen counts in Southern  
17 Ontario in '99, and as you can see, there are very, very  
18 large differences in pollen counts, and you can see it  
19 reaches up to 3,000 particles per cubic meter on one day,  
20 but if you look at it two or three days later, it's down to  
21 about 50 or so particles per cubic meter. So, if you  
22 happen to schedule your day-in-the-park study on a day when  
23 pollen counts are very low, you're going to get very poor  
24 sensitivity of your study.

25 We've been designing the exposure chamber over

1 | the last couple of years and we have gone through several  
2 | versions of a pilot chamber in an academic setting, and  
3 | we're now in the process of validating our 3,000-square-  
4 | foot chamber. It's been designed with a unique air flow  
5 | system to exclude external allergens, mold or diesel  
6 | particulates or pollution, and we've really designed it  
7 | specifically for ragweed.

8 |           We have been able to show that it can  
9 | consistently deliver a pollen count of anywhere from almost  
10 | zero to four and a half thousand grains, but the working  
11 | range is about two and half to four and a half thousand  
12 | grains, which if you look back at the slide or if you think  
13 | back, it's about the highest pollen count you're going to  
14 | see on a very heavy pollen day.

15 |           Capacity for our unit is 110 persons.

16 |           We feel that there are a number of major  
17 | advantages with using this model in doing studies with  
18 | rhinitis, specifically that we can have the maximum  
19 | possible symptoms. There are differences in terms of  
20 | patient response to a given pollen level, and I think that  
21 | one of the drawbacks of traditional studies is the  
22 | assumption when you analyze them that every patient with  
23 | rhinitis responds in the same way, but there is a huge  
24 | variability in response for a given pollen count.  
25 | Different patients will have different degree of symptoms,

1 and so we can push the pollen count up to a level where  
2 everybody will have as much symptoms as they're going to  
3 have.

4 Symptoms are very typical of rhinitis symptoms,  
5 and in fact it is more sensitive, I feel, because we are  
6 excluding external other allergens, such as pollution and  
7 diesel particulates, and so it's more specific in that way.

8 Compliance obviously is 100 percent, and we can  
9 have accurate readings of diary and peak flow.

10 We've been thinking about bioequivalence,  
11 looking at the draft guidance, and grappling with issues of  
12 dose response. We feel that one of the drawbacks, as has  
13 been mentioned, is the assumption that everybody with  
14 rhinitis responds in the same way. In fact, I'm an  
15 allergist, so I work in a clinic, and we know that there is  
16 a huge difference in the degree of symptoms people get with  
17 rhinitis, and also the response to the drug is different.  
18 So, there's a variability in response to the drug and a  
19 variability in response to the allergen. Put these two  
20 together and the difference is large.

21 What we can do is look at onset of action to  
22 look at dose response and look at clinical efficacy,  
23 measuring symptom scores of peak nasal inspiratory flow  
24 rates.

25 I wanted to just briefly present this article

1 done by Jim Day's group, a colleague of mine, in Kingston,  
2 and what they've done is in an exposure chamber setting,  
3 taken a group of allergic rhinitis ragweed-sensitive  
4 patients and exposed them sequentially every day to ragweed  
5 pollen and treated them in the morning with triamcinolone,  
6 which is a nasal steroid.

7           They plotted here the cumulative percentage of  
8 patients who reach 25 percent improvement in nasal symptom  
9 scores. 25 percent was felt to be a significant  
10 improvement, so that was chosen. As you can see, 40  
11 percent or so roughly get a significant improvement on day  
12 1, but there are a number of people who take 6, 7 days to  
13 reach 25 percent significant improvement levels. So, there  
14 is a variability of individual response to the given  
15 constant pollen count in the exposure chamber. We feel  
16 that there may be a way of using this type of a model to  
17 show a dose response with controlling other variabilities,  
18 such as pollen, et cetera.

19           Incidentally, there was quite a large placebo  
20 effect as well here, as we've discussed before.

21           This briefly is just the raw numbers of other  
22 symptoms. Congestion, rhinorrhea, itching, et cetera, and  
23 all of these also show an improvement.

24           So, briefly, just to present our pilot study,  
25 we're in the draft stages of designing a dose-response and

1 a response variability study of a nasal steroid in the  
2 treatment of rhinitis in an exposure chamber.

3 The objectives of the study are to determine if  
4 there's a dose response for nasal steroids using a placebo,  
5 100 milligrams every other day, 100 micrograms a day, 200  
6 micrograms a day, 200 micrograms a day, and 400 micrograms  
7 a day, and also we would like to look at the response  
8 variability or the CV of response.

9 Briefly, this is the design in the exposure  
10 chamber. Each one of these arrows represents an 8-hour  
11 session in the exposure chamber where we will be measuring  
12 rhinitis nasal symptom scores, peak nasal inspiratory flow  
13 rates, patient global assessment, and physician global  
14 assessment. There is a priming session here of between one  
15 and five sessions. We feel an average of about three  
16 priming sessions of about 3 to 4 hours each, followed by  
17 weekly changes in the amount of doses the patients will  
18 get. Each one of these we feel is a similar design to Jim  
19 Day's study that we presented, so that we can assess the  
20 response of daily treatment with nasal steroid over a week  
21 period.

22 Now, as this protocol is drafted, we actually  
23 are looking at putting in a washout here just to reduce the  
24 carryover from one group to the next, but we would like to  
25 look at from one group to the next the degree of response

1 and see if there's an earlier onset of response in the  
2 subjects who were responding at 6 and 7 days if we can get  
3 them to respond earlier with higher doses. We've actually  
4 looked at every other day, but looking at Wally Adams'  
5 presentation, that's something that we need to sort of  
6 discuss, but certainly in the clinic we know that patients  
7 tend to use inhaled steroids intermittently, either  
8 consciously or unconsciously, because they're noncompliant,  
9 and certainly get a good clinical response from it.

10 So, finally, what we were planning on analyzing  
11 is the percentage change from baseline for each day at each  
12 treatment level, calculate the AUC of the rhinitis index  
13 score, and peak nasal inspiratory flow rates.

14 Incidentally, that's been shown in a couple of studies by  
15 Jim Day to be a significantly more reliable measure than  
16 actual nasal congestion. We'll be measuring them for each  
17 8-hour session in the EEC, and compare that for each day  
18 and each treatment level and plot mean symptom scores for  
19 the study for each symptom.

20 That's it. We're hoping to do this study this  
21 fall, and I just wanted to share the design and see if we  
22 can get some feedback from the committee on this. We're  
23 hoping to do this this fall and hopefully we'll get the  
24 data by the winter.

25 Thank you.

1 DR. LEE: Thank you very much. I think you  
2 need to show us the data first.

3 DR. PATEL: We will.

4 DR. LEE: All right. Thank you very much.  
5 Any questions?

6 DR. AHRENS: Can I make a comment?

7 DR. LEE: Yes.

8 DR. AHRENS: In the pilot design that you  
9 showed there, one of the concerns that I would have is that  
10 you have progressively increasing doses as time goes on,  
11 and so that you have the time effect that you showed in  
12 your previous slides to be thoroughly confounded with the  
13 dose effect. So, a randomized allocation of the  
14 treatments, as opposed to sequentially increasing, so you  
15 could put things like first-order carryover in the model  
16 and look at that, would be I think extremely important.  
17 It's a valuable study, but I think the tweaking of the  
18 study design is really important.

19 DR. PATEL: Thank you. I appreciate that. I  
20 think we need an adequate washout between the periods also  
21 to reduce the carryover effect.

22 DR. AHRENS: That would certainly help, but not  
23 be a substitute for randomization of the doses.

24 DR. LEE: One last question. Dr. Roman?

25 DR. ROMAN: It requires some tweaking indeed,

1 | because if you go do the washout, then priming will have to  
2 | be repeated. Secondly, if you do it in the ragweed season,  
3 | which you are saying you intend to do, then obviously they  
4 | will be primed in various ways, different patients. So,  
5 | just for your thinking, not so much discussion.

6 | DR. PATEL: Well, the priming seems to last,  
7 | from Jim Day's work, about 40 days, so that is probably not  
8 | an issue. If we start during the ragweed season, that  
9 | means that we don't need to prime as much as we would do if  
10 | we do it off-season, because the subjects are naturally  
11 | primed.

12 | DR. ROMAN: However, the washout of steroids is  
13 | at least 2 weeks.

14 | DR. PATEL: Yes.

15 | DR. LEE: Thank you very much.

16 | Before we adjourn for the morning, I would like  
17 | to remind the subcommittee that we have work to do in the  
18 | afternoon, and Wally has proposed two specific questions  
19 | for us to address and they are addressed in the context of  
20 | allergic rhinitis. It was prompted by this issue of  
21 | particle size distribution and I think that you can read  
22 | over those two questions, but we do have to come back and  
23 | provide him with some guidance. The purpose is to develop  
24 | a consensus. We are not going to take a vote.

25 | So, we're going to adjourn for lunch. We are

1 way ahead of schedule, so to anticipate what will be a long  
2 afternoon, I would just say that we are going to come back  
3 at 1 o'clock instead of 1:30.

4 Thank you very much.

5 (Whereupon, at 11:58 a.m., the committee was  
6 recessed, to reconvene at 1:00 p.m., this same day.)  
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## AFTERNOON SESSION

(1:10 p.m.)

1  
2  
3 DR. LEE: Will you please take your seats so we  
4 can continue with the deliberation? As I mentioned before  
5 lunch, the subcommittee has work to do and we hope that we  
6 can quickly come to some consensus, so that we can all move  
7 on to something else.

8 But on the screen is the background to the two  
9 questions that the subcommittee is asked to address, and  
10 Wally, correct me if I misspoke, when you were in the  
11 process of evolving the guidance, you encountered an issue  
12 of particle size distribution which was difficult to handle  
13 experimentally, and therefore the thought was should a  
14 clinical study be used to determine whether the particle  
15 size distribution difference, if any, might affect  
16 performance. Is that right?

17 DR. ADAMS: That's correct.

18 DR. LEE: That's correct, okay. So, that being  
19 the case, can we have the next slide?

20 DR. ADAMS: Before we get to those two  
21 questions, I'll read that preliminary information.

22 DR. LEE: Okay.

23 DR. ADAMS: Because that's critical to the  
24 responses to these two questions, to realize what we're  
25 proposing here as a package of information necessary to

1 establish equivalence. So, this information that's  
2 projected before you now is the lead-in for those two  
3 questions, and I'd just like to read through that, just so  
4 that we all understand what that's saying.

5 "To establish bioequivalence of suspension  
6 formulation nasal aerosols and nasal sprays for allergic  
7 rhinitis, the June 1999 draft guidance, Bioavailability and  
8 Bioequivalence Studies for Nasal Aerosols and Nasal Sprays  
9 for Local Action, recommends the following: equivalence of  
10 formulation, both qualitatively and quantitatively;  
11 equivalence of device; equivalence of in vitro studies; and  
12 equivalence of systemic exposure or systemic absorption."

13 So, going in, then, to these two questions is  
14 the idea that, as we indicated, prior to a clinical study  
15 being done, as Dr. Meyer pointed out this morning, that  
16 there would be Q1 and Q2 formulation equivalence, device  
17 comparability or equivalence. There would be all of the in  
18 vitro studies that we request, which do not include a  
19 validated particle size distribution, however, and also a  
20 systemic exposure or systemic absorption study, preferably  
21 a PK systemic exposure study.

22 "The in vitro studies, however, do not assure  
23 equivalence of particle size of the suspended drug.  
24 Because particle size differences between test and  
25 reference products have the potential to alter the rate and

1 extent of delivery of drug to local sites of action in the  
2 nose, differences in clinical effectiveness could result.  
3 For this reason, the draft guidance also recommends the  
4 conduct of a clinical study for allergic rhinitis to  
5 confirm equivalent local delivery."

6 And recall what we said this morning was that  
7 the Q1/Q2 in the case of the formulation is the same, the  
8 in vitro assure that the amount of drug X actuator is the  
9 same between test and reference products, and assures that  
10 the distribution of the drug to the various sites of action  
11 in the nose is the same, and that a PK study or, if  
12 necessary, systemic absorption study, is done in order to  
13 assure equivalent exposure systemically. Given all of that  
14 information as a package, then the clinical rhinitis study  
15 would be conducted.

16 "For this reason, the draft guidance also  
17 recommends the conduct of a clinical study for allergic  
18 rhinitis to confirm equivalent local delivery. Providing  
19 equivalence of each of the items" above in the rhinitis  
20 study -- and then we turn to the two questions which we  
21 have in the other format, so if we could do that.

22 Then the two questions to the committee are,  
23 first, "does the committee believe that a placebo-  
24 controlled traditional two-week rhinitis study conducted at  
25 the lowest active dose is sufficient to confirm equivalent

1 local delivery of suspension formulation nasal sprays and  
2 nasal aerosols for allergic rhinitis?" And second, "does  
3 the committee believe that a placebo-controlled park study  
4 or environmental exposure unit study conducted at the  
5 lowest active dose is an acceptable option to confirm  
6 equivalent local delivery of suspension formulation nasal  
7 sprays and nasal aerosols for allergic rhinitis?"

8 So, I felt it was important to read that  
9 introductory, lengthy paragraph to set the stage for the  
10 questions that we're asking in 1 and 2, which is given that  
11 prior package of information that we have on the  
12 formulation, the in vitro and the PK study, given all of  
13 that, is the rhinitis study conducted at the lowest active  
14 dose appropriate under those circumstances?

15 DR. LEE: Everybody understands that? Leslie,  
16 do you have a question for Wally?

17 DR. HENDELES: It just occurred to me that the  
18 whole morning we talked about seasonal allergic rhinitis,  
19 and I guess my question is whether everything you said  
20 about seasonal in terms of flat-dose response curve is also  
21 true for something like nasal stuffiness and perennial  
22 allergic rhinitis.

23 DR. CHOWDHURY: The answer is yes, that  
24 whatever is true for SAR usually translates, and it does,  
25 to PAR.

1 DR. LEE: Dr. Ownby, you have a question?

2 DR. OWNBY: The question I really had, are we  
3 assuming that given all of the in vitro data and the dosing  
4 study, a PK study, that we will then automatically move on  
5 to a clinical study, that the clinical study is actually  
6 necessary, or do you need consensus on that question first?

7 DR. ADAMS: I would say that the package of  
8 information which we have in the June 1999 guidance and  
9 which we're presenting at this subcommittee meeting is the  
10 result of many deliberations from the technical committee  
11 or the working groups within the technical committee, and  
12 it's our feeling that because of this particle size  
13 distribution issue, that a rhinitis study at the present  
14 time should be conducted.

15 Does that answer the question?

16 DR. OWNBY: My follow-up on that, though, is  
17 that in all the information presented this morning, that  
18 there was nothing about the degree of particle size  
19 disparity within essentially identical systems, and can you  
20 give us any idea of how much variation you really think  
21 exists in those, once you've got Q1 and Q2?

22 DR. ADAMS: Yes. I would say that they're two  
23 separate issues, because Q1 and Q2 doesn't speak at all to  
24 particle size and particle size distribution of the drug  
25 within the formulation. We do know that the drug, the

1 active pharmaceutical ingredient which is formulated into  
2 these suspension formulations, is micronized drug, down in  
3 the low numbers of microns in the median diameter range,  
4 even though the droplets from these drugs are much larger,  
5 up in the 30 to 40 or so micron range. The micronized drug  
6 that's formulated into the products is much smaller than  
7 that. But there's clearly a potential for test and  
8 reference products to differ substantially in that degree  
9 of median particle size.

10 DR. HENDELES: I just want to comment. You say  
11 there's the potential for them to differ, but how would you  
12 possibly measure it if you can't distinguish between 256  
13 and 32 micrograms of budesonide?

14 DR. ADAMS: Well, in fact, we're not asking  
15 that the particle size distribution be determined by the  
16 firms in a validated method. The guidance does ask for  
17 studies to be done by the firms to examine particle size  
18 distribution of the active pharmaceutical ingredient, but  
19 that is for their own benefit and information, because  
20 there are concerns about the potential for differences in  
21 -- possibly PK may be more sensitive in the clinical  
22 rhinitis study. So, there are potential for differences  
23 between the products. So, that is a recommendation to  
24 assist firms, but we will not be asking for that to be  
25 compared in a statistical sense, I believe.

1 DR. LEE: Let me set a stage because I think it  
2 turns into a grilling session for Wally.

3 DR. ADAMS: That's fine.

4 DR. LEE: Let me say this. We have the  
5 question in front of us. We're looking at a condition of  
6 allergic rhinitis that's very specific. We're looking at  
7 local delivery. We are not looking at systemic delivery  
8 per se.

9 We have an issue about particle size  
10 distribution. I think the in vitro data suggested by the  
11 guidance already have shown there might be equivalence.  
12 However, there's no assurance that this dosage form or this  
13 formulation, upon administration in the nose, might behave  
14 differently.

15 I'm going to go around the table and I think  
16 what I'd like to do is to have the committee address the  
17 question. What is your personal feeling? Are there  
18 sufficient scientific reasons to believe that the first  
19 question posed is appropriate? And then also express, if  
20 any, some concerns.

21 Is that all right?

22 DR. ADAMS: Vince, if I could just interject  
23 one comment before you start that. The paradigm that we're  
24 talking about does not necessarily require that the  
25 particle size distribution be the same between test and

1 reference products. It requires total nasal symptom scores  
2 to be equivalent and it requires the PK to be equivalent,  
3 but if that can happen with different particle size, then  
4 that would be acceptable.

5 DR. LEE: Shall we proceed? Leslie, you were  
6 about to say something, so let me start with you.

7 DR. HENDELES: In considering this, is there  
8 the possibility that a firm could choose for one of the  
9 treatment arms a below-labeling dose of the medication? In  
10 other words, you could say that 16 is no different from  
11 placebo, but 32 is. Some statement like that. Let's use  
12 budesonide as the example.

13 DR. ADAMS: I would say, to start on that  
14 question, Les, one of the requirements is that the lowest  
15 active dose that's on the slide be statistically greater  
16 than the placebo dose, so it has to be an active dose.

17 DR. HENDELES: But how do you know that that  
18 dose is not on the top of the dose-response curve? I mean,  
19 the lowest dose in the labeling may be at the top of the  
20 dose-response curve.

21 DR. ADAMS: Well, it may be. It may be at the  
22 top of the dose-response curve.

23 DR. HENDELES: So, all you want to do is show  
24 that it works.

25 DR. ADAMS: All we want to do, in this paradigm

1 that we're talking about, is to show that that low dose has  
2 equivalent efficacy in terms of total nasal symptom scores.  
3 Just show that the two of them, the test and reference  
4 products, are equivalent. Why the lowest dose? Because it  
5 puts us as far down on the dose-response curve as we can  
6 get, but all we're asking in that paradigm is that the test  
7 and reference products be equivalent in their total nasal  
8 symptom score. That assures equivalence of efficacy and  
9 then we move on to the other studies for equivalence of  
10 safety.

11 DR. HENDELES: In my mind, it doesn't show  
12 equivalence of efficacy if they're at the top of the dose-  
13 response curve, because that means that the test product  
14 could deliver a fraction of the drug that the reference  
15 product delivers to the active site and still be  
16 equivalent, and that's okay.

17 DR. ADAMS: That's correct. You know, we have  
18 to live with the products that are marketed in the lowest  
19 possible dose that we can give, and if that lowest daily  
20 dose is at the top of the dose-response curve and the study  
21 is done and shows equivalent total nasal symptom score for  
22 both test and reference, we know then that it meets the  
23 criteria for equivalence, even though the fraction of the  
24 drug which reaches the local sites of activity in the nose  
25 may be different, but they're still equally efficacious.

1           It also raises the question, of course, that  
2           that difference in particle size distribution which would  
3           cause that effect of differences in the amount of drug  
4           reaching the local sites of action may also have different  
5           systemic absorption. That's why we need to couple this  
6           with some measure of systemic absorption to assure that  
7           indeed they're just as -- have equivalent --

8           DR. HENDELES: And I don't have any trouble  
9           with the systemic absorption part of it. That seems  
10          justifiable to me, but I still have a problem with the  
11          topical efficacy part.

12          DR. LEE: So, you're not comfortable with that?

13          DR. HENDELES: I don't think it's necessary. I  
14          think that it's just way overkill for all of the reasons I  
15          listed in the previous hour. I don't think this question  
16          is relevant because I don't think that, by and large,  
17          unless there were some exceptional circumstances where you  
18          couldn't use a more sensitive assay and do pharmacokinetic  
19          studies, et cetera, that maybe it would be reasonable, but  
20          we're talking about a disease that is mild.

21          Let me give you an example. Hydroxyzine is  
22          used for treating acute urticaria. You have approved  
23          generic hydroxyzine based upon in vitro dissolution tests.  
24          You didn't even require those products to be tested for  
25          bioavailability.

1           So, I don't understand why you're applying such  
2 a stricter criteria in this situation when the clinical  
3 circumstances don't warrant it.

4           DR. ADAMS: I'd certainly be interested in  
5 other of our FDA colleagues responding to that question,  
6 but let me just indicate that we're trying to put in place  
7 a practical approach at the present time.

8           Now, Les, you talked about PK studies as one  
9 possibility, and indeed we had taken that question about  
10 comparable in vitro performance and in vitro studies only  
11 to our April 26 of 2000 subcommittee meeting, and certainly  
12 there is some possibility of doing that, but there are some  
13 practical issues involved here.

14           Of course, we're dealing with drugs which are  
15 intended for local action which have very low levels in the  
16 plasma, and it's a challenge to develop sensitive  
17 analytical methodology to adequately characterize that PK  
18 profile.

19           So, if you were to do something that you are  
20 talking about, where we're dealing with levels already that  
21 are very low and in some cases may be approaching the limit  
22 of quantitation, if you then use an approach of saying,  
23 well, I will use charcoal block as part of my approach such  
24 that the plasma levels are due only to the nasal or  
25 nasopharyngeal or whatever absorption and not gut

1 | absorption, then to the extent that the drug being seen  
2 | systemically is due to gut absorption, you've cut that  
3 | amount of it out of there and you've made the analytical  
4 | challenge all that much greater.

5 | Dale talked about fluticasone propionate, where  
6 | the oral bioavailability is less than 1 percent and the  
7 | nasal bioavailability, according to the labeling, is less  
8 | than 2 percent, and so if just roughly 50 percent of that  
9 | area under the curve is getting into the gut, you've cut  
10 | that portion out.

11 | DR. HENDELES: There's no area under the curve  
12 | with fluticasone getting into the gut from oral inhalation.  
13 | Are you saying that when you administer it nasally, you're  
14 | getting drug into the --

15 | DR. ADAMS: I don't have the data at hand, but  
16 | when I look at the approved labeling, it indicates that the  
17 | nasal bioavailability is less than 2 percent after nasal  
18 | dosing, and after oral dosing it's less than 1 percent.

19 | One more point. Just to further elaborate upon  
20 | that, there was a paper published on beclomethasone  
21 | dipropionate very recently by Glaxo, and in that they did  
22 | PK studies with and without charcoal block, and what they  
23 | found when they used charcoal block was that the nasal  
24 | bioavailability was less than 1 percent. Most of the drug  
25 | is coming in through the gut.

1                   So, while you could have measurable levels  
2 after nasal dosing without charcoal block, with charcoal  
3 block, I think it's going to cut the levels way, way down.  
4 So, there's certainly a practical issue involved in that.

5                   DR. LEE: We will come back to Les.

6                   DR. HENDELES: Well, just to respond to the  
7 practical issue, I think it's not practical to do these  
8 clinical rhinitis studies, given all the information that  
9 I've seen here today. We'll have to agree to disagree,  
10 Wally.

11                   DR. LEE: All right. That's what we're here  
12 for.

13                   Mark, are you ready to offer your comments?

14                   DR. DYKEWICZ: I can make some comments, yes.  
15 What I'd like to do is just to step back and take a bigger  
16 picture view of this dilemma, and that is what we're really  
17 trying to do is to establish whether these nasal drugs are  
18 safe and effective, and by extension, whether a new  
19 formulation or -- I shouldn't say that, but a new test  
20 product would be relatively equivalent in effectiveness and  
21 equivalent in safety.

22                   To me as a clinician, the most straightforward  
23 thing is to do a study in the human being in terms of  
24 looking at effectiveness and safety, and as elegant as many  
25 of these pharmacokinetic studies may be, we've discussed

1 some of the misgivings that we have in terms of particle  
2 distribution and size and so forth. I don't think for a  
3 sponsor it would be that odious to require that there be  
4 one clinical study demonstrating reasonable equivalence in  
5 safety and efficacy.

6 So, my feeling is that it is an appropriate  
7 question to ask. I think ultimately clinicians, and  
8 probably patients, would have greater confidence in a new  
9 test product if it were demonstrated, if you will, in real  
10 life, with some misgivings, in a clinical trial with kind  
11 of a standard 2-week assessment. So, that's the way I  
12 would do it.

13 DR. LEE: Mark, this is a very specific  
14 suggestion, which is one single dose.

15 DR. DYKEWICZ: Yes. I'm comfortable with what  
16 we've talked about. If we're looking at some sort of  
17 equivalent efficacy, going to the lowest dose may not be  
18 beyond the top part of the dose-response curve, but in real  
19 life that's the lowest dose people would be taking -- one  
20 puff or one spray or whatever -- and although you could  
21 say, well, why don't we go down to one-tenth the dose and  
22 see whether there's an equivalent sort of response, that in  
23 my mind is probably not clinically necessary either. We're  
24 trying to look at what people are actually going to be  
25 using.

1           In a similar way, looking at toxicity, safety,  
2           the second big question, I think that would be reasonably  
3           met by looking at the high end of either the labeled dosing  
4           or, as they mentioned, maybe even just a little bit beyond  
5           to see if, because in real life people might be taking more  
6           extra puffs, that that was equivalent in safety with the  
7           reference product.

8           DR. LEE: Thank you.

9           DR. OWNBY: Well, I'm still having misgivings.  
10          I'm not entirely sure that a clinical study is necessary  
11          from what I've seen, but I would be willing to accept a  
12          clinical comparison that showed no difference, provided we  
13          have a high-dose study showing that there is equal safety  
14          from these.

15          It just seems that the biggest problem is that,  
16          as we've seen, these clinical studies are very, very blunt  
17          instruments, and we've talked about a couple of the  
18          reasons. One, that there's probably an active placebo  
19          effect, which makes it harder to distinguish active drug.  
20          The second thing that was mentioned is the imprecise  
21          measurement, that we're using questionnaires and summing  
22          the scores, which have questionable validity.

23          But the other problem is that there's a small  
24          response, and that could be either that these drugs are  
25          just not very effective, which I think a lot of my patients

1 | would tell you is true, or that we have a poor choice of  
2 | subjects. No one has mentioned the fact that as you enroll  
3 | patients in these clinical studies, I don't think a lot of  
4 | these patients have true seasonal allergic rhinitis or it's  
5 | very mild, and that's why you either have to superchallenge  
6 | them to see an effect or you have to be more selective.  
7 | So, I think there are still a lot of issues in how we set  
8 | up clinical trials that should have been answered.

9 | DR. LEE: Thank you.

10 | Dr. Ahrens?

11 | DR. AHRENS: For the reasons that have already  
12 | been mentioned, I would come down on the side of I think  
13 | you do need a clinical trial, and because it hasn't been  
14 | brought up yet, I would like to briefly examine maybe the  
15 | other side of that, of would you need to go so far as to do  
16 | a dose-response relationship, which is I think one of the  
17 | questions that's been put to us today.

18 | It seems to me that, for all of the reasons  
19 | that have been said, it would be, given the current state  
20 | of the art, very difficult to accomplish that, and while it  
21 | is entirely possible that there might be a few people who  
22 | have real dose-response relationships that are getting lost  
23 | in between-patient variability and a bunch of patients who  
24 | are at the top of their dose-response curve, we just don't  
25 | have the technology to look at that at this point.

1 I guess, taking that a little further, I'd like  
2 to ask the clinicians in the group here how many of you  
3 think that you see dose-response relationships with  
4 intranasal steroids? I think when you ask that question of  
5 most clinicians about inhaled steroid use in the treatment  
6 of asthma, most will respond indeed dose does make a  
7 difference there. Maybe not all, but most.

8 But I'd like to now ask the question about  
9 nasal steroids. Do any of you think you see dose-response  
10 relationships within the nasal steroids?

11 DR. DYKEWICZ: I think it may occur in  
12 individual patients. I mean, there are situations where  
13 I'll start somebody at a lower dose and I'll bump them up  
14 and they seem to do better, but then the question, of  
15 course, is are they going to be doing better anyway because  
16 that's kind of the progress of the allergy season.

17 I guess it also brings up the other point.  
18 Whenever you're looking at these mean results, you may be  
19 missing differences that might exist for individual  
20 patients that are just kind of getting averaged out.

21 So, there's no clear way of demonstrating this  
22 objectively, I suppose, other than you can probably in  
23 individual patients have different washout periods and  
24 different doses, maybe for perennial allergic rhinitis, but  
25 it would be very difficult to truly assess this

1 | analytically for seasonal allergic rhinitis.

2 |           DR. HENDELES: In Florida, we don't have  
3 | seasonal allergic rhinitis, or at least not very much. We  
4 | have a big problem with dust mite, and in that situation,  
5 | because it's ongoing, the biggest problem is patients not  
6 | taking their medicine. So, when somebody's not responsive,  
7 | we call their pharmacy and find out how often they're  
8 | getting their prescription refilled, and it's always a  
9 | month's supply is lasting six months.

10 |           So, I don't know of any patients in our clinic  
11 | where we've ever tried raising the dose. Usually we try  
12 | and get them to take the medicine.

13 |           DR. AHRENS: I have fiddled around with that  
14 | some. I guess I have not ever felt that I have seen a  
15 | dose-response relationship either. So, it sounds like as  
16 | close as I got is maybe a qualified "it is possible."

17 |           With that as a given, it seems to me that this  
18 | is one more reason why this is a very different situation  
19 | than topical steroids for the treatment of asthma. I don't  
20 | think we have this clinical impression even that is very  
21 | strong that there is a dose-response relationship here.  
22 | So, to go through all the difficulty that would be created  
23 | to try to come up with some suitable model that would just  
24 | about have to be some kind of complicated crossover design,  
25 | probably be an environmental challenge kind of system, you

1 | would have to deal with the issues that Dr. Roman brought  
2 | up about how do you deal with priming, how do you deal with  
3 | period effect. It may be possible to do that, but it would  
4 | be a major challenge. .

5 |           Given the fact that we don't even seem to have  
6 | much of a clinical impression that this is important at  
7 | all, again unlike asthma, as somebody who has spent a major  
8 | part of his professional career thinking about how you make  
9 | dose-response relationship comparisons between topical  
10 | drugs mainly in asthma, I don't think you need that kind of  
11 | crossover study here.

12 |           So, I think you do need some kind of study.  
13 | Again, for reasons that have already been mentioned, I am  
14 | not comfortable with just going with the pharmacokinetics,  
15 | but I think the kind of simple single dose versus single  
16 | dose -- or one dose level of each would be sufficient.

17 |           DR. LEE: Thank you very much.

18 |           Gloria?

19 |           DR. ANDERSON: For the two questions, my answer  
20 | would be yes, I would like to qualify the "believe." I  
21 | have a concern about that, and that is more as a chemist  
22 | than anything else. I had a professor once who said that  
23 | scientists don't believe things.

24 |           Let me just say that I think that you ought to  
25 | proceed.

1 I have a few concerns. One, of course, is that  
2 there are so many variables that apparently cannot be  
3 controlled the way that some of the things that I do can be  
4 controlled. I have a concern with the "sufficient to  
5 confirm equivalent local delivery."

6 But more importantly, the concern I have is  
7 related to your last statement before the questions, and  
8 that is that the assumption is that the items in sentence 1  
9 are equivalent or have been determined I guess I should  
10 say.

11 The one that I have a concern about is systemic  
12 absorption. You go on to say that particle size has effect  
13 on the rate and the extent of delivery of the drug to the  
14 desired site. I am sure that is correct because that is a  
15 fundamental theory. The problem is, it seems to me like  
16 from what I know, that absorption also is affected by  
17 particle size. This is particularly a problem in  
18 suspensions. I haven't seen anything down here about  
19 homogeneity in terms of suspensions as well, which may be a  
20 problem.

21 I am not suggesting that you look into them. I  
22 would ask you to comment on systemic absorption. My  
23 concern is that the answer to questions 1 and 2 depend on  
24 an assumption that these things are equivalent, and it is  
25 the systemic absorption that I would like for you to

1 comment on.

2 DR. ADAMS: I am not sure what you meant by  
3 homogeneity of absorption. Could you explain that please?  
4 You mean the physical product? The particle size  
5 distribution?

6 DR. ANDERSON: I did not mean for you to  
7 comment on that. I guess I threw that in because in a  
8 suspension you have got a lot of things happening, but my  
9 question is related to absorption because the size of the  
10 particle should affect the rate of absorption. The  
11 questions that you are asking require an assumption that  
12 all these things are equivalent. And I am just asking you  
13 in your expert opinion to comment on systemic absorption.

14 DR. ADAMS: Well, of course, that is one of the  
15 elements in this package, the pharmacokinetic study, and if  
16 there are differences in the rate of absorption which would  
17 be likely if particle size distribution were substantially  
18 different, that would be captured in a PK study. So, we do  
19 look at that.

20 DR. ANDERSON: In fact, then the answer to 1  
21 and 2 may not have the assumption of all of these things in  
22 sentence number 1. That is my concern.

23 DR. ADAMS: I think there is a distinction here  
24 that perhaps you are going down the same path that Dr.  
25 Hendeles was going down with the use of the PK study. If

1 | you don't use charcoal block, then the rate and extent of  
2 | absorption which you see in the PK study would be either  
3 | due to the nasal absorption, which may be very low, and/or  
4 | gut absorption. It would be a combination of both of  
5 | those, or possibly pulmonary absorption, if that happened.

6 | DR. ANDERSON: I am not an M.D.

7 | My concern is this statement, providing  
8 | equivalence. I don't mean to belabor the issue here, but  
9 | the answer to questions 1 and 2 depends on the statement  
10 | above, which includes systemic absorption.

11 | DR. ADAMS: Yes, it does.

12 | DR. ANDERSON: And all I'm saying is that there  
13 | should be a problem with this. If I answered this yes, I'm  
14 | assuming that there is no problem. Now, I'm answering this  
15 | yes, but I want to point that out. That is all I'm saying.

16 | DR. ADAMS: Well, again, the PK study with  
17 | comparable AUC and Cmax and Tmax, if that were to be looked  
18 | at, does not necessarily assure that the drug is getting to  
19 | the sites of local delivery at the same rate and extent  
20 | because the plasma levels which you see are a combination  
21 | of drug which comes in via more than one route potentially,  
22 | as Dr. Conner had in his slides. So, that systemic PK  
23 | study does not separate out nasal absorption from gut  
24 | absorption. So, there is still an issue about rate and  
25 | extent to local sites of action.

1 Dr. Meyer, did you have an additional thought  
2 on that?

3 DR. ANDERSON: Excuse me. I'm not going into  
4 that much detail. I think the problem here is a different  
5 one for me, and that is what you're seeing down here is  
6 that there must be equivalence in terms of items in that  
7 sentence to the extent possible. That's the problem I  
8 have.

9 DR. ADAMS: Well, to the extent possible, for  
10 the PK study, it refers statistical equivalence.

11 DR. MEYER: I was just going to reflect that I  
12 think what we are saying there -- if I hear you correctly,  
13 you are saying particle size does matter. It is going to  
14 impact on the absorption. What we are saying under our  
15 supposition or the way we framed these questions is that  
16 although we can't assess the comparability of the particle  
17 size in the test and reference product in a suspension  
18 nasal spray because of the difficulties of the interference  
19 from the excipients and so on, it has gotten to the point  
20 where that systemic bioavailability has not shown a  
21 difference.

22 So, at the point where we are asking you to be,  
23 in terms of answering these questions, we are saying that  
24 we have not assessed in vitro in a validated manner the  
25 comparative particle size, but we have gotten to the point

1 | where whatever pharmacokinetic data have been generated  
2 | don't show a difference. So, yes, particle size could  
3 | impact on that, but we're down a pathway where, for  
4 | whatever reason -- maybe it is similarity of the particle  
5 | size that we haven't been able to assess in vitro -- we're  
6 | not seeing a difference in systemic bioavailability.

7 | DR. ANDERSON: Maybe my question is then, what  
8 | do you mean by "providing equivalence of each of the terms  
9 | in the first sentence exists"? Maybe that's the question I  
10 | need to raise. Maybe I'm not understanding it.

11 | DR. ADAMS: Maybe it could be written more  
12 | carefully, although there was an attempt at that.

13 | DR. ANDERSON: That doesn't mean the test and  
14 | the reference -- all these things are equivalent in the  
15 | test and the reference. Is that correct?

16 | DR. ADAMS: Yes, it does.

17 | DR. ANDERSON: Okay. That's the way I  
18 | interpreted it. The device, the Q1, the Q2, the in vitro  
19 | studies, all of that.

20 | Then you come to systemic exposure and systemic  
21 | absorption, which to me, according to this sentence, says  
22 | that they're equivalent, but in the next sentence you talk  
23 | about particle size.

24 | I'm not going to belabor it because you guys  
25 | are the experts.

1 DR. MEYER: I think the point is maybe the part  
2 about the systemic exposure and absorption should have  
3 followed the sentence about the in vitro studies, but the  
4 point is you do the in vitro studies, and if everything you  
5 can assess looks equivalent, you then do the systemic  
6 bioavailability studies. If they then look equivalent,  
7 then you get to the clinical study. The clinical study  
8 doesn't trump these and the systemic bioavailability study  
9 does not trump the in vitro. You are building to this.

10 DR. LEE: Is it clear?

11 DR. ANDERSON: Well, I'm finished. I still say  
12 particle size will have an effect on that, maybe that's not  
13 a part of that sentence.

14 DR. LEE: Let me summarize the prevailing  
15 opinion on this side of the table, which is that there is a  
16 need for a clinical study.

17 So, let me now turn to my left. Leon?

18 DR. SHARGEL: I have some concerns whether the  
19 clinical study, as designed here, is really appropriate for  
20 determining bioequivalence. In terms of bioequivalence, as  
21 Dr. Conner mentioned, we're looking at the performance. We  
22 are comparing the bioavailability of a test drug product  
23 against a reference drug product. Generally when we do  
24 that kind of test, whether we do a blood level time curve  
25 for all drug pharmaceuticals or pharmacodynamic kind of

1 study, we make the assumption that if it is shown to be  
2 bioequivalent under whatever standards we have, which is  
3 usually Cmax/AUC, that the performance of these products  
4 will give a similar clinical efficacy and safety as well.

5 Now, if we look at this study -- and the  
6 question seems to be this morning a discussion whether it  
7 really can be sensitive to look at different doses, and  
8 even if we use only one dose and we see no difference in  
9 the clinical effect, can we then assume that the products  
10 are bioequivalent? And that is what we seem to be doing.  
11 We can say, well, both products give the same clinical  
12 endpoint. But you really don't know where you are on the  
13 log dose response for sure.

14 So, unless you're able to really have some more  
15 objective measurements, in my mind, to distinguish whether  
16 we're at the appropriate dose and at small differences in  
17 dose or particle size, which in a sense -- and other kinds  
18 which lead to changes, say, in the rate of absorption, will  
19 make a difference in terms of bioequivalence because one of  
20 the parameters or metrics is rate of absorption. Many  
21 times we see small changes in particle size makes no  
22 difference. In other cases, it may.

23 So, are we really measuring particle size here?  
24 I'm not sure in my mind that we are. Or rate of  
25 absorption? We are saying, okay, we've got a clinical

1 endpoint. Both give the same clinical efficacy, and  
2 therefore we're bioequivalent. I'm not sure I'm happy with  
3 that.

4 I am happy, though, if you say bioequivalent on  
5 some objective means such as, say, the blood level time  
6 curve. I think throughout the years in the last 20 years,  
7 we've seen that that is a pretty good guess, particularly  
8 if the Q1/Q2, quantitative/qualitative excipients are the  
9 same, there is less likelihood of any untoward effects on  
10 that case and the dose is about the same and the  
11 pharmaceutical equivalence and follow all the in vitro  
12 things.

13 So, I agree with Les. I think this is somewhat  
14 of an overkill, that the clinical endpoint really achieves  
15 what we're really looking for.

16 DR. ADAMS: Walt?

17 DR. HAUCK: Well, I will start with what I'm  
18 going to call question 0, the one the committee has put on  
19 the table as to whether the clinical studies should be done  
20 at all. In my mind I've not heard enough to reach a  
21 judgment on that.

22 The problem is that what we have heard that is  
23 that particle size distribution matters, but what we  
24 haven't heard or seen data on is for two products that are  
25 Q1 equivalent, Q2 equivalent, equivalent devices,

1 equivalent on this battery of in vitro tests, and  
2 equivalent on the systemic exposure, whether they could  
3 still differ enough in particle size distribution to  
4 matter. I don't know. Data probably doesn't exist on  
5 that, but that seems to be the relevant question, and I  
6 don't know that we've heard that. So, I'm going to restate  
7 the question and not try to answer it because you're also  
8 moving outside my expertise.

9 In regard to questions 1 and 2, what is the  
10 alternative? The alternative is to study more than one  
11 dose. It would seem sensible to say that you would want  
12 equivalence of the dose-response curves. It would not seem  
13 sensible, though -- let me add this -- the statistical  
14 significance of the dose-response curves is irrelevant for  
15 a bioequivalence study. The test and the reference could  
16 have equally flat dose-response curves, and that's  
17 equivalent and that should be fine.

18 I think that what we're hearing is that even  
19 the lowest recommended dose is still on the flat part or  
20 not far off of it, so that studying more than one dose then  
21 becomes a waste of time because you know you're on the flat  
22 part. And if you've shown it for the one dose, you've  
23 shown it for the rest of the doses.

24 So, from that perspective, my answer to  
25 questions 1 and 2 would be yes. I just don't know which of

1 | 1 of 2 I would answer yes to because there are really two  
2 | parts to the question. Do we study one dose and then which  
3 | design? And on the design issue, I haven't heard enough to  
4 | make a decision on that.

5 |           My only concern would be that if a guidance is  
6 | being developed based on the current state of products,  
7 | that they need to have some sort of mechanism in place to  
8 | worry about when it's no longer the case that the lowest  
9 | recommended dose is right near the flat part of the dose-  
10 | response curve. I mean, 5 years from now or 10 years from  
11 | now, if a new body of products is coming up, that maybe  
12 | that doesn't hold, you may want to rethink your choice of  
13 | using a single dose.

14 |           DR. LEE: So, Walt, am I hearing that you're in  
15 | favor of the --

16 |           DR. HAUCK: I'm ambivalent. Or no. I can't  
17 | decide on the need for a clinical study. If there is a  
18 | clinical study, then I say yes to one dose, and I've not  
19 | heard enough to say for me whether or not it needs to be  
20 | the 2-week study or the natural study or the EEU study. I  
21 | don't think we heard enough. So, that's what I'm saying.  
22 | I'm saying yes to 1 or 2. I just don't know which of the  
23 | two I'm saying yes to.

24 |           DR. LEE: Okay. Maybe Dr. Roman is going to  
25 | help us in that regard.

1 DR. ROMAN: Yes, and I hope I help Walter and I  
2 help the rest of you.

3 I know through doing the study and reviewing  
4 literature that the second question at the moment cannot be  
5 answered successfully. We do not know if the unit exposure  
6 or park study can give us any better answer than natural  
7 exposure 2-week studies, particularly for steroids. So, in  
8 terms of which study to choose, I will say, yes, natural  
9 exposure design, which is point 1.

10 Since we are not able to determine dose  
11 response with existing methodology, if you choose one,  
12 three, or five doses, 8 times difference, 16 times  
13 difference, and twofold difference, you will still, more or  
14 less, see a flat dose response as we saw so far.

15 I agree again with Dr. Hauck that maybe in the  
16 future when the methodology will be more sensitive to  
17 determine differences between the doses, we could go back  
18 to the dose-response question.

19 However, in my mind exactly as I asked Walter,  
20 what is the difference between particle sizes in low dose  
21 and high dose of the same product, when you study dose  
22 response for an innovator product, do you study particle  
23 sizes when you do such a study? Do you know that the low  
24 dose new steroids have similar particle size distribution  
25 or just a correlative number, or whatever you measure, as

1 high dose? Do you correlate the particle sizes in  
2 different doses to the efficacy and safety? And this is  
3 obviously a question to pharmacologists, pharmacists.

4 DR. MEYER: I have to apologize because we were  
5 having a side bar in the earlier part of your discussion.  
6 But if you would repeat the question, I would appreciate  
7 it.

8 DR. ROMAN: Do we know what is the particle  
9 size distribution and contribution in the efficacy of low  
10 dose and high dose of the same innovator drug?

11 DR. MEYER: For the nasal products. I don't  
12 believe we do know, no.

13 DR. ROMAN: So, we're asking a very important  
14 question to be compared for generic and marketed product,  
15 but we don't know what is the contribution of particle  
16 sizes in even an innovator product to the dose response or  
17 efficacy.

18 DR. MEYER: Right. I think the place where we  
19 end up with the innovator product is we know what the  
20 particle size distribution looked like in the clinical  
21 trial batches and we know what they look like in the  
22 marketed batches. And we put some criteria on those to  
23 keep them within the same range, as much as feasible, so  
24 that hopefully we don't see a shift. But we don't know  
25 where in that distribution of particles the efficacy is

1 coming from. If it is restricted, if it's broad, we don't  
2 know that, so we don't know what would be critically  
3 different if you were to go to a test product or a generic  
4 product that would be substitutable.

5 DR. ROMAN: So, as I say, medically it makes  
6 sense to do the study, and number 1 is the one I will  
7 choose. That's the opinion I have. Thank you.

8 DR. LEE: So, does the subcommittee know where  
9 we stand? We have two members who feel that this is  
10 overkill. We have one member who says it all depends, and  
11 then we have the others who feel that it's appropriate.

12 DR. HENDELES: If you are going to overkill,  
13 then I think number 1 is appropriate.

14 (Laughter.)

15 DR. LEE: Yes.

16 DR. ROMAN: Dr. Lee is looking at me so I will  
17 have first chance.

18 We know where we stand in terms of development  
19 of models for sensitivity for studying nasal allergy in  
20 terms of an endpoint, which is very subjective, symptomatic  
21 and all that. Is there at all the possibility to develop  
22 the comparison of the particle sizes? Isn't it more you  
23 attach something to it that you can compare A to B, or is  
24 the science so difficult that it is impossible to compare  
25 particle sizes or look for the methodology to do so? Or is

1 | it too naive a question?

2 |           DR. ADAMS: No, I don't think it's an  
3 | unreasonable question. In fact, we are very interested in  
4 | that issue, Dr. Roman, and we are giving it consideration  
5 | in our own laboratories. But at the present time, we don't  
6 | have a methodology which is validated.

7 |           DR. OWNBY: I've got a follow-up on a comment  
8 | Dr. Meyer made and Dr. Adams just added to. It's my  
9 | understanding you said that for innovator products, you  
10 | looked at the particle size distribution in the test lots  
11 | that were used for clinical studies, and then when they  
12 | went into manufacturing, you also looked at the particle  
13 | size distribution and said they were substantially the  
14 | same. Therefore, they could go ahead with their  
15 | distribution. Is that correct?

16 |           DR. MEYER: Let me be clear about that because  
17 | I may have said things in an unclear manner. There I was  
18 | talking primarily about the micronization of the drug  
19 | substance before it's put into the formulation because the  
20 | issue about a validated manner to assure the sameness of  
21 | the particle size in the formulation itself holds no matter  
22 | what product you are talking about.

23 |           But where an innovator firm can and does  
24 | monitor the micronization process in their drug substance,  
25 | a generic firm has no way of acquiring that data from the

1 innovator product or from the reference product to assure  
2 that whatever micronization they achieve is the same as the  
3 micronization of their reference product. So, we're  
4 actually talking a step back. I'm talking about drug  
5 substance before it's formulated.

6 DR. OWNBY: Would you clarify? In my mind, it  
7 seems like we're talking about two different things. One  
8 is the particle of the steroid itself, the micronized  
9 steroid that's going to be put in the suspension, and the  
10 second thing is going to be the droplet size as that  
11 particle is delivered with the excipients and the vehicle  
12 around it from the nozzle of the device. Is that correct?

13 DR. MEYER: What we're focusing on today,  
14 though, is the particle size of the drug particles in the  
15 suspension. We feel like there are ways to characterize  
16 the droplet distribution. There are techniques for doing  
17 that, and I would leave it to my colleagues who know more  
18 about this than I to talk about that. But the unknown that  
19 we end up with at the end of the in vitro assessment is the  
20 particle size of the drug within the formulation itself,  
21 not so much the droplet size, plume geometry, those other  
22 things that we feel we can characterize.

23 DR. OWNBY: As a follow-up to that, when you  
24 talk about the particle size, you say that a secondary firm  
25 doesn't have access to the micronization statistics. Do

1 | you also think that once it's put into the formulation,  
2 | that the micronized particles again begin to clump together  
3 | so they change their size once they're in the formulation?

4 | DR. MEYER: There probably is some  
5 | agglomeration and aggregation of the particles, but because  
6 | of the difficulties of assessing that in a suspension  
7 | formulation with other particulate excipients, I think the  
8 | degree of that may be difficult to know with surety.

9 | DR. LEE: It seems to me that we should have  
10 | scheduled someone to come and talk about suspensions.

11 | DR. ADAMS: We may be able to have some  
12 | additional thought on particle size distribution if Dr.  
13 | Poochikin would like to make a comment. Let me ask.  
14 | Guirag, would you be interested in making a comment with  
15 | regard to this topic?

16 | DR. POOCHIKIN: There were too many questions  
17 | asked. I don't know where to start from.

18 | As a matter of fact, with regard to particle  
19 | size for these type of drug products, we're dealing with  
20 | many aspects.

21 | First, we're dealing with the particle sizing  
22 | of the incoming drug substance, as Dr. Meyer and you were  
23 | talking about.

24 | Second, we're talking about we have to consider  
25 | also particle size of the excipients. In this case, methyl

1 celluloses, for example. Those are critical. They need to  
2 be controlled adequately.

3 Third, we have the particle size of the active  
4 in the formulation, as you were referring.

5 And fourth, we have the droplet size of the  
6 emitted spray.

7 On top of it, of course, we have a fifth  
8 complication which is the manufacturing aspects. Once we  
9 have the active and the excipient with appropriate particle  
10 size, will it create agglomeration? And that will depend  
11 on the environmental condition after formulation, but on  
12 top of it, it will also depend on the manufacturing  
13 procedures. So, that's a fifth complication that you will  
14 have to achieve similar spray from these type of drug  
15 suspension products.

16 If there are other questions on that issue, I  
17 can elaborate.

18 DR. OWNBY: To follow up on that, is there  
19 information about how much this affects the systemic  
20 availability of the drug or the local delivery of the drug?

21 DR. POOCHIKIN: As was discussed all day long,  
22 it depends on the particle size of the emitted or sprayed  
23 dose. That was discussed quite frequently this morning.  
24 That's the extent I can comment on that.

25 DR. ROMAN: Could you tell me then, since there

1 are so many various things, variables, which you deal with  
2 when you produce intranasal steroids, since we are  
3 discussing them, that you could assure the characteristic  
4 of this delivery system from batch to batch for the  
5 innovator product from one formulation of a dose to another  
6 formulation of a different dose by the same company? So,  
7 are there enough guidelines, requirements, that they  
8 characterize the delivery of intranasal steroids?

9 DR. POOCHIKIN: Of the same product.

10 DR. ROMAN: Of the same product.

11 DR. POOCHIKIN: Yes, because as I indicated  
12 earlier, all those aspects that I discussed are monitored  
13 and controlled at the manufacturing level, including  
14 manufacturing itself. So, if you control everything that  
15 goes into the product, hopefully what comes out will be of  
16 the same quality.

17 But on top of it, of course, there are certain  
18 additional tasks which can be measured with regard to the  
19 pump or spray, as well as certain attributes of the drug  
20 product after it's manufactured, and of course, we have  
21 stabilities studies also. So, there are additional aspects  
22 that are being monitored.

23 Of course, you have to assume that it is always  
24 being done in the same environment by the same personnel,  
25 by the same experienced people. So, that's the assumption

1 | there.

2 | DR. ROMAN: If you don't mind, this will be my  
3 | last question. I won't say anything else. This was my  
4 | question actually to you, Robert, and now I will ask it  
5 | again.

6 | So, what you are controlled is a new product  
7 | when it's manufactured. During the clinical studies, when  
8 | you do dose response for a new product, do you know if the  
9 | particle sizes of a low dose formulation versus high dose  
10 | formulation, when you do dose response, because they  
11 | formulate different concentrations, are of the same size?  
12 | Is this at all looked upon?

13 | DR. MEYER: I think that we have the same  
14 | technical difficulties assessing that for a nasal  
15 | suspension in terms of comparing two different formulations  
16 | from an innovator company that we would a test and  
17 | reference in a generic sense. So, I guess in essence we  
18 | really don't fully know that, but I think we are cognizant  
19 | of the fact that alterations in the concentration and other  
20 | aspects of the formulation can lead to different  
21 | performances of those formulations.

22 | One of the discussions earlier got to could we  
23 | use even lower doses of the test or the reference. Well,  
24 | in the generic world, you're not allowed, as a generic  
25 | company, to manipulate your comparator product, number one.

1 | But number two, doing so may change the characteristics of  
2 | that formulation anyway. So, we are cognizant of that  
3 | being an issue, but we don't have strict assurance, no.

4 | DR. ROMAN: Could it be, in part, responsible  
5 | for this flatness of dose response? Theoretically I can  
6 | imagine that if you load more product, you change particle  
7 | sizes, don't you or not?

8 | DR. MEYER: You might. I think it would  
9 | confound the interpretation if you saw a dose response. I  
10 | don't think it likely would lead, in my mind, to a  
11 | flattening of the dose response. I suppose it could.

12 | DR. CHOWDHURY: I just want to comment on that  
13 | because for the dose-response studies many times is the  
14 | same drug product which is used, but differing the number  
15 | of sprays.

16 | DR. ROMAN: But then you can only modulate two  
17 | times, twofold, fourfold. When you got to 16-fold, it's a  
18 | different concentration.

19 | DR. CHOWDHURY: That's correct, but again, what  
20 | you see for a flat dose response actually even goes for the  
21 | lower like one-fold, two-fold changes.

22 | DR. POCHIKIN: With regard to different  
23 | strengths of the same product, if I understood correctly,  
24 | what Badrul was talking about, what Dr. Meyer was talking  
25 | about was the same product given one spray versus two sprays

1 | versus four sprays and eight sprays, et cetera, as opposed  
2 | to the same product manufactured at different strengths.  
3 | As you know, there aren't that many nasal suspensions with  
4 | different strengths. Those that are available, the  
5 | concentrations are so low, I suspect if that will make any  
6 | particle size distribution differences under the same  
7 | conditions.

8 |           Having said that, of course, we have to  
9 | consider the limitations of the test that we have. Based  
10 | on the available data that we have on those very limited  
11 | number of products, there isn't that much difference for  
12 | different strengths of the same product because they are  
13 | manufactured under the same conditions using the same  
14 | spray, the same pump, the same excipient, the same drug  
15 | substance.

16 |           DR. LEE: Dale, you wanted to make a comment?

17 |           DR. CONNER: One thing that impresses me about  
18 | the last 10 or 15 minutes' discussion is we seem to be  
19 | concentrating on strictly particle size like it is an end  
20 | in and of itself. The only reason that particle size is  
21 | important is because what it implies to what we're really  
22 | interested in, which is are the two products, the resulting  
23 | products, of which particle size is one component,  
24 | therapeutically equivalent. Will they give the same  
25 | therapeutic responses? So, particle size is simply

1 something that contributes to that endpoint, which is what  
2 we're really interested in. We're saying, obviously, if we  
3 had our choice, the easiest thing is just to measure  
4 particle size directly, and if it's exactly the same, it  
5 essentially answers our worries about what could happen  
6 down the road about what we're really interested in.

7 In that we've said we can't do it directly,  
8 then we have no choice to jump over that and measure what  
9 we're really interested in anyway, which is therapeutic  
10 equivalence. That's what we're proposing to do, to say now  
11 we're kind of going a little bit further down the chain  
12 actually measuring what's happening presumably in the  
13 patient and assuring that it's the same. When we do that  
14 effectively, we say it really doesn't matter if there's a  
15 difference in particle size. I'm measuring what I'm  
16 actually interested in, the endpoint.

17 It's not the other way around, that the  
18 particle size is the end that I'm interested in. We were  
19 only interested in particle size because it has some  
20 implication on what we really want to know. So, we've just  
21 simply jumped over it and said, well, we're going to  
22 measure what we want to know more directly. Maybe there's  
23 no particle size difference at all. Maybe it's huge, but  
24 I've shown that it doesn't matter.

25 DR. ROMAN: Yes, but this is the only thing

1 | which we cannot characterize properly. I understand that  
2 | everything else can be done in vitro with the exception of  
3 | this one. So, if you have the same active moiety and the  
4 | only difference is particle size, so we are doing this  
5 | clinical study just because we cannot characterize this  
6 | particular aspect --

7 |           DR. CONNER: If some brilliant person -- and  
8 | many have tried over the past few years unsuccessfully --  
9 | if we could get a very convincing, validated measure of  
10 | particle size and be able to compare it in the finished  
11 | product, we may not need to do this. We were hoping that  
12 | that effort would be successful and that we could not have  
13 | to do this clinical trial, that we would have the last  
14 | piece of the puzzle. We don't have that right now. So,  
15 | we're forced to confirm it through other means by looking  
16 | at the endpoint of what we're really interested in rather  
17 | than measuring that particular factor directly.

18 |           DR. LEE: Okay. I think that we are going  
19 | around and around expressing our discomfort about our  
20 | respective positions.

21 |           Let me state, in all fairness -- yes, Wally.

22 |           DR. ADAMS: Yes. I think listening to each of  
23 | the subcommittee members, I think I hear what the  
24 | recommendations are or the feeling of the various  
25 | individuals. I'm wondering if we could, however, put this

1 on the record that in Dr. Meyer's presentation, he talked  
2 about the rhinitis study as being either confirmatory or  
3 pivotal in terms of the bioequivalence assessment. I would  
4 be very interested in hearing specifically that issue  
5 addressed. I think it has been said in so many words, but  
6 if we could have that on the record as to how the people  
7 feel about that, it would be helpful. I think that also  
8 gets to the issue of one dose versus two doses.

9 DR. LEE: This is exactly what I'm about to  
10 say. Thank you very much for framing the statement.

11 Wally stated a point about your feeling about  
12 confirmatory versus pivotal. Should I start with Dr.  
13 Roman?

14 DR. ROMAN: I always have an opinion to share,  
15 so let me share my opinion with you.

16 The way I understood Dr. Meyer's presentation  
17 of this pivotal versus confirmatory is that their  
18 situation, even at present, is that you cannot do  
19 pharmacokinetic comparison. That is, the drug levels in  
20 blood are so low or the test method to measure drug level  
21 is so insensitive -- whatever, we don't know any better --  
22 that therefore the complete profile of blood level is not  
23 possible to determine.

24 In this case, you don't have any in vivo data  
25 for bioequivalence, and the only one you have is clinical

1 study. In this situation, I will call it pivotal.

2 If on the other hand, you have a sensitive  
3 method to determine the pharmacokinetic profile of the  
4 product, that for me would be only confirmatory because of  
5 this particle size situation.

6 So, it can be defined different ways or with a  
7 different definition for a different situation.

8 Now, I would like to hear, because I think that  
9 I also understood from Dr. Meyer that if it is pivotal, he  
10 would like to see dose response, and he would be willing to  
11 agree with one dose for a confirmatory study. This is what  
12 I was trying to ask you actually immediately after your  
13 presentation.

14 DR. MEYER: I think from my own viewpoint that  
15 if one is asking the study to establish bioequivalence and  
16 that's going to be your primary basis for that, then I  
17 think you need to show sensitivity to the effects of dose  
18 so that you can assess what the meaning is of any different  
19 scene between the test and the reference in the clinical  
20 study.

21 DR. ROMAN: And here, of course, we share the  
22 understanding that with the available methodology and  
23 sensitivity of the methodology, it's almost impossible, and  
24 with the limitation of having an already formulated product  
25 so the fold difference could be no more than four in terms

1 of different dose levels.

2 DR. LEE: Walt?

3 DR. HAUCK: Well, we spent the afternoon pretty  
4 much trashing the clinical study. So, given that we've got  
5 a clinical study now that at least, I would say, about half  
6 the committee views is of uncertain value, confirmatory  
7 would be the best we could call it, certainly not pivotal.

8 On a different level, if we were to set a  
9 principle of calling the clinical study pivotal, which  
10 would almost be reopening all the bioequivalence guidances  
11 that we've got, so as far as I'm concerned, the entire  
12 tenor of all the bioequivalence approaches is the clinical  
13 approaches are not pivotal. Everything is trying to find  
14 an alternative to doing a clinical trial.

15 DR. SHARGEL: I would go along with  
16 confirmatory, looking at what Dr. Meyer has here. I think  
17 the whole idea of bioequivalence studies in any regard, the  
18 final analysis or assumption of a bioequivalent test, if  
19 you do any other kind of thing, is that predictably it's  
20 going to have the same clinical effect. Therefore, if you  
21 put it in a clinical situation, it has the same effect,  
22 that's the endpoint that you're looking for in terms of  
23 substitution of a generic brand or different lots of the  
24 brand or different lots of the generic. So, I would tend  
25 to think that this would confirm the fact that both

1 products behaved in a clinical situation in a similar  
2 fashion within perhaps statistical parameters. Whether it  
3 has slight differences in bioavailability I'm not sure  
4 you'd get from that kind of study. Therefore, I don't look  
5 at it as pivotal.

6 DR. LEE: Thank you.

7 Gloria? Richard?

8 DR. AHRENS: I'd agree that it's confirmatory  
9 without additional comment. I think it has all been said.

10 DR. OWNBY: I would agree that confirmatory is  
11 the best I think we could reasonably expect in this  
12 circumstance.

13 DR. DYKEWICZ: Confirmatory.

14 DR. HENDELES: Ditto.

15 DR. LEE: There's a consensus on confirmatory I  
16 suppose.

17 I think what we would like to do is to propose  
18 a break so that we can clear our heads. Then we'll come  
19 back and once again we address this issue. But I'd like to  
20 come a little bit to some kind of a consensus about how we  
21 feel about the first two questions posed.

22 Yes, Wally.

23 DR. ADAMS: Just one point for clarity to Dr.  
24 Roman. You indicated that provided the plasma levels could  
25 not be measured, the rhinitis study would be pivotal. But

1 | could that be broadened to say that whether a PK study or  
2 | an adrenal axis suspension testing were not possible, that  
3 | you would view it as pivotal?

4 | DR. ROMAN: You don't have anything else then.  
5 | If you cannot do plasma levels, so you're really comparing  
6 | based on all in vitro work, and therefore I dare to call it  
7 | pivotal, but I don't know if those responses are doable as  
8 | a pivotal. Maybe it will be defined pivotal for efficacy,  
9 | this one dose level study, and then we should discuss the  
10 | safety study, which is a different issue. What we were  
11 | touching on this morning is that the low effective dose,  
12 | which I assume will be close to the labeled dose or will be  
13 | from an efficacy standpoint, and then some kind of a high  
14 | dose for systemic safety.

15 | DR. ADAMS: So, if either the high dose PK or  
16 | the high dose adrenal axis suspension testing could be  
17 | done, then the rhinitis study is confirmatory. Is that  
18 | what you're saying or not?

19 | DR. ROMAN: Let me repeat it. If PK cannot be  
20 | done and HPA axis cannot be done --

21 | DR. ADAMS: Can be done, then would you view  
22 | the rhinitis study as confirmatory?

23 | DR. ROMAN: Right.

24 | DR. ADAMS: Okay, good. Thank you.

25 | DR. LEE: Wally, let me ask you a question

1 before we break so that we can really think about it. Is  
2 it fair to say that these two questions would not have been  
3 posed if we had access to information about the particle  
4 size distribution?

5 DR. ADAMS: That's a very interesting question,  
6 Vince.

7 (Laughter.)

8 DR. ADAMS: I would deflect that question to  
9 say that should at some time a validated particle size  
10 distribution method become available, then we will take  
11 that to our working group and discuss it. It's not an  
12 issue that we've had the luxury of addressing at this time.

13 DR. LEE: All right. I think it is time for a  
14 time-out. Let's say that we come back at about -- would  
15 2:45 be too generous?

16 DR. ROMAN: It would be right.

17 (Laughter.)

18 DR. LEE: Okay. 2:45, and we come back and  
19 address those two questions one more time. Thank you.

20 (Recess.)

21 DR. LEE: So, we have to reconvene. I hope  
22 that this time-out was helpful to everybody.

23 Let me try to bring some focus to this  
24 concluding session, the final session. I promise that we  
25 will be done before 4:00 p.m. today.

1 We have two questions posed to us, and let me  
2 start out by saying that if we were to address one of these  
3 two scenarios, which one would you prefer? Would you have  
4 much confidence in the EEU and the park study? Dr. Roman?

5 DR. ROMAN: Yes, again, the question is number  
6 one point or number two, a clinical study of 2 weeks'  
7 duration at least, et cetera versus EEU or park study. My  
8 answer is number one, a classical or traditional exposure  
9 study.

10 DR. HAUCK: I'm going to go along with whatever  
11 the rest of the committee decides on that.

12 (Laughter.)

13 DR. HAUCK: I'm getting my arm twisted. It's  
14 number one.

15 (Laughter.)

16 DR. SHARGEL: I'm twisting his arm also. I go  
17 along with number one. I think it confirms that both  
18 products have similar clinical endpoints.

19 DR. LEE: Thank you.

20 Gloria?

21 DR. ANDERSON: Number one.

22 DR. AHRENS: Number one.

23 DR. OWNBY: I'll go with number one also. I  
24 hope it's the right door.

25 (Laughter.)

1 DR. DYKEWICZ: Number one.

2 DR. HENDELES: I would go with number one also  
3 unless somebody came up with an innovation on number two  
4 that allowed you to look at like an inhaled steroid with  
5 its onset of action.

6 DR. LEE: Okay. I'm a bit worried because  
7 you're the one who has to leave at 4:00.

8 So, there seems to be some consensus developing  
9 for number one. Is that right?

10 DR. ROMAN: Number one at the moment.

11 DR. LEE: And the follow-up question is are you  
12 comfortable with the statement made.

13 DR. HENDELES: What do you mean?

14 DR. LEE: The lowest active dose is sufficient  
15 to confirm equivalent local delivery of a suspension  
16 formulation intended for allergic rhinitis.

17 DR. SHARGEL: May I make a comment on that? In  
18 terms of lowest effective dose, if we're dealing with a  
19 bioequivalent product of another manufacturer that's coming  
20 out, it would be the lowest effective dose or the lowest  
21 dose that's on the label. Indication. Is that what we're  
22 talking about, not necessarily the lowest effective dose,  
23 but the dose that the manufacturer of the brand has already  
24 established? Are we distinguishing between lowest  
25 effective dose, which means I have to find the lowest

1 effective dose, or the dose that the manufacturer has  
2 indicated on the label?

3 DR. LEE: What I'd like to do is to take the  
4 question as stated and then you can agree, disagree. And  
5 if you disagree, please propose an alternative.

6 DR. SHARGEL: Well, I would like to propose the  
7 alternative being the lowest dose that the innovator has  
8 proposed.

9 DR. ADAMS: Lowest labeled dose.

10 DR. SHARGEL: The regulators will give me the  
11 proper term, but the lowest labeled dose, whatever appears  
12 on the insert.

13 DR. LEE: Walt?

14 DR. HAUCK: I'm generally okay. The statement  
15 "confirm" really seems overly strong for me given the  
16 nature of the study. We were given a choice of  
17 confirmatory versus pivotal, and there probably should have  
18 been a third choice there. So, with the caveat that all  
19 we're really doing is saying there's been an opportunity to  
20 find a large difference in particle size and whatever else  
21 and we didn't find it, and if that's what's meant by  
22 confirmatory, then it's okay as worded. Otherwise, I would  
23 work on that wording.

24 DR. LEE: Izabela?

25 DR. ROMAN: I would agree that if the label

1 states the dose range, it should be the lowest approved  
2 dose. The problem I have is what if there is no dose range  
3 in the labeling but a dose or the dose. Will we then  
4 accept that this is the optimal dose?

5 DR. LEE: Thank you.

6 Les?

7 DR. HENDELES: I have a small problem with the  
8 wording. It says "confirm equivalent local delivery," and  
9 I don't think you can do that. I guess maybe if you  
10 replace the word "equivalent" with "to confirm therapeutic  
11 comparability" or something like that. What you're doing  
12 is confirming therapeutic comparability, but not local  
13 delivery because it's possible that you may deliver half as  
14 much drug and not detect that difference.

15 DR. ADAMS: Les, we should have had you help  
16 write the question. That thought hadn't occurred to us.  
17 You're absolutely right.

18 DR. HAUCK: Let me add that was the better  
19 stating of what I was trying to get to.

20 DR. DYKEWICZ: And that was stating what I was  
21 about to state. I don't know if it's an incorrect semantic  
22 approach of saying "to confirm bioequivalent local  
23 delivery" or that's really a misappropriation of the term  
24 "bioequivalence," but that's exactly the concern, that you  
25 may not be getting similar delivery but it's becoming

1 equivalent in terms of clinical outcome.

2 DR. LEE: Dennis?

3 DR. OWNBY: Yes. I agree that we're really  
4 talking about therapeutic endpoints. That's the only thing  
5 you can say is equivalent.

6 DR. AHRENS: I wasn't about to say Les' comment  
7 in a different way, but I agree with it. And with that  
8 said, the lowest labeled dose.

9 DR. LEE: Gloria?

10 DR. ANDERSON: I agree as well. I still have  
11 problems with "believe."

12 DR. LEE: You don't believe?

13 DR. ANDERSON: I don't think I have enough  
14 information to say I believe that. I just wish you could  
15 rewrite that word.

16 DR. HENDELES: And this committee member does  
17 not believe.

18 (Laughter.)

19 DR. ROMAN: Dr. Conner came with this nice  
20 definition of therapeutic equivalence, which is what we are  
21 studying in a clinical study, therapeutic equivalence.

22 DR. MEYER: If it makes people feel more  
23 comfortable, I think what I had tried to say in my talk --  
24 and perhaps we should have chosen wording to better reflect  
25 this -- is that where we are with a confirmatory trial is

1 really saying that given whatever unknowns may still exist  
2 from all the other data that get us to that point, we're  
3 confirming that those differences don't matter clinically  
4 with this confirmatory trial; that therapeutically whatever  
5 unknowns remain from all the in vitro parameters, from the  
6 PK being the same, everything else being the same, the  
7 unknowns, such as particle size distribution, in the  
8 formulation don't matter clinically. So, it's not the  
9 establishment in a bioequivalence. Perhaps this is  
10 overworded. It's really just to say that whatever  
11 differences might remain or whatever we don't know about,  
12 we've taken to a clinical trial and we've not seen an  
13 important difference.

14 DR. LEE: Very well. So, we throw out question  
15 number two, and we all feel comfortable about the 2-week  
16 study. There's some discomfort about the wording, and we  
17 all propose the writer of that question ought to be sent to  
18 English school.

19 (Laughter.)

20 DR. LEE: I think that he got the gist of how  
21 we felt about the wording, and he will come up with  
22 different wording for the public record.

23 DR. ADAMS: Dr. Lee, I would point out with  
24 regard to the wording of that question --

25 (Laughter.)

1 DR. ADAMS: -- somehow our sign-off initials  
2 were down in the lower left of that page, and so you can  
3 see that that was not a single person's effort.

4 (Laughter.)

5 DR. ADAMS: It managed to get past a number of  
6 individuals. But I certainly take the comments which have  
7 been made around the table and completely agree with them  
8 with regard to the wording of the question.

9 In view of the fact that two days from now on  
10 Thursday there's to be a report of the OINDP Subcommittee  
11 to the full ACPS, and it is a short time period and we will  
12 not have the transcript in order to make sure that this  
13 report is accurate. Would we be able to present our  
14 summary bullets for you and the committee to consider and  
15 make sure that we have these right and make any changes to  
16 them? If we could just spend a few minutes doing that.

17 DR. LEE: Sure. Who will be doing that?

18 DR. ADAMS: That would be Dr. Singh.

19 DR. LEE: Dr. Singh, please be to the point.

20 DR. SINGH: I was given the task of keeping  
21 quiet till the end and then give my perception in the form  
22 of a couple of conclusions. I'll put three or four  
23 statements, as you said, to the point, and these statements  
24 are statements only relevant to the main issues discussed  
25 this morning and partly this afternoon.

1                   This has been a key issue although it's not  
2 directly stated in the two questions that Wally put up and  
3 the two questions that we just finished discussing.

4                   The key issue in my opinion has been  
5 demonstration of the dose response with the difficulties  
6 associated with it. What I've heard is that based on the  
7 current technology and methods, the demonstration of dose  
8 response may not be possible at this moment. That's the  
9 number one conclusion I made, and it's open for the  
10 committee's comments, Dr. Lee.

11                  DR. LEE: Is that what the subcommittee says?  
12 They all agree. Good job.

13                  DR. HAUCK: Well, with a caveat. At least part  
14 of my comment was it's also irrelevant for the  
15 bioequivalence context whether you can demonstrate a dose  
16 response or not.

17                  DR. SINGH: Yes. I think what we heard from  
18 Dr. Chowdhury and Dr. Meyer and others is that whether it's  
19 with regard to the bioequivalence determination or  
20 bioavailability, thus far we cannot determine dose response  
21 for at least these steroid formulations. Am I right in  
22 that, Dr. Chowdhury?

23                  DR. CHOWDHURY: Yes, you are right on that.

24                  DR. SINGH: Thank you.

25                  DR. MEYER: I just wanted to comment on what

1 | Dr. Hauck just said that it is not material to the actual  
2 | determination of bioequivalence, but the use of it is  
3 | actually to establish the study could have detected a  
4 | difference if a difference existed. It's to show assay  
5 | sensitivity in the study, and then you can do your  
6 | bioequivalence based on a determination of how the two  
7 | single doses relate.

8 |           DR. HAUCK: That's where your placebo comes in  
9 | and why I asked about the placebo earlier this morning.  
10 | It's the fact that you have the placebo control which is  
11 | giving your assay sensitivity.

12 |           DR. MEYER: I actually don't agree with that  
13 | because if you have a binary answer where 32 micrograms  
14 | looks no different from 256, and you are studying, say, 128  
15 | micrograms, the failure to show a difference in that  
16 | doesn't suggest that no difference exists or doesn't  
17 | establish that no difference exists.

18 |           You can show a difference from placebo with a  
19 | corticosteroid with fair regularity. There are very few  
20 | well-done trials that fail with a steroid, but they act  
21 | very binary. There's either an effect or there's not. So,  
22 | you need to show sensitivity to dose. It's not just  
23 | whether there's sensitivity to active versus placebo; you  
24 | have to show sensitivity to dose if you wanted to establish  
25 | bioequivalence in a pivotal setting.

1 DR. SINGH: Then the committee went into  
2 discussions like there were some opinions expressed, do we  
3 really need a clinical study or in vitro and PK can be  
4 enough. Dr. Hendeles took the lead on that. I think what  
5 I heard the committee say, based on that initiative by Dr.  
6 Ahrens, is yes, under circumstances a clinical study is  
7 needed to establish equivalence of suspension nasal  
8 products. Any comments on that?

9 DR. SHARGEL: I have one comment on that  
10 because I think we wound up saying that it was confirmatory  
11 to the bioequivalence rather than establishing equivalence,  
12 which is a little different.

13 DR. SINGH: I'm coming to that point. This is  
14 in a slide later on.

15 DR. HAUCK: Wait a minute. I'm not sure I  
16 agree with this statement. At best, I thought this was an  
17 open question. I can understand that there's enough  
18 information to make this a question as to whether there's a  
19 need for the study, but for me there wasn't enough  
20 information to -- I was going to say confirm --

21 (Laughter.)

22 DR. HAUCK: -- to conclude that the clinical  
23 study was going to add anything in the context that it's  
24 being used, that is, on top of all the other equivalence  
25 studies. So, I don't buy this for me. Maybe it's a

1 | consensus, if not unanimous, for the committee.

2 | DR. LEE: I think the majority of the  
3 | subcommittee felt that a clinical study would be necessary.

4 | DR. SINGH: That's what my perception was. I  
5 | think the difficulty may be with regard to the word  
6 | equivalence here, which I'm coming to later on whether it's  
7 | confirmatory.

8 | DR. MEYER: Right, but if we're trying to  
9 | capture the sense of the committee, I think we would have  
10 | to reflect perhaps that the majority felt a clinical study  
11 | would be useful in the examination of --

12 | DR. HENDELES: But not establishing  
13 | equivalence.

14 | DR. MEYER: Not establishing equivalence, but  
15 | useful as a part of the comparison between a generic and a  
16 | reference product for nasal suspension sprays.

17 | DR. SINGH: That's right.

18 | DR. ADAMS: Gur Jai Pal, could you just modify  
19 | that sentence, because as we move through this, if we could  
20 | get the wording correct, as we go through it, it will be  
21 | very helpful.

22 | DR. ROMAN: If you would add to establish, as  
23 | it was stated, therapeutic equivalence, would it be  
24 | sufficient?

25 | DR. SHARGEL: I think that the clinical study

1 | doesn't actually establish bioequivalence as a pivotal  
2 | equivalence. We're taking the total data and submission,  
3 | which includes a lot of in vitro measurements, and this  
4 | clinical study only confirms that there's no difference  
5 | between the products as opposed to looking at rate, extent,  
6 | and those kinds of parameters. So, as it was written, I  
7 | don't agree with that. I'm not sure I see the need for a  
8 | clinical study, but if we were doing a clinical study, it's  
9 | basically for a confirmation that there is no difference  
10 | between the products, that whatever was found in vitro in  
11 | terms of particle size and characteristics of plume  
12 | geometry and all the good stuff that's in there, we are  
13 | confirming it with the clinical study.

14 |           DR. SINGH: I think all my comments reflect is  
15 | what Dr. Lee said, the majority of the committee said that  
16 | some kind of clinical study is necessary.

17 |           Now I deleted two words "establish  
18 | bioequivalence," and I just put "to compare suspension  
19 | nasal products," whatever manner we want to compare it.  
20 | Wally, do you want to modify it further?

21 |           DR. MEYER: I thought perhaps the committee  
22 | might be more comfortable with the word "useful" rather  
23 | than "needed," a clinical study is "useful" in the  
24 | comparison of nasal suspension products. I don't want to  
25 | put words in anybody's mouth, though, because I know some

1 | people were more definitive about this than others and  
2 | that's softening the language.

3 | DR. ADAMS: Does the subcommittee feel  
4 | comfortable with a clinical study is "useful"?

5 | DR. SHARGEL: I disagree with any term that  
6 | just says "useful." There's a lot of stuff that's useful.  
7 | I know that when we submit applications, I get feedback  
8 | from the regulatory people that things are recommended as  
9 | useful. I think we really need to know whether it's needed  
10 | scientifically.

11 | DR. HENDELES: As I understand it, this  
12 | clinical study is going to confirm that there are no  
13 | problems with this product. So, something along that line  
14 | I think was the wording you used. So, instead of useful,  
15 | it's going to confirm that there are no apparent  
16 | bioequivalence problems. How about that?

17 | DR. ADAMS: So, Les, are you saying that a  
18 | clinical study is needed to confirm?

19 | DR. HENDELES: I'm not saying that.

20 | (Laughter.)

21 | DR. HENDELES: It's still hard for me to  
22 | understand how you can put a bolus of this stuff in  
23 | somebody's nose at the site of action and question whether  
24 | it's going to work or not.

25 | DR. MEYER: Just to help, because I think we're

1 going to get to some of what you were just saying, Les, in  
2 the later summary of slides. I think the crux of this is  
3 does the committee feel like there is a role for a clinical  
4 study in what we're proposing or not. My sense is that  
5 there was a majority of opinion that there was but not a  
6 consensus, if you use consensus to be synonymous with a  
7 unanimous agreement. I think we can reflect that to the  
8 full committee.

9 DR. SINGH: Okay. The next bullet is with  
10 regard to the two types of studies that were put up there  
11 in question two, what I heard was for study number one,  
12 which was a placebo-controlled traditional 2-week rhinitis  
13 study may be appropriate for whatever we want to achieve  
14 here, and a lot has been said about that. And the dose  
15 that should be studied where the generic and the reference  
16 product should be compared is the lowest active dose and  
17 that is the lowest dose in the label. If there's only one  
18 dose, then that's the dose, as it was said.

19 DR. ADAMS: Gur Jai Pal, that should read -- I  
20 think what I heard was lowest labeled dose is the feeling  
21 of the committee.

22 DR. SINGH: I have that in the parentheses,  
23 "label."

24 DR. ADAMS: Strike the word "active."

25 DR. SINGH: Okay.

1 DR. ADAMS: We're trying to get this wording so  
2 that it correctly reflects at the present time before we  
3 wrap up today. So, the "lowest labeled dose."

4 DR. SINGH: And the last one is what is the  
5 significance of the rhinitis study, the clinical study, and  
6 I think we heard that it's not a pivotal study. It's a  
7 confirmatory study.

8 And those were my bullets.

9 DR. LEE: Dr. Ownby, you have a question about  
10 the previous slides?

11 DR. OWNBY: Yes, could we have the previous one  
12 back up? I thought this was a comparative study between  
13 two active drugs and not a placebo-controlled trial, or did  
14 we decide that a placebo arm was needed with the two  
15 active?

16 DR. ADAMS: Yes, it is a placebo-controlled  
17 study, as reflected by our guidance, and the intention here  
18 is that this be a placebo-controlled study.

19 DR. DYKEWICZ: My only other comment is about  
20 "may be appropriate." I think we were coming to some sort  
21 of a consensus or opinion that that was the most  
22 appropriate of the various types of studies that were being  
23 proposed.

24 DR. MEYER: Maybe the correct way for us to  
25 word this later is if a clinical study is done, a placebo-

1 controlled, traditional 2-week rhinitis study is  
2 appropriate or is the most appropriate.

3 DR. DYKEWICZ: I like that.

4 DR. LEE: Yes, Walt.

5 DR. HAUCK: On the last transparency you had,  
6 Gur.

7 DR. SINGH: Okay, this was the last one. It's  
8 not a pivotal study; it's confirmatory.

9 DR. HAUCK: The committee did take a vote on  
10 that, but then there was a later phrasing by Dr. Meyer that  
11 actually expressed both the purpose and what was being  
12 accomplished with this clinical study. I'd rather see you  
13 capture that than to have confirmatory, which has all sorts  
14 of common language meanings in addition to whatever  
15 specific meaning we may or may not have agreed on today.  
16 So, I would find the single word potentially very  
17 misleading, and Dr. Meyer's summary would be something I  
18 would be very happy with as a statement of the purpose and  
19 significance of the rhinitis study.

20 Should I summarize so everybody is clear about  
21 what I'm referring to? It was the notion that there were  
22 potentially many unknowns, of which particle size  
23 distribution was one, and this is just ensuring that  
24 whatever the impact of those unknowns were, that they were  
25 not clinically important.

1 DR. ADAMS: Gur Jai Pal, I took a note when Bob  
2 said that. That statement could read that the rhinitis  
3 study is useful to confirm whatever differences exist don't  
4 matter clinically. Whatever unknowns remain don't matter  
5 clinically.

6 DR. OWNBY: Is it better to say don't matter  
7 clinically or don't materially affect the clinical outcome?

8 DR. MEYER: Whatever wording you're comfortable  
9 with. I actually like the way Dr. Hauck said it and the  
10 way Wally captured what I said probably better than what I  
11 said.

12 (Laughter.)

13 DR. HAUCK: I think I said "was not important  
14 clinically," something like that, which is closer to your  
15 phrasing rather than it does not matter. It should be an  
16 equivalence phrasing rather than a no-effect statement.  
17 You could say "was not clinically important" or "had no  
18 material clinical effect," either of those.

19 DR. SINGH: I think, Walter, that when we put  
20 it in writing --

21 DR. ADAMS: Well, if we could just make that  
22 statement. To capture it now would be helpful. "Are not  
23 important clinically." Walter, was that what you said?

24 DR. HAUCK: That's all right with me.

25 DR. LEE: Wally, may I make a proposal?

1 DR. ADAMS: Please.

2 DR. ADAMS: Everyone is going home except  
3 Gloria and myself. Would it be possible to have these  
4 written and e-mailed to the subcommittee and give everybody  
5 a day to respond so that when we do have to report to the  
6 full committee on Thursday morning, that we have at least  
7 some sense for the degree of enthusiasm for the wording?

8 DR. ADAMS: I think that's an excellent idea.  
9 So, you're proposing that sometime by maybe tomorrow  
10 morning --

11 DR. LEE: Yes. Somebody get busy tonight and  
12 start writing.

13 DR. SINGH: Yes, I think we can handle that.

14 DR. MEYER: I would just make the point that as  
15 somebody who's contributed in virtual working groups by  
16 e-mail, the one problem with doing that is that if people  
17 do minor wordsmithing, you end up in a position where you  
18 don't have time to then go through with reiterations and so  
19 on. So, people would just need to confine their comments  
20 to important points and maybe really focus on the substance  
21 and not have specific wording recommendations, but the  
22 substance of what we would need to change back so we can  
23 integrate and come up with something that's satisfactory to  
24 all.

25 DR. LEE: The other alternative is to empower

1 me to speak on their behalf.

2 DR. HAUCK: I'm willing to empower you.

3 (Laughter.)

4 DR. HAUCK: Not that we could stop you anyway.

5 (Laughter.)

6 DR. LEE: Don't forget, English is not my

7 native language.

8 (Laughter.)

9 DR. LEE: Any other comments, questions?

10 I understand that some of you might be on  
11 vacation. For those of you on vacation, please do not feel  
12 compelled to respond, but in case you do, we obviously  
13 would welcome your input.

14 Anything else? Wally, do you have enough to  
15 move on to the next phase?

16 DR. ADAMS: What is that phase?

17 (Laughter.)

18 DR. LEE: You should know. To finish the  
19 guidance.

20 DR. ADAMS: I'd like to ask Ms. Winkle if she  
21 has any comments to add.

22 MS. WINKLE: No. I just want to thank  
23 everybody today for their participation in the discussion.  
24 I think it will be extremely useful in helping us in CDER  
25 to finalize this guidance and to be able to capture exactly

1 | what we need to ensure equivalence. So, I appreciate  
2 | everyone's attention to these issues and look forward to  
3 | coming out with a guidance soon that is able to directly  
4 | talk to these issues. Thank you.

5 | DR. ADAMS: Yes, I also would like to reflect  
6 | Helen's comments, that we're very appreciative to the  
7 | subcommittee for their willingness to come on short notice  
8 | I guess and participate in these deliberations. It moves  
9 | the draft guidance one step further along towards the  
10 | process. So, we're very appreciative of that and thank you  
11 | very much to each of you for your expertise in this matter.

12 | DR. LEE: Okay. Thank you very much. Is there  
13 | any further business?

14 | (No response.)

15 | DR. LEE: A move for adjournment?

16 | DR. DYKEWICZ: So moved.

17 | DR. LEE: So moved.

18 | Second?

19 | DR. HENDELES: Second.

20 | DR. LEE: Let's go. Thank you very much.

21 | (Whereupon, at 3:20 p.m., the subcommittee was  
22 | adjourned.)

23 |

24 |

25 |

7-17-2001

- 0 -

0-3 54:23 59:10 63:25  
0-6 62:2

- 1 -

1-week 58:23 60:13  
61:20 63:17  
10-20 67:7  
10-fold 65:18  
10.5 57:19  
100 95:19 120:8 122:5  
122:5  
10:30 68:17  
10 63:11 155:10 166:18  
110 119:15  
115 109:7  
11:58 126:5  
11 36:11 56:10 68:15  
109:17  
12-hour 59:4 60:16  
61:24 63:22  
125 91:15  
128 183:14  
12 56:11 59:6 60:12  
63:17  
12a-30 6:23  
14 58:20 62:24  
15 61:18 64:3 64:5  
64:12 64:13 64:20  
117:20 166:18  
16-fold 61:22 63:4  
165:17  
16 134:10 156:12  
18 6:17 61:19  
1990 36:10  
1992 61:19  
1993 36:15  
1995 36:22 69:6  
1996 37:8  
1999 11:19 38:3 38:11  
114:10 128:7 131:8  
19 50:25  
19th 14:17 14:17  
1:00 126:6  
1:10 127:2  
1:30 126:3

- 2 -

2-week 94:8 105:3  
113:12 140:11 155:20  
156:7 180:15 188:12  
2000 11:21 12:21 38:15  
38:20 106:2 106:5  
107:9 137:11  
200 61:3 122:5 122:6  
208(b) 6:17

20 64:12 86:14 93:19  
153:6  
20th 14:18  
21 62:15 63:9  
24-hour 44:17 44:18  
256 59:18 60:24 132:12  
183:14  
25 121:8 121:9 121:13  
26 38:15 137:11  
26th 12:21  
28 62:14 62:24  
2:45 174:15 174:18

- 3 -

3,000-square 119:3  
3,000 118:19  
30 57:24 57:25 62:17  
86:14 132:5  
32 59:18 63:15 132:13  
134:11 183:13  
350 117:20  
3:20 194:21

- 4 -

4-week 58:24  
400 60:25 61:3 61:4  
122:6  
40 121:10 125:7 132:5  
4:00 174:25 176:7

- 5 -

50 57:16 118:21 138:8

- 6 -

68 106:24

- 7 -

70 22:10

- 8 -

8-hour 122:10 123:17  
80 22:10 91:14  
85 109:6  
8:34 6:2

- 9 -

9.5 57:19  
90 91:16  
99 36:21 94:23 118:17

- A -

a.m 6:2 126:5  
AAPS 38:6 105:16  
ability 82:23 99:24  
absence 37:24  
absolutely 67:24  
178:17  
absorbed 20:17 20:23  
95:10 98:18 99:6  
academic 119:2  
accept 141:11 178:4  
acceptable 14:10 37:2  
102:21 130:5 134:4  
acceptance 107:25  
108:3  
accepted 96:19  
access 43:6 43:9 160:25  
174:3  
accompanying 37:22  
accomplish 71:18  
142:20  
accomplished 190:12  
accordance 6:17  
according 38:24 39:8  
93:5 138:7 150:21  
account 101:21  
accounts 100:3  
accumulation 101:19  
accuracy 39:7  
accurate 120:9 181:13  
achieve 18:13 18:15  
20:12 27:3 27:14 28:25  
44:6 160:2 162:14  
188:13  
achieves 27:11 27:12  
153:14  
acknowledge 49:24  
acoustic 75:8  
ACPS 181:11  
acquiring 159:25  
across 24:14 27:11  
Act 12:13 85:20 183:20  
acting 9:10 10:6 15:19  
26:13 39:11 50:11 51:5  
51:10 68:25 95:24  
112:10 113:25 116:5  
action 13:6 13:8 35:19  
37:20 43:5 43:16 48:5  
54:10 72:15 120:21  
128:9 129:10 136:4  
137:15 148:25 176:5  
187:23  
actions 116:15  
activated 96:25 97:4  
active 14:6 14:10 37:14  
40:3 42:3 45:23 47:15  
48:8 57:11 57:24 58:2  
60:7 62:19 73:4 86:12  
86:15 86:16 86:17 87:9  
87:15 115:5 115:11

129:25 130:5 130:13  
132:18 134:15 134:16  
135:15 141:18 141:19  
162:3 162:9 168:3  
176:14 183:23 188:16  
188:24 189:13 189:15  
actives 115:6  
activity 23:11 24:16  
24:17 25:10 27:5 27:9  
27:12 28:7 28:11 29:7  
35:3 46:20 79:25 96:4  
96:11 96:17 135:24  
acts 86:12 87:18  
actual 123:16  
actuators 44:5  
actuator 41:7 41:10  
41:12 41:13 41:23 42:4  
47:10 47:16 98:11  
129:8  
acute 136:22  
ad 11:5 11:6  
add 93:25 154:13  
178:18 184:23 185:22  
193:21  
added 159:8  
addition 42:24 97:24  
106:11 107:18 110:5  
110:22 190:14  
additional 18:6 18:24  
19:4 21:23 43:22 93:3  
106:15 110:4 113:23  
114:8 161:12 163:18  
163:21 172:9  
Additionally 7:11 46:15  
address 7:24 10:22  
11:23 12:3 14:24 15:4  
15:11 68:24 71:12 88:7  
100:14 106:2 115:20  
116:12 125:19 127:9  
133:16 172:19 174:19  
175:2  
addressed 12:8 12:21  
72:16 72:17 105:18  
125:19 169:5  
addresses 6:9  
addressing 12:10  
174:12  
adds 25:9  
adequate 37:15 114:25  
124:20  
adequately 28:23 30:4  
137:17 162:2  
adherence 99:18  
adherent 99:18  
adjourn 88:16 125:16  
125:25  
adjourned 194:22  
adjournment 100:7  
194:15  
adjustment 18:24  
administer 138:13  
administered 17:20  
administration 27:4  
50:2 80:10 115:11  
115:11 133:13  
ado 15:17

adrenal 44:16 46:23  
48:21 49:2 173:2 173:16  
advantage 28:15  
advantageous 11:22  
advantages 32:19  
108:19 119:17  
adverse 48:18 94:13  
94:19  
advice 12:10 69:8  
advisory 10:11 11:5  
11:24 12:12 12:14 12:17  
12:18 14:15 14:16 14:19  
14:21 36:16 36:17 38:19  
112:13 113:22  
aerodynamic 34:4  
aerosol 42:23 56:3  
60:9 61:5 64:9 82:16  
82:18 83:8  
aerosols 11:21 13:5  
13:13 13:15 14:7 14:12  
35:16 49:6 51:11 51:16  
51:20 51:24 51:25 52:4  
52:9 64:23 128:6 128:8  
130:2 130:7  
affect 37:18 43:4 43:15  
97:8 127:15 147:10  
191:7  
affected 146:16  
affects 162:19  
afternoon 104:17  
112:3 125:18 126:2  
171:3 181:25  
agency's 6:22  
agency 12:10 110:25  
111:18 112:14  
agenda 7:18 34:16  
88:13 105:12  
agents 53:15  
ages 56:11 58:22 60:12  
63:17  
agglomeration 161:5  
162:10  
aggregation 161:5  
agree 19:15 85:16  
86:18 87:22 102:16  
103:5 113:9 113:12  
139:9 153:13 156:15  
170:11 172:8 172:10  
177:4 177:25 179:3  
179:7 179:10 181:7  
182:12 183:12 184:16  
186:7  
agreed 12:16 190:15  
agreement 188:7  
agreements 7:12  
agrees 116:17  
AHRENS 9:13 9:13  
90:8 90:9 90:9 90:20  
91:3 91:7 91:11 91:19  
91:21 124:6 124:8  
124:22 142:10 142:11  
144:13 172:8 175:22  
179:6 184:6  
aim 98:19  
air 119:4  
airways 33:8 69:12

69:12  
Ajaz 50:4  
albuterol 109:25  
allergen 53:16 53:25  
73:21 74:8 82:5 120:19  
allergens 52:21 53:23  
119:5 120:6  
allergic 13:16 14:8  
14:12 51:11 51:17 52:11  
52:11 53:9 53:10 53:14  
56:11 58:22 60:12 63:16  
71:23 72:2 72:7 72:25  
74:23 113:17 121:3  
125:20 128:6 129:4  
129:17 130:2 130:7  
130:18 130:22 133:6  
142:4 143:24 144:3  
176:16  
allergist 120:15  
Allergy 8:24 9:4 9:15  
9:18 9:21 36:16 53:24  
74:20 83:20 86:9 114:9  
117:18 143:16 158:19.  
Allied 117:17  
allocation 124:13  
allow 7:3 24:8 24:10  
73:10 74:13  
allowed 164:24 176:4  
allowing 117:3  
allows 73:8 107:17  
alter 13:21 40:7 128:25  
alterations 164:19  
altering 97:18  
alternate 49:21  
alternative 110:4  
154:10 154:10 171:14  
177:5 177:7 192:25  
ambitious 38:16  
ambivalent 155:16  
American 105:25  
analogous 18:10  
analysis 109:15 109:24  
171:18  
analytical 40:24 137:17  
138:3  
analyze 119:22  
analyzed 106:23 106:24  
analyzing 123:10  
anatomy 69:11  
and/or 78:15 148:3  
ANDAS 39:20 39:22  
ANDERSON 9:11 9:11  
12:15 145:19 147:6  
147:20 148:6 148:12  
149:3 150:7 150:13  
150:17 151:11 175:21  
179:10 179:13  
angle 41:13 98:11  
Annals 114:9  
announcement 6:9  
answer 29:10 29:11  
29:16 33:24 71:13 71:16  
87:3 102:9 113:23  
130:23 131:15 145:19  
146:23 147:20 148:9  
154:7 154:24 156:6

175:8 183:13  
answered 13:25 39:14  
142:8 148:13 156:5  
answering 148:14  
149:23  
answers 29:4 167:5  
anticholinergics 35:19  
52:7  
anticipate 108:23  
108:25  
antihistamine 52:6  
antihistamines 35:20  
87:10  
anybody's 186:25  
Anybody 10:2 81:16  
anymore 62:25  
anyway 73:10 143:15  
165:2 167:9 193:4  
anywhere 119:9  
apologize 157:4  
apparent 187:15  
appearance 6:11 23:10  
23:10 96:5 96:10  
appears 24:16 58:8  
92:2 177:11  
applicant 40:24 49:9  
application 17:16  
applications 72:18  
187:7  
applied 82:5 116:8  
apply 44:10 99:8  
appreciate 124:19  
157:6  
appreciated 67:18  
appreciative 194:6  
194:10  
approach 39:15 78:6  
94:25 102:18 107:7  
107:8 107:9 137:7  
137:22 137:23 178:22  
approached 93:8  
approaches 50:10  
112:20 171:12 171:13  
approaching 137:21  
appropriate 39:10  
39:23 72:15 101:18  
109:8 109:11 110:3  
110:6 110:12 113:10  
113:13 114:21 115:8  
116:18 117:2 130:14  
133:19 140:6 151:19  
152:16 158:11 158:13  
162:9 188:13 189:20  
189:22 190:2 190:2  
appropriately 113:17  
approval 17:16 17:25  
39:23 52:14 55:11 72:8  
72:20 73:16 74:25  
approvals 19:2  
approve 16:16 18:3  
approved 61:10 75:2  
113:7 136:22 138:16  
approving 18:11  
approximately 57:16  
57:24 62:22  
April 12:21 36:22 38:15

106:5 107:9 137:11  
AQ 36:9  
aqueous 36:24 37:10  
37:20 52:2 60:9  
arbitrarily 46:4  
architect 34:17  
aren't 25:16 84:19  
166:3  
argue 58:12 69:23  
70:10 96:12  
argued 96:12  
argument 37:17 37:21  
37:24  
arm 11:5 102:11 102:12  
175:13 175:16 189:14  
arrive 15:14  
arrows 122:10  
article 120:25  
artificially 96:24  
artificial 53:21  
aside 68:15  
asking 80:2 80:8 80:17  
85:11 85:12 130:10  
132:14 132:24 135:6  
147:11 147:12 149:22  
157:13 170:15  
asks 43:23 44:2  
aspect 40:5 97:15  
168:6  
aspects 50:13 51:18  
89:25 161:20 162:8  
163:12 163:21 164:20  
assay 32:12 65:20  
118:9 136:18 183:4  
183:11  
assess 24:23 25:15  
65:11 77:10 82:23  
116:25 122:19 143:25  
149:16 150:5 151:5  
170:18  
assessed 71:25 72:5  
73:23 76:3 84:21 149:24  
assessing 28:24 72:7  
74:17 89:17 92:21 92:23  
113:11 116:19 161:6  
164:14  
assessment 65:7 73:9  
73:10 94:19 112:21  
122:13 122:14 140:11  
160:19 169:3  
assessments 75:7 92:19  
assist 132:24  
associate 9:19  
associated 182:6  
Associates 7:16 8:10  
Association 105:25  
assume 24:8 67:20  
95:13 96:15 96:21  
152:9 163:23 173:12  
assumed 89:13  
assuming 99:11 131:3  
148:14  
assumption 119:22  
120:13 146:8 146:24  
147:11 147:21 163:25  
171:18

**Assurance** 41:4 133:12  
165:3  
**assure** 13:18 19:9 37:16  
41:15 48:22 49:2 49:10  
49:14 49:16 90:13 91:5  
128:22 129:8 129:13  
136:6 148:18 159:20  
163:3  
**assures** 76:10 129:9  
135:8  
**assuring** 19:9 102:3  
167:13  
**asthma** 91:22 92:2  
99:16 114:9 117:19  
143:6 144:19 145:7  
145:10  
**Atlanta** 9:12  
**attach** 158:23  
**attempt** 150:12  
**attended** 38:7  
**attention** 34:13 65:23  
111:16 117:2 194:2  
**attribute** 42:6  
**attributes** 90:2 163:19  
**AUC** 44:9 100:16  
101:5 101:11 101:18  
102:22 123:12 148:17  
**authors** 114:15  
**automatically** 131:4  
**availability** 95:7 114:4  
116:25 162:20  
**average** 99:18 108:21  
122:15  
**averaged** 143:20  
**aware** 7:20 11:3 33:12  
40:6 75:10 82:10 92:6  
92:11 92:13 93:20  
**axis** 44:16 46:17 46:18  
46:23 48:21 49:2 84:2  
173:2 173:16 173:20  
**azelastine** 52:6  
**Azzam** 114:10

- B -

**b.i.d** 56:13 57:14 57:15  
58:5 58:6 58:8 58:9  
61:4 66:21  
**BA/BE** 8:21 34:17 36:21  
38:3 38:17 39:15 49:25  
88:8 106:3 106:12  
112:5 112:7 112:14  
112:25 113:14 113:23  
116:17 116:22  
**BA** 13:4 13:5 13:6 13:11  
14:25 38:9  
**back** 11:19 12:18 18:9  
24:23 36:8 36:10 42:6  
68:17 71:20 86:20 98:25  
106:18 106:19 119:12  
119:13 125:22 126:2  
139:5 139:15 156:17  
160:4 172:19 174:14  
174:18 189:12 192:22

**background** 11:2 15:13  
35:7 75:21 76:11 76:21  
81:7 81:14 88:6 88:11  
127:8  
**backgrounds** 11:12  
**backward** 96:14  
**Badrul** 9:2 165:24  
**balance** 109:6 109:11  
109:13  
**bar** 58:4 60:23 64:6  
157:5  
**bars** 57:7  
**baseline** 53:2 53:6  
57:5 57:23 58:23 58:23  
59:13 59:15 59:17 60:13  
61:7 61:20 62:12 63:17  
64:2 73:3 73:6 123:11  
**baselines** 57:21 59:15  
**bases** 28:23  
**basically** 11:5 11:10  
11:13 11:14 11:16 12:2  
13:13 13:24 14:23 59:20  
69:3 88:17 94:16 94:18  
186:9  
**batch** 107:23 108:6  
163:4 163:4  
**batches** 157:21 157:22  
**battery** 110:11  
**BDP** 115:2 115:3  
**beclomethasone** 66:5  
114:12 138:20  
**becomes** 18:19 23:19  
154:21  
**becoming** 178:25  
**Beconase** 36:9  
**begin** 161:2  
**behalf** 105:22  
**behave** 133:13  
**behaved** 29:21  
**belabor** 66:25 148:8  
150:24  
**beliefs** 24:2  
**believes** 116:22  
**below-labeling** 134:9  
**below** 45:24  
**benefit** 132:19  
**benign** 99:13 99:22  
**between-patient**  
142:23  
**between-unit** 108:15  
**bias** 115:13  
**big** 51:23 141:2 144:4  
**bigger** 139:15  
**biggest** 141:15 144:5  
**binary** 183:13 183:21  
**bioassay** 7:13  
  
**bioavailability/bioequivalence**  
35:10  
**bioavailability** 20:7  
20:9 20:14 21:11 25:5  
79:4 79:20 83:25 84:6  
96:23 100:2 100:13  
102:2 104:7 128:7  
136:25 138:6 138:7  
138:17 138:24 149:20

150:6 151:6 151:8  
151:22 172:3 182:20  
**bioequivalency** 109:20  
**bioequivalent** 19:3  
19:6 19:25 39:21 152:2  
152:10 153:2 153:4  
171:18 176:19 178:22  
**biopharmaceutics** 8:16  
**biopsies** 94:17  
**biostatistical** 7:10  
**biostatistics** 8:14  
**bit** 20:11 20:12 71:9  
141:4 167:11 172:20  
176:6  
**black** 32:14  
**block** 98:6 100:19  
100:23 102:2 102:9  
102:13 137:23 138:22  
138:23 139:2 139:3  
**blockade** 97:4  
**blockage** 72:13  
**blocked** 97:9  
**blocking** 97:7  
**blocks** 97:17 100:23  
**blood** 23:10 24:15  
24:15 24:24 24:24 25:5  
25:17 27:10 28:9 28:10  
28:15 28:22 29:2 29:11  
29:20 32:10 32:19 32:22  
32:25 83:17 83:19 89:3  
89:14 95:13 95:20 95:21  
96:3 96:3 96:5 100:14  
100:24 102:17 102:24  
104:3 151:24 153:5  
169:20 169:22  
**bloodstream** 28:6  
**blowups** 26:4  
**blue** 32:14 57:10  
**blunt** 141:16  
**Bob's** 95:4  
**Bob** 8:23  
**body** 20:18 22:24 27:16  
155:11  
**bolus** 187:22  
**books** 30:3  
**bottom** 57:7 61:6 64:22  
**boxes** 23:23  
**brand-name** 89:6  
**brand** 23:21 41:5  
171:23 171:24 176:23  
**break** 68:16 88:3 95:25  
172:18  
**briefly** 51:15 109:20  
120:25 121:21 121:24  
122:9 142:14  
**brilliant** 168:7  
**bringing** 75:14 77:14  
78:25  
**brings** 42:20 82:17  
115:13 143:17  
**Bristol-myers** 7:8  
**broadly** 76:10  
**Brown** 9:12  
**budesonide** 132:13  
134:12  
**Building** 6:24 151:9

**bulk** 43:6  
**bullet** 39:2 39:3 39:4  
39:5 44:4 71:12 188:9  
**bullets** 39:16 181:14  
189:8  
**bump** 143:13  
**bunch** 142:23  
**burning** 50:22  
**bury** 92:3  
**business** 194:13  
**busy** 192:11  
**button** 34:23  
**buy** 184:25

- C -

**calculate** 123:12  
**Callaway** 9:11  
**calling** 58:14 171:9  
**Canadian** 60:11  
**capabilities** 107:14  
**Capacity** 119:15  
**capture** 185:9 190:13  
191:22 193:25  
**captured** 147:18 191:10  
**career** 145:8  
**careful** 80:9  
**carefully** 150:12  
**carries** 24:15 28:10  
**carryover** 122:24  
124:15 124:21  
**Casale** 114:10  
**category** 22:11  
**caused** 48:12  
**caveat** 177:18 182:13  
**CDER** 8:21 8:25 12:6  
36:22 193:24  
**cells** 55:7  
**cellulose** 82:23  
**center** 42:21 50:2 60:11  
**centering** 35:15  
**centers** 56:10 58:20  
61:19 63:15  
**cetera** 100:16 121:18  
121:22 136:19 175:7  
**CFR** 38:24 39:6  
**chain** 167:11  
**chair** 6:4 9:10 12:16  
**challenge** 43:12 81:23  
81:25 82:3 137:16  
138:4 144:25 145:4  
**challenges** 45:18  
**challenging** 70:9  
**chamber** 41:12 73:22  
73:25 117:12 117:23  
118:25 119:2 119:4  
121:2 121:15 122:2  
122:10 122:11  
**CHAMBERLIN** 6:8 9:8  
9:8  
**chances** 64:18  
**changed** 18:8 38:13  
**characteristic** 33:22  
71:7 163:3

**characteristics** 20:15  
20:22 21:11 23:12 24:24  
27:15 30:14 42:10 69:13  
79:23 80:18 102:5  
186:11  
**characterization** 80:17  
**characterize** 26:4 87:23  
137:17 160:15 160:22  
163:8 168:5  
**characterized** 93:23  
**charcoal** 96:25 97:4  
97:12 97:17 97:20 98:6  
100:19 100:23 100:25  
102:2 102:8 102:12  
137:23 138:22 138:23  
139:2 139:2  
**charge** 88:5  
**chase** 16:3  
**chemical** 20:10 51:21  
**chemist** 145:21  
**Chemistry** 9:12  
**chemokines** 55:7  
**chi-square** 109:22  
110:5  
**chlorpheniramine**  
57:12 86:24 87:9  
**choose** 71:14 134:8  
156:8 156:11 158:7  
**chosen** 24:21 121:10  
179:24  
**CHOWDHURY** 9:2 9:2  
10:24 14:20 34:15 35:13  
43:25 51:3 51:6 66:7  
67:11 67:24 68:13 70:8  
70:11 72:10 72:23 73:19  
77:2 77:17 86:20 86:22  
87:8 104:18 104:23  
130:23 165:12 165:19  
182:18 182:22 182:23  
**Cindy** 105:21 111:21  
**circumstance** 172:12  
**circumstances** 130:14  
136:17 137:3 184:6  
**claim** 37:23 108:5  
109:7 109:9  
**clarify** 71:17 88:14  
160:6  
**clarity** 100:9 172:23  
**class** 6:16 103:24  
**classic** 61:12  
**classical** 175:8  
**classically** 54:7  
**clear** 51:19 56:16 78:5  
91:23 93:13 96:14  
110:23 143:21 151:10  
159:16 172:18 190:20  
**clearance** 97:13  
**clinic** 120:15 123:6  
144:10  
**clinically** 72:6 75:9  
78:15 79:15 140:23  
180:3 180:8 190:25  
191:4 191:5 191:7  
191:14 191:17 191:23  
**clinician** 94:16 94:18  
139:22

**clinicians** 16:20 88:10  
140:7 143:2 143:5  
**closer** 98:15 191:14  
**clump** 161:2  
**Cmax/auc** 152:3  
**Cmax** 44:10 100:16  
101:5 101:11 101:17  
102:20 148:17  
**CMC** 12:24 38:8 38:16  
41:21 50:14 105:18  
106:2 106:10 106:20  
110:8 111:17  
**co-founder** 7:15  
**cognizant** 70:7 93:12  
164:18 165:2  
**cohort** 74:8  
**Collaboration** 105:23  
106:2 106:22  
**colleague** 103:23  
106:11  
**colleagues** 92:12  
137:5 160:17  
**collected** 106:22 109:15  
**College** 9:12 9:17  
**color** 57:10  
**combination** 148:4  
148:20  
**combine** 102:10  
**comfort** 98:12  
**comfortable** 72:5  
136:12 140:15 145:14  
176:12 179:23 180:15  
186:22 187:4 191:8  
**comment** 46:15 78:22  
79:2 97:22 102:16  
103:9 124:6 132:10  
133:23 146:22 147:7  
147:13 159:7 161:13  
161:14 162:24 165:12  
166:16 172:9 176:17  
179:6 182:14 182:25  
184:9 189:19  
**comments** 7:4 78:10  
139:13 139:14 181:6  
182:10 184:8 186:14  
192:19 193:9 193:21  
194:6  
**committee's** 182:10  
**committee** 6:14 6:18  
10:12 11:6 11:24 12:13  
12:14 12:17 12:18 14:15  
14:16 14:19 14:21 36:16  
36:17 38:2 38:4 38:19  
50:3 88:13 106:17  
112:13 113:22 117:4  
123:22 126:5 129:22  
129:23 130:3 131:10  
131:11 133:16 153:18  
171:6 175:11 179:16  
181:14 184:5 185:9  
186:15 186:21 188:3  
188:8 188:21 190:9  
192:6  
**committees** 16:6 20:3  
**companies** 7:11 54:13  
**Company** 7:6 8:17

83:15 163:6 164:16  
164:25  
**comparability** 44:22  
80:22 113:19 115:21  
128:17 149:16 178:11  
178:12  
**comparable** 39:20  
41:14 44:23 45:4 45:5  
57:18 59:15 76:20 79:22  
79:24 98:2 137:10  
148:17  
**comparative** 20:25  
21:5 21:5 21:20 22:19  
31:5 39:3 39:4 42:11  
48:17 58:17 73:2 149:25  
189:12  
**comparator** 164:25  
**compare** 77:12 114:16  
114:18 114:22 123:17  
158:23 158:24 168:10  
186:18 186:19  
**compared** 25:7 56:3  
107:19 108:22 109:22  
132:25 157:14 188:16  
**comparing** 92:20  
110:6 151:22 164:15  
173:5  
**comparison** 22:16  
81:3 85:4 87:9 90:16  
102:24 141:12 158:22  
169:19 185:15 186:24  
**comparisons** 75:23  
76:4 76:19 85:10 90:12  
114:2 145:9  
**compartment** 96:15  
96:16  
**compelled** 193:12  
**compendial** 38:8  
**completed** 105:4  
106:10  
**complex** 57:4 69:11  
92:14  
**compliance** 109:16  
118:11 120:8  
**complicated** 12:5 12:7  
28:13 144:24  
**complication** 162:8  
162:13  
**comply** 106:25  
**component** 72:12 93:7  
110:25 116:24 166:23  
**composite** 59:24  
**composition** 40:22  
**compound** 95:10  
**comprehensive** 84:22  
88:9  
**conceivable** 90:2  
**concentrate** 85:16  
**concentrating** 166:19  
**concentration-time**  
101:4  
**concentration** 28:10  
29:2 29:20 32:18 32:20  
32:22 40:20 40:25 86:16  
95:13 98:3 164:19  
165:18

**concentrations** 28:16  
40:23 44:6 164:11  
166:5  
**concepts** 107:10  
**concern** 69:19 77:23  
79:9 79:15 83:6 110:19  
145:21 146:4 146:6  
146:11 146:23 147:22  
148:7 155:5 178:24  
**concerning** 106:6  
110:15  
**concerns** 46:21 100:15  
103:12 106:5 124:9  
132:20 133:20 151:18  
**conclude** 184:22  
**concludes** 10:4  
**concluding** 174:24  
**conclusion** 81:18  
116:17 182:9  
**conclusions** 109:14  
181:22  
**condition** 133:5 162:11  
**conduct** 30:5 47:5  
129:4 129:17  
**conducted** 14:5 14:9  
56:9 56:10 129:15  
129:24 130:4 130:13  
131:14  
**confidence** 91:17 98:12  
140:8 175:4  
**confident** 111:17  
**confine** 192:19  
**confirm** 14:6 14:10  
75:17 100:2 129:5  
129:18 129:25 130:5  
146:5 168:15 171:25  
176:15 177:15 178:8  
178:10 178:22 184:20  
187:12 187:15 187:18  
191:3  
**confirmation** 103:19  
186:9  
**confirmatory** 75:25  
76:9 76:14 78:8 80:24  
83:16 89:4 89:9 89:13  
103:6 169:2 169:12  
169:17 170:4 170:11  
171:6 171:16 172:8  
172:10 172:13 172:15  
173:17 173:22 177:17  
177:22 179:25 180:4  
184:10 185:7 189:7  
190:8 190:13  
**confirming** 115:18  
178:12 180:3 186:13  
**confirms** 175:17 186:4  
**conflict** 6:10  
**confound** 165:9  
**confounded** 124:12  
**confuse** 115:21  
**confused** 16:8 16:20  
17:12 20:6  
**confusing** 113:18  
**congestion** 55:3 59:9  
60:3 60:20 63:24 72:12  
121:22 123:16

**connection** 18:6 113:24  
**Conner's** 80:6  
**CONNER** 9:5 9:5 15:18  
 15:20 33:9 35:6 39:10  
 65:15 80:9 89:2 95:2  
 97:4 98:14 99:10 148:22  
 151:21 166:17 168:7  
 179:19  
**consciously** 123:8  
**consensus** 15:16  
 125:24 127:6 131:6  
 172:15 172:20 176:8  
 188:6 188:6 189:21  
**consequently** 43:18  
 47:19  
**considerably** 31:6  
**consideration** 107:14  
 159:4  
**considerations** 15:19  
**considering** 134:7  
**consist** 44:24  
**consistent** 45:25 62:24  
 108:8  
**consistently** 45:17  
 99:21 119:9  
**consisting** 69:15  
**constant** 121:15  
**constructed** 78:20  
**construction** 116:13  
**constructively** 112:8  
**consulting** 7:11  
**consumer** 107:19  
**contain** 96:13 110:21  
**contained** 106:3 106:6  
 106:16 107:12 110:9  
**container** 41:18  
**containing** 17:4 17:9  
**contains** 42:25 110:15  
**contemplating** 79:16  
 93:6  
**contended** 37:15  
**content** 7:13 41:17  
 41:19 41:20 42:2 106:22  
 106:23 107:5  
**contention** 79:6  
**context** 116:5 125:19  
 182:15 184:23  
**continue** 127:4  
**continues** 114:2  
**contracted** 7:9  
**contrast** 110:12  
**contributed** 192:15  
**contribution** 157:9  
 157:15  
**control** 23:5 23:9 26:21  
 26:23 57:12 163:14  
 183:10  
**controlled** 71:8 109:10  
 129:24 146:3 146:4  
 162:2 163:13 164:6  
**controlling** 121:17  
**controls** 53:3  
**controversial** 19:2  
**conveniently** 28:20  
**conveyed** 73:19  
**convinced** 97:6

**convincing** 32:7 168:9  
**convincingly** 69:24  
**copy** 6:21  
**correct** 67:11 67:12  
 67:24 86:21 91:13  
 115:19 127:10 127:17  
 127:18 135:17 146:14  
 150:15 159:15 160:12  
 165:19 185:20 189:24  
**correctly** 28:25 92:23  
 95:8 116:14 149:12  
 165:23 189:2  
**correlates** 116:15  
**correlation** 110:24  
**correlative** 156:25  
**corticosteroid** 183:19  
**corticosteroids** 35:19  
 35:22 44:15 46:23 48:24  
**cortisol** 44:18 44:18  
**count** 66:2 66:7 66:9  
 119:9 119:13 119:24  
 121:15  
**counterparts** 89:7  
**country** 61:10  
**counts** 66:9 66:11  
 66:12 68:4 74:12 118:6  
 118:16 118:16 118:18  
 118:23  
**couple** 23:23 50:21  
 90:9 101:3 117:24  
 123:14 136:5 141:17  
 181:22  
**course** 13:3 43:9 44:7  
 66:8 67:21 77:11 94:21  
 98:13 101:18 108:18  
 137:14 143:15 147:14  
 162:7 163:17 163:20  
 163:23 166:8 170:21  
**cover** 54:16  
**covering** 28:23  
**covers** 35:18  
**coworkers** 114:11  
**create** 29:8 96:7 162:10  
**created** 144:22  
**criteria** 41:25 44:10  
 90:18 91:11 91:14  
 103:2 107:25 108:3  
 109:11 135:23 137:2  
 157:22  
**criterion** 47:24 47:25  
 91:16  
**critical** 17:12 19:19  
 19:21 20:5 22:15 26:20  
 30:6 30:9 41:11 106:20  
 110:24 111:16 127:23  
**critically** 71:14 77:14  
 80:19 85:7 158:2  
**critique** 115:16  
**CRO** 8:9 117:17  
**cromolyn** 52:7  
**cromones** 35:20  
**cross** 27:8  
**crosses** 74:15  
**crossover** 54:3 92:5  
 92:8 144:24 145:11  
**crucial** 45:9

**crux** 188:2  
**cubic** 118:19 118:21  
**cumulative** 121:7  
**current** 7:24 55:7 96:21  
 107:12 107:19 108:16  
 108:22 109:5 109:21  
 110:10 110:20 112:17  
 142:19 155:6 182:7  
**currently** 12:24 93:6  
 109:2 113:7  
**curve** 26:2 26:2 29:23  
 30:6 31:12 31:14 31:17  
 46:9 46:10 46:20 46:21  
 46:25 48:11 48:14 49:18  
 59:7 59:21 65:15 67:2  
 67:2 67:19 89:14 101:5  
 102:24 130:20 134:18  
 134:20 134:22 135:5  
 135:13 135:20 138:9  
 138:11 140:18 142:24  
 151:24 153:6 155:10  
**curves** 46:19 80:25  
 98:3 101:11 154:12  
 154:14 154:16  
**CV** 122:8  
**Cynthia** 105:17  
**cytokines** 55:6

- D -

**daily** 46:2 46:8 94:13  
 122:20 135:19  
**Dale's** 46:12  
**Dale** 9:5 34:9 34:12  
 39:25 43:14 46:3 91:13  
 94:22 97:3 97:24 138:5  
 166:16  
**dare** 173:6  
**database** 106:23 109:15  
 109:18 110:13  
**date** 38:20 75:2 76:22  
 97:10 106:10  
**daunting** 77:24  
**Day's** 122:19 125:7  
**day-in-the-park-type**  
 78:2  
**day-in-the-park** 52:16  
 53:13 55:23 56:7 72:19  
 118:22  
**day-in-the** 66:10 74:7  
**day-in** 65:2  
**dead** 34:21  
**dealing** 13:10 32:5  
 42:19 99:12 137:14  
 137:20 161:19 161:21  
 176:18  
**dealt** 30:17 50:6 92:17  
 116:10  
**deaths** 99:15  
**December** 37:7  
**decide** 155:17 189:14  
**decided** 11:21 107:4  
**decides** 175:11  
**decision** 155:4

**decisions** 12:4 15:5  
**default** 91:14  
**define** 67:4 79:23  
**defined** 22:3 90:15  
 107:22 170:6 173:8  
**definition** 16:12 17:18  
 17:22 17:24 18:22  
 110:23 170:7 179:20  
**definitions** 16:10 21:23  
**deflect** 174:8  
**degree** 118:9 119:25  
 120:16 122:25 131:18  
 132:8 161:8 192:7  
**deleted** 186:17  
**deliberation** 127:4  
**deliberations** 131:10  
 194:8  
**deliver** 44:7 46:5 85:21  
 98:9 119:9 135:14  
 178:13  
**delivered** 25:2 32:16  
 39:11 80:19 98:4 104:25  
 108:4 160:11  
**delivering** 41:23 42:3  
 47:2 47:9 47:10 86:12  
**delivers** 46:5 135:15  
**delivery** 13:12 13:21  
 14:6 14:11 14:25 18:20  
 30:20 35:11 36:4 37:5  
 43:24 45:3 45:4 45:9  
 45:10 45:14 48:13 49:10  
 49:14 86:7 113:12  
 129:5 129:18 130:6  
 133:7 133:7 146:5  
 146:13 148:19 162:20  
 163:4 163:8 176:15  
 178:8 178:13 178:23  
 178:25  
**demonstrate** 48:3  
 85:13 182:15  
**demonstrated** 140:9  
**demonstrates** 70:2  
**demonstrating** 140:4  
 143:21  
**demonstration** 114:11  
 182:5 182:7  
**Dennis** 9:16 94:7  
 179:2  
**depend** 146:23 162:10  
 162:12  
**dependence** 113:20  
 118:13  
**dependent** 71:15  
**depending** 11:8 54:20  
 82:3 98:10 98:11 118:6  
**depends** 23:2 33:11  
 75:22 100:20 148:9  
 158:10 162:22  
**deposit** 42:16 98:20  
**deposited** 42:13  
**deposition** 34:9 83:2  
**descending** 39:6  
**describe** 20:21 26:10  
 46:16  
**descriptive** 20:15 20:24  
**designing** 118:25

121:25  
**designs** 41:10 43:25  
71:5 71:6 72:18 77:6  
77:20 85:22 112:25  
**desirable** 24:18 29:8  
**desire** 47:6  
**desired** 146:14  
**detail** 23:25 90:21  
149:4  
**details** 71:9  
**detect** 82:20 115:9  
178:14  
**detected** 78:16 115:4  
183:3  
**determination** 182:19  
183:2 183:6  
**determine** 13:14 20:9  
28:17 33:14 40:25  
110:5 117:13 122:3  
127:14 156:10 156:17  
169:23 170:3 182:20  
**determines** 26:3  
**determining** 42:21  
43:11 151:20  
**develop** 15:16 33:19  
107:4 113:15 115:22  
125:23 137:16 158:21  
**developing** 12:22 13:3  
26:18 176:8  
**deviation** 108:2  
**device** 41:4 41:9 44:21  
49:7 80:18 82:14 128:11  
128:16 150:18 160:12  
**devices** 49:8 63:20  
153:25  
**devoted** 15:13  
**diameter** 34:4 41:12  
132:3  
**diaries** 94:13  
**diary** 120:9  
**Dick** 90:9  
**diesel** 119:5 120:7  
**differ** 13:19 45:21 47:14  
47:20 80:13 132:8  
132:11 154:3  
**differences** 25:4 43:14  
48:6 48:9 48:12 76:11  
77:3 77:10 78:16 78:17  
79:8 82:10 84:14 86:3  
89:5 89:21 89:24 101:13  
101:15 102:25 114:24  
115:4 118:18 119:19  
128:24 129:2 132:20  
132:22 136:3 143:19  
147:16 152:16 156:17  
166:6 172:3 180:3  
180:11 191:3  
**differentiate** 115:6  
115:7  
**differently** 98:9 98:22  
133:14  
**differing** 72:17 165:14  
**difficulties** 26:5 51:4  
79:11 149:18 161:6  
164:14 182:5  
**difficulty** 25:12 51:14

144:22 185:5  
**dilemma** 139:16  
**dimensions** 41:11  
**dipped** 82:5  
**dipropionate** 138:21  
**director** 7:15 8:9 8:23  
9:5 9:20 10:6 117:17  
**disagree** 102:17 139:9  
177:4 177:5 187:5  
**disclose** 7:5 7:7 7:14  
**discomfort** 168:19  
180:16  
**discriminate** 76:25  
**discriminating** 76:18  
89:24  
**discuss** 11:9 11:19  
29:19 106:21 107:2  
108:25 109:4 109:20  
110:8 110:18 117:22  
123:6 173:9 174:11  
**discussed** 6:13 50:7  
80:2 112:23 118:2  
121:20 139:25 162:21  
162:23 163:12 181:24  
**discussing** 8:22 22:7  
30:16 33:12 66:25 74:22  
87:20 90:22 163:3  
182:3  
**discussion** 15:22 25:22  
35:15 52:10 68:15 88:13  
125:5 152:6 157:5  
166:18 193:23  
**discussions** 6:20 7:17  
20:4 164:22 184:2  
**Disease** 9:15 19:5 71:23  
71:24 72:4 99:12 99:22  
136:20  
**disparity** 131:19  
**display** 22:15 25:25  
30:4  
**displaying** 22:8  
**disposition** 97:8  
**disruption** 72:2  
**dissolution** 37:19 43:15  
136:23  
**distant** 28:10  
**distantly** 16:9  
**distinction** 147:23  
**distinguish** 99:24  
114:25 132:12 141:19  
152:15  
**distinguished** 117:4  
**distinguishing** 47:21  
176:24  
**Ditto** 172:14  
**Division** 8:24 9:3 9:6  
9:14 10:24 18:19 69:7  
69:7 70:15 71:6 74:20  
95:4  
**divisional** 74:19  
**doable** 173:7  
**docket** 78:22  
**document** 43:23 45:20  
94:25  
**domain** 55:17  
**dosage** 17:8 17:8 18:14

20:2 22:11 22:12 22:16  
22:17 22:19 22:21 22:23  
23:2 23:8 23:18 23:19  
25:4 26:23 27:16 29:18  
80:11 89:2 113:7 133:12  
**dose-ranging** 54:13  
58:16 58:18 63:13  
113:5  
**dose-response** 26:2  
29:23 29:23 31:14 31:17  
45:15 45:18 46:9 46:10  
46:17 64:24 65:15 66:3  
67:19 80:25 91:24 92:3  
113:24 121:25 134:18  
134:20 134:22 135:5  
135:20 140:18 142:16  
142:22 142:24 143:3  
143:9 144:15 144:21  
145:9 154:12 154:14  
154:16 156:18 165:13  
**doses** 45:21 45:21  
45:23 47:3 58:12 59:2  
59:18 60:5 63:6 85:21  
86:3 107:23 113:4  
113:6 114:16 115:3  
122:17 123:3 124:10  
124:23 143:24 152:7  
154:23 156:12 156:17  
157:2 164:23 169:8  
183:7  
**dosing** 46:8 60:16  
61:4 61:21 63:19 72:15  
131:3 138:18 138:18  
139:2 141:3  
**double-blind** 60:13  
63:18  
**DPI** 108:10  
**DPIS** 13:7 34:8  
**draft** 13:2 13:2 13:3  
13:11 34:17 36:21 38:3  
49:25 74:23 77:21 78:10  
79:10 80:2 80:8 83:23  
88:8 93:5 93:12 106:3  
106:6 107:13 107:20  
108:16 109:3 110:9  
112:25 113:14 115:20  
120:11 121:25 128:7  
129:3 129:16 194:9  
**drafted** 122:22  
**drafting** 8:21 8:25  
**dramatically** 99:20  
**draw** 26:12 81:18  
**drawbacks** 119:21  
120:12  
**drawn** 29:25 31:14  
**droplet** 37:12 42:5  
42:11 42:14 47:12  
160:10 160:16 160:21  
162:5  
**droplets** 82:19 132:4  
**Drs** 34:14  
**Drugs** 9:4 9:7 11:8  
13:21 15:19 16:16 17:17  
24:6 24:11 24:25 30:14  
31:25 35:18 35:21 36:15  
36:16 37:3 39:11 48:23

51:10 52:14 55:13 58:2  
61:10 61:13 65:7 65:14  
65:18 67:16 75:3 92:20  
96:23 97:12 103:13  
103:17 103:21 104:25  
105:6 112:23 132:4  
137:14 139:17 141:24  
145:10 189:13  
**duration** 53:4 53:8  
55:25 58:20 74:18  
113:12 175:7  
**dust** 144:4  
**DYKEWICZ** 9:19 9:19  
92:18 92:18 103:9  
103:11 103:11 103:23  
139:14 140:15 143:11  
172:13 178:20 189:19  
190:3 194:16

- E -

**e-mail** 192:16  
**e-mailed** 192:4  
**easier** 43:7  
**easiest** 167:3  
**easily** 24:25 70:18  
82:11  
**EEC** 123:17  
**EEU** 14:9 52:17 53:21  
53:24 54:6 54:7 54:8  
66:13 72:19 73:14 75:3  
78:2 81:11 85:17 92:13  
155:20 175:4 175:7  
**effectively** 25:14 29:22  
167:14  
**effectiveness** 13:23  
67:6 129:2 139:20  
139:24  
**efficacious** 58:9 135:25  
**efficacy** 18:17 28:12  
28:18 39:12 40:8 40:15  
43:17 43:20 46:19 46:25  
48:4 53:7 56:17 57:25  
59:4 59:7 60:16 61:24  
62:4 63:22 65:7 69:22  
72:22 73:9 74:13 76:20  
86:2 92:19 92:21 93:22  
99:10 103:19 112:21  
120:22 135:2 135:8  
135:12 136:11 140:5  
140:17 152:4 157:2  
157:9 157:17 157:25  
173:8 173:13  
**efficiency** 107:17  
**efficient** 19:8  
**eight-fold** 59:19 63:20  
64:20 77:2  
**elaborate** 94:18 138:19  
162:17  
**elaborating** 73:11  
**electronic** 34:22  
**elegant** 139:24  
**element** 116:20  
**eliminate** 33:20