things that you could do with this. You could maybe normalize and go back to one of the f2 or the chi square type statistics because you have weighted the distribution appropriately to the important end.

Or, the approach that I actually took, certainly from a radiolabel perspective, was just to do a sum of all of the weighted fractions to get what I have called a theoretical deposition factor. I call it this simply because these weights are based on what might get into the lung. This is the amount of material in each fraction and the sum gives you some measure.

I admit it is not a perfect measure. It absolutely won't marry what happens in a patient but it is some measure of quality in terms of that fraction of the distribution that gets into the airways.

[Slide.]

Can you apply this sort of approach to real data. I have to thank Bo Olsson and Mike Rebe for allowing me to use the data that the European group generated on MDIs a few years ago. What I have done here is calculated this theoretical deposition fraction, looked at the SDs, both for a set of MLI data across five different labs and across the Anderson across five different labs.

Basically, they all come out reasonable similar. I have not completed the statistics on here but within these

standard deviations, these are all the same. There was one odd one. It is interesting that the consortium, or the group, themselves, noted that this dataset was odd.

You will notice the theoretical deposition factor is low. The reason is, when you look on the raw data, there is missing material down on this bottom stage that is on this top stage. I only put that in to try and demonstrate that this number appears to be sensitive to what is happened to the distribution.

[Slide.]

I am going to skip through this one pretty quickly. This is where, I guess, this investigation started, trying to look at matches between radiolabel and drug. I would emphasize, however, that the process is just as valid to look at the match between two size distributions.

Finally, where does that leave you? It is an alternative approach. The advantage I see is you have got flexibility. That is also the major disadvantage. In order to apply weightings to the distributions, rather than going back and doing an f2 or a chi square or the distance statistic, everybody has to agree on what weighting factors would be appropriate.

I think that would probably be a tough job. If you got a group of people in this room together and try to

agree on these, it would probably take some while. But it is flexible and you can actually apply to it to different products. For example, systemic; you would want to look at what was deposited maybe in the peripheral lung. Local drugs; maybe the whole lung. Or maybe a combination of the two.

You can apply some simple statistics to the number afterwards. You don't have to go through a huge sum of the squares of the distances between the distribution. I believe it has physical relevance in that it notices the difference between an 8-micron and a 1-micron aerosol which the f2 and the chi square statistics, as proposed, don't.

Disadvantages; choosing the weighting factors. Quite how you deal with distribution pattern, as proposed. If you only use one set of weighting numbers, you can either get some number that is proportional to lung or some that is proportional to alveolar, but you don't get both.

The other disadvantage, which I guess Dr. Ahrens and I have been talking about, and it is actually not a primary measure. You are taking a raw dataset and you are imposing some weighting factors on top of it.

I guess, work in progress. I don't quite know where to go from here in terms of whether this theoretical deposition fraction is a good approach or whether, having weighted the distribution, you could then go back and take a

look at the standard sort of distance-type statistics and see if you could apply those a little bit better with a bit more sensitivity to what is important about the change in size distribution from one end to the other.

That's it. Thanks.

DR. LEE: If you could stay for a minute. I wonder what is your bottom line about the proposed chi square approach.

DR. CLARK: If what you are trying to do is compare experimental variability, I think it is a very valid approach. If what you are trying to do is look at a innovator product versus a generic, it doesn't have the sensitivities in the right places to judge the differences between those two parts appropriately.

I am sure Dr. Tsong and I will argue about it for a while.

DR. LEE: Thank you.

Before I invite the next speaker up to the platform, I would like to remind the committee members that there are a number of questions that we need to address. There are quite a few of them and we need to move quite quickly.

So, to continue with this British theme, I would like to have David Ganderton to come and talk to us about his views about DPIs, in vitro test performance and

comparability.

DPIs: In Vitro Tests for Performance and Comparability

DR. GANDERTON: Thank you very much, Mr. Chairman, for the introduction. I hope, by now, the audience is getting used to the accent. I would have a particular note of thanks to Wally Adams. I think we have argued long and hard over a number of years, very constructively, and, of course, it was his agency which brought me here.

[Slide.]

I think, in arguing the case for the in vitro evaluation of dry-powder inhalers--I am going to ask your indulgence. If you really go quite back to the beginning, of course, in Europe, and I am speaking first, personally, and second, with a European perspective. You will have to distill out of this what is relevant to the system, as you see it.

But, in Europe, I think in all submissions, we would see a big pharmacodynamic component and a big in vitro deposition component. Some submissions would have pharmacokinetics and some may have in vivo deposition, that is particularly using gamma scintigraphy.

It is important, I think, to remember that all these contributions are flawed in one way or another. I think the pharmacodynamics element, of course, is accurate but it is very imprecise and, of course, the reverse is true

of in vitro dependence.

Pharmacokinetics is often not applicable and, if we are going to do gamma scintigraphy, of course, we have got to modify the formula. So, I want to certainly make the case that, in any overall assessment, you have really got to synthesize contributions perhaps from all these elements. Of course, the way in which that synthesis is carried out will depend upon the relative strengths of each one.

Of course, this will vary very much from case to case. I am going to argue strongly for the value of in vitro deposition because--well, he would, wouldn't he? It is an area which I have been attempting to promote for a number of years.

[Slide.]

In an absolutely super review, Pauwels said that, "The quantity of a drug deposited in the airways is the primarily determinant of the local airways response to the drug." I would like to extend that a little bit and say, "The quantity of drug deposited," and I would add, "depends upon the concentration of the drug in the cloud, the particle size distribution in the cloud and the actual inspiratory maneuver by the patient."

I think all these things can be properly modeled and I think, if we do this carefully and well, we will get a very useful in vitro surrogate.

[Slide.]

It is going to be based upon inertial behavior because this will accommodate the way in which the capture mechanisms work in the lung. So we shall have our modeling also based on inertia methods and we won't admit any other technique, although, of course, you can validate them and use them in aspects of product quality judgment.

But, as I say, we are basically going to be rooted very, very strongly in the areas of impactors.

[Slide.]

Our particular problem, if we look at the next slide, is really to model the way in which the patient's inspiration through the device is going to separate the particles, because they are normally aggregating devices, produced to produce the respirable cloud.

In this respect, the powder aerosol, the DPI, is going to be very different from the MDI.

[Slide.]

So if we look at this next slide, we can see here--oh; we can't see here. Oh, dear; oh, dear. Well, never mind. I shall have to do some translations here. What I am doing here is I am basically contrasting the performance of a PMDI and the DPI as a function of the flow rate.

Oh; the wonders of technology. The slide, when I made it, was really quite legible and now it is even better.

What we have got here is some of our gamma scintigraphic work where we are looking at the deposition of cromolyn sodium as a function of rate of inspiration.

You can see that at 30 liters per minute, we are getting 11.8 percent of the dose into the lungs. But, at the faster inspiration, that value is dropping quite significant. Quite the reverse is true with the dry-powder inhaler because here, at 60 liters a minute, we are getting--and this is the gamma scintigraphy work--we are getting 0.5 percent of the drug into the lung. But at the faster inspiration of 120 liters per minute, we are getting 13.1.

One thing I think to point out on this slide is the enormous variability from patient to patient, always an aspect, I think, that we keep in mind as we compare methods.

[Slide.]

Now, that effect of inspiration rate on cromolyn sodium is, in fact, mirrored in some earlier work, years ago, by Auty and his colleagues at Phizens, when it was Phizens. You can see, here, across this peak inspiration flow rate, you can see this enormous dominating influence of the inspiration rate on defining the respirability of the cloud compared with this question of the depth of the penetration.

It is quite clear that, in assessing dry-power inhalers, this effective inspiration rate in generating dose

completely overshadows the fact that the dose now generated at a relatively high speed will have a lower respirability.

So, all this, of course, leads to the model.

[Slide.]

If we go on to this next slide, we can basically pursue some of these arguments by looking at a comparison now in which we are looking at a Turbuhaler, a dry-powder inhaler, compared with a pressurized metered-dose inhaler. This is a lung-function response to the administration of either 250 micrograms or 500 micrograms given by these two methods.

This is work published by AstraZeneca. You can see that, if we compare the 0.25 250 micrograms from the Bricanyl PMDI, we can see we get this response. This is very much significantly doubled, or very significantly increased, if we increase the dose to 0.5 milligrams, 500 micrograms.

If we compare the data for the dry-powder inhaler, we don't, in fact, see this differentiation between dose for reasons which I am sure Richard Ahrens would give us an explanation in terms of where we are on the dose-response curve.

So that is, if you look, a PD, a lung-function evaluation. Let's go on to the next slide and see how this is reflected in a lung-deposition study.

[Slide.]

This is not gamma scintigraphy, now. This is basically being done by the charcoal-block method. But we can see here that, if we look at lung deposition--that is in vivo deposition studies--we can see a difference between the 2.5 milligrams given by the Turbuhaler or by the PMDI is equally reflected, the relative efficiency is equally reflected, in a lung-deposition study.

So the lung deposition, now, reflects the greater deposition which we did not see when we were looking at a pharmacodynamic response.

I asked Lars Borgstrom, who basically published this data, if he would look back in his archives and see exactly how this would be reflected in an in vitro evaluation. He kindly carried this out. These were the results that we got.

[Slide.]

This is, in fact, some batches of the PMDI where we have got here a test done with an Anderson of 28.3 liters a minute, and we are characterizing the amount of material in the cloud which was less than 4.7 micrometers. We can see here we have got an average figure of something like 20 percent efficiency lung deposition predicted from this value, from the in vitro test.

If we carry out exactly the same procedure--in

fact, we are now using a five-stage liquid impinger because we have to be able to vary the flow rates for reasons which we shall discuss in a moment, we can see that this ratio of 2 to 1, the Turbuhaler being twice as efficient as the pressured metered inhaler, nicely sustained.

So, again, we are building across these contributions. In this case, we have got a beta agonist. We have got an imperfect PD. We have got a very interesting lung in vivo deposition which is nicely reflected in an in vitro model.

[Slide.]

What we have got here, and this is also not easy to read. But let me take you through this. We have got here some work that we did at Bath on measuring the peak inspiratory flow rates through a number of devices.

This was the control. We were using both volunteers and asthmatics. This was the Rotohaler. This was the Spinhaler. This is the Turbuhaler. This is a Boehringer device with the inhalator. And this is a Pulvinal, which is a device which is marketed by an Italian company called Chiesi.

Obviously, these devices vary very, very greatly in their resistance. This is reflected in the actual peak inspiratory flow that patients and volunteers can, in fact, inspire through them. It is quite clear that in my model

and in my techniques, I have got to, basically, try to control that characteristic if we are going to use any sort of sensible comparison.

So we look at the performance of these different devices which we have got to accommodate. If we basically say what we will do is we will impose a pressure drop of 4 kilopascals, which reflects, if you like, the minimum inspiratory pressure drop that a patient can impose across devices and then we will operate it at the flow rate which derives from that.

We see that these are the four kilopascal figures which would allow us to make a comparison between one device and another.

[Slide.]

What I want to do now is, again, to turn a little bit back to the power of these correlations. Again, I am indebted to Bo Olsson. This data is made available by Bo Olsson and his colleagues at AstraZeneca.

Essentially, we are looking at the fine particle dose in the sort of modeling that I have been describing for dry-powder inhalers against lung deposition established by an in vivo technology which is essentially based on their charcoal-block technology.

You can see that what we have got here is some sort of correlation. The in vivo deposition, which you

remember, going back to Pauwels' original statement relating to availability, to real availability of the dose, is broadly correlated to the fine particle dose as established by these in vitro inertial techniques.

The point that this makes, where we have got here the Turbuhaler, a PMDI, the Cyclohaler and the Rotohaler, you have to give much attention to the way the model is made. If you notice here, we have got here a bold throat which is an old configuration originally introduced into this sort of evaluation.

[Slide.]

This is a USP throat where we have now got a right angle, much more sensitively and properly reflecting the oropharyngeal capture in our in vitro model. We come onto that correlation again in the next slide.

[Slide.]

We can see how it has improved. In other words, good modeling, now. I think this is an excellent relationship between fine-particle dose and in vivo lung deposition established by a validated method.

[Slide.]

Now let's look at this issue of flow rate and the way it affects particle sizes and fine-particle doses. This, again, is data for the Turbuhaler and you can see that, as the flow rate moves from 35 liters a minute to up

to 80 liters a minute, which is probably the broad spectrum of flow rate you might expect to have through this device, you can see how this is reflected in the efficiency of the device.

This would allow you to say that, from the study of the variability of flow rate through that device in patients, it would allow you to say that, very much, most of the patients would get a dose which was adequate. But you might have to do something strange at the lower end if you had patients which were highly compromised and you might, perhaps, have to restrict it in some aspects of pediatric use.

But the in vitro model, really, is very, very useful in assessing that effect for an individual device. It is really quite hard to see how you could get some useful information other than by very, very complex and expensive experimentation over wide ranges of patients.

[Slide.]

If we come to the comparison, it is a bit more difficult because here is the Turbuhaler data, and I have got some data here from this Pulvinal device, which is a much higher resistance device and so, consequently, patients are inspiring through this at much lower rates.

In fact, the average flow rate that a patient would get through the Pulvinal device is about 35 to

38 liters per minute. For the Turbuhaler, the average value is 55, 56--he wants me to use 60. So we will use 60. The value there would be 60 liters per minute.

For the Rotohaler, which is a low-resistance device, patients are, in fact, drawing through the device at a much higher rate. So, using the fine particle dose comparison is much more difficult. I suppose you would probably have to say that if you wanted to do a comparison between one device and another, you would probably be looking at the device which broadly had the same sort of slope of generation of fine-particle dose against inspirational flow rate and probably which had the same overall resistance.

Of course, this means a very, very close relationship between the design of the formula and the design of the device. So I think our technology is going to be much less adequate and much less powerful in working in a comparative way. Its power, as I am saying, will be in the basic characterization of the efficiency of the device and I really believe that it can make a major contribution to this overall assessment.

We shouldn't have our in vitro and our in vivo and our PDs and our PKs in different compartments. They are part of the story.

[Slide.]

Let's just finish with a word on methodology because, in this slide, these were configurations, experimental configurations, in this case to vary the flow rate through the device according to the principle which I have described. This was elaborated in a very positive series of meetings that we had between the European Pharmacopeia and its working party on what, because of their classical upbringing, the Europeans call "Inhalanda," which is Latin, compared with the Americans pressurized and powdered inhaler dosage forms.

But the importance of this was that there was good harmony between the two groups and what is being suggested really is very similar between what is done in Europe and what is done here.

[Slide.]

Basically, now, what we are doing; we have exactly the same configuration except we now are leading from our device through an induction port, sensibly designed, into a multistage impactor where we shall have some elaboration of the fine-particle distribution and the derivation of the fine-particle dose.

That is really where we are. The methodology, as I say, is being widely used in Europe with the harmonization process. I think I would implore the American scientific community, the FDA, the USP, and so on, basically to embrace

this technology. It is not perfect but, on the other hand, it is state of the art and we are beginning to derive a lot of very, very useful data on in vitro characterizations.

It is about time we also derived some useful data on actual clinical and PD determinations because some of these studies out there are very, very seriously flawed. We are in a position, I think, to collect data using this type of technology and comparing it with properly designed clinical studies.

That is where we are. Where we are going--of course, this isn't a stationary situation. At the moment, there is a European-American cooperation in designing a new impactor. You must remember that we are employing impactors which were designed from completely different purposes and we have shoe-horned them into what we need.

Perhaps, for the first time, we are going to have an impactor which is, in fact, designed specifically for aerosols for delivery to the lung concentrating on 1, 2, 3 micrometers as the important dimensions. We are also not necessarily finished at this point of the activity. I know that there are some very, very interesting academic industrial cooperation going on in attempting to study different casts of a oropharynx to see whether this is, in fact, the best design.

So the situation is far from standing still. To

me, it is a lively, powerful contribution to the assessments of products and one which I would hope the regulators, both here and in Europe, will take fully into account in making these very important assessments.

Thank you very much.

DR. LEE: Thank you. Before you leave, I wonder if the members of the committee have any questions.

DR. LI: I have a question. I would like to ask Dr. Ganderton whether there has been any progress in developing anatomical models for nasal inhalation where the particle size distribution importance is different plus that right angle would not necessarily apply.

DR. GANDERTON: First of all, you raise a very important issue that the geometries are different. I think that the modeling is far less advanced. This has attracted a lot of attention, but it is capable, of course, of being a model. I know of no important elements that are contributing to that assessment at the moment that are very specific to nasal deposition.

I think there is one aspect of where the modeling--we are certainly, in extending the pulmonary delivery, looking at inspirational profiles rather than the simple square wave where you apply a pressure drop across the device perhaps building it up more in the way that the patient would, in fact, breathe in.

DR. LI: In your model, what is the relative importance of larger particles, say greater than 5 microns, in lung deposition or deposition in airways?

DR. GAMBERTON: I think, in that model, they are discounted. They are actually completely discounted. At the moment, we are in a relatively crude statement in defining a fine-particle dose, which is that part of the cloud which is less than 5 micrometers and discounting that which is above.

We are seeing some interesting developments in the two preceding speakers where they are beginning to tease apart and compare and contrast these distributions. So I think there are some intelligent steps to be taken in dividing the inspired cloud into fractions, possibly relating to deposition depths, and then, perhaps, carrying out an analysis on that basis, hopefully a lot simpler than the ones that were disclosed this morning.

DR. LEE: Thank you very much.

DR. GANDERTON: Thank you.

DR. LEE: Thank you for getting us back on schedule.

Subcommittee Discussion

DR. LEE: We now come to the part of the agency where the subcommittee has to deliberate. There are a number of questions prepared by the agency to get your

opinion.

The first lot of questions concerns profile analysis. The first one asks, "Should all stages in the cascade impactor be considered in a comparison of test and reference products?"

Anyone?

DR. DALBY: I have a few concerns about some of these methods. Maybe Andy or Guirag could talk about them a little bit. My question is, in all of these techniques that essentially use a point-by-point comparison, it would seem to me that there is a real danger that, if you had a very tight particle-size distribution, or two that were very similar means but very close together, that happened to correspond to the difference between two stages, you could end up, by the particle size distribution being very close for two products, test and reference, and yet the amounts deposited on two adjacent stages could vary dramatically and all of these tests would falsely interpret those products as being vastly different.

That is kind of one concern that I have. The other one is that I am sort of intrigued by Dr. Ganderton's last diagram. I don't know, really, what it implies but has that cascade impactor connected to a variable-flow control valve been used to imply that it is possible deconvolute the particle deposition in the impactor when it is operated at

different flow rates or has it been used to suggest that the particles have been separated aerodynamically but we won't actually know what size particle impacts on each stage and, therefore, it is comparative between products but its absolute meaning is no longer interpretive.

So I would be interested in hearing what is the thrust of that kind of approach.

DR. GANDERTON: An important part, I think, of the development of inertial techniques to accommodate different flow rates is that we now have got to have calibration methods apply to each stage. Consequently, we do have real particle-size data from this analysis.

The only complication, of course, is that these particles are necessarily going faster. Consequently, we have always got to bear in mind, although we are properly characterizing the particle size as the materials move through the device and making appropriate inertial characteristics, there are implications, I think, for the actual basic respirability which might change with very, very fast inspirations.

Is that an answer? No; he is not happy. You can tell by his face.

DR. LEE: Any other opinions about these questions on the floor?

DR. HARRISON: I have an opinion. I think that

all stages should be measured, but this is a bioequivalence comparison and it is really hard to know what value each stage has versus safety or efficacy. What we did talk about is weighting, and we can debate that. It may be that you should weight stages more than others, but I have not heard any rationale why we shouldn't have at least all the stages in the equation.

Again, this is a bioequivalence analysis.

DR. CLARK: I will try and answer Richard's first question. The difference between f2 and chi square is f2 actually works on a cumulative distribution. If you look at it as a cumulative distribution, you don't actually get too much into the problem of it being only a stage 6 or stage 5, because, cumulatively, it will smooth itself out.

To answer the second question that David tried to answer, what he is proposing is using his impactor as a model of the lung not as a sizing instrument anymore. If you vary the flow, it becomes a model lung. It doesn't become a sizing instrument.

DR. BEHL: I support, also, the measurement of all stages mainly because the clear effects of particle size versus the efficacy has not been precisely studied. Therefore, cutoff at a certain particle size may not give the right results.

DR. DERENDORF: I would like to come back to the

f2. We have to differentiate. There were two different proposals. One is the f2 factor and the other one is the f2 ratio which includes the variability of the reference.

I think you can come to very different conclusions depending on the variability of the reference including particle size, areas, ranges that may not be relevant that will have an effect on the variability and, therefore, an effect on the conclusion depending on where the goalposts are. So that needs to be considered.

The number 50 is not a god-given number for f2. So that may be debated if that is reasonable or not.

DR. LEE: Hearing no other response or comments, I assume that the committee shares the view of Lester Harrison and Charan that all stages ought to be considered.

The second question we have kind of drifted into is, "Should a statistical approach rather than a qualitative comparison be used for profile comparison? If yes, does the chi-square comparative profile approach seem appropriate?"

Walter, you are the expert.

DR. HAUCK: So what do you think I am going to answer to the first part of this question? Let's take that as given; yes. I guess the bottom line on the second part is I don't think we are ready to answer that question. I actually did want to congratulate Yi Tsong and Dr. Clark for their presentations. I think it is a very difficult problem

that they are tackling and it is good work that is helping to move us forward on this.

The kind of key issue that we are working around, both with the first question and then that Dr. Clark got to at the end of it, is how do you combine across the stages. That is kind of the goal of both lines of work. It seems to be a desirable goal to not have to look at each stage separately, partly to just make sense of all that and part of sort of the issue that Richard was just raising, which would really be exaggerating.

I know that the chi square is geared towards downweighting stages that seem unimportant in terms of how much is there, so it is doing a type of weighting. If it was possible to get away from kind of an empirical weighting to a if you want to call it a clinical weighting if the weighting is actually based on some clinical notion of which of those stages are relevant, that would seem to be highly desirable.

So I am going a long-winded way saying this is a good problem. I think there are some good work being done, but I don't think we have an answer to the second part of that question.

DR. LEE: Are you ready to offer some guidance as to which way they should be going?

DR. HAUCK: No. I don't think so. Again, I think

Dr. Clark summarized it pretty well, that there are these kind of two tracks. If you go the sort of clinical weighting approach, we kind of get to sit back and kind of watch you guys try to make sense of all that.

It has been clear previously that the notion that there should be sort of one criterion that applies to everything doesn't make a lot of sense to me but to say that, for every single product, that you have to sit down and form a committee and agree on weighting, that would just sort of bring the whole process to a halt, too.

[Slide.]

So there has got to be something in between there. I don't know quite what it would be. So that is where I kind of said, no, I don't really--I would like to see both of them proceed on what they are doing. It probably takes us back to an earlier discussion. We need to seem some real data with both of them applied to and get a better feel for what they do and what they don't do.

I think that the notion of using f2-50, there is no particular value to that, as was just commented. So part of the discrepancy that we are seeing between the two things Dr. Clark presented were that the 10 percent and the 50 percent don't have to be comparable. So the fact that they were not comparable doesn't tell us anything.

There is just so much to do there. My guidance is

to encourage them to continue doing it.

DR. LEE: Thank you.

Anyone else?

DR. SZEFLER: The way I see it in terms of the complicated issues, there are drug, there is delivery device, and there are accessory devices. When you put all these three together, I think you wind up with four categories. I keep getting confused between where the questions are trying to sort out, how do you start putting these various questions into categories.

The way I see the categories is, first there is characterization of those three. Then there is categorization, in terms of trying to find pigeon holes where these things fit into. Once you have got that, then you get into the issues of equivalence and where equivalence plays a role is how much testing gets done beyond a certain product.

Then there is the standardization process. So I see where we are asking the question now is in terms of standardization in the question because all the other ones have to be done before you kind of get to the simple question of simple testing.

So, for us to kind of move to that level, I think the agency and the pharmaceutical firms have to get together how are they going to characterize these systems, categorize

them and then start going after questions of equivalence. Then you can start sorting out what are the simple and critical areas.

Once you have kind of put things into pigeon holes, then you can kind of narrow down the things you do for standardization. I think the different delivery devices point to those issues. It may be that, once you kind of get these things pigeonholed, then, for kind of the simple standardization tests, you can pick those critical variables and then kind of narrow it down to certain tests.

But, until all these things kind of get pigeonholed, it is going to be very hard to kind of put everything into that one category and say one simple test is going to do it for all.

I am not answering the question in terms of that specific, but I think before you get to that area, you have got to kind of start pigeonholing things so that it is easier to communicate, and then to simplify the level of testing.

DR. LEE: Thank you.

DR. BEHL: I am a little confused as to why we have to do this as opposed to a quality test or a quality comparison. It would seem to me that the stat approach should be done in conjunction with a quality comparison. They both should be equivalent and should be done because

the implication could be that they are qualitatively different and yet I am going to show the bioequivalence by showing a statistical confirmation of the product.

So maybe the question should be worded that should the stat approach be combined with a quality comparison of the product, because I don't see how you can do the stat comparison without a quality comparison of the products.

DR. LEE: Are you expecting a response?

DR. BEHL: Just a suggestion that the question be looked at in a different light. Both are important.

DR. LEE: Thank you.

DR. ADAMS: I think, Charan, the question concerning the qualitative versus the quantitative comparison of the cascade-impactor data comes in that if we are looking at these data and it is not quantitative, then it is going to be a subjective evaluation as to whether the numbers are, in fact, the same or whether they are different.

Different people would look at those numbers and might decide that they are the same. So it is very helpful to have a quantitative measure of equivalence.

But I would like to, if I could, just make a comment concerning Andy's slide--it is his last slide--in which he talks about choosing weighting factors. The approach that we have been using with the chi square or the

f2 which doesn't use specific weighting factors as opposed to the approach that Andy talked about using weighting factors based upon the physiologic deposition from a Rudolph model, that is an interesting approach.

He gets to the issue about choosing weighting factors based upon receptor distribution. I think that would be another approach. For instance, we may look at comparison of cascade-impactor data and put a lot of emphasis on stages 3, 4 and 5 where the drug is deposited. But, in fact, are those the right stages to be looking at when we are talking about a specific drug--for instance, and anticholinergic which is deposited principally in the central region of the airways or a steroid which may be more broadly distributed.

I think that these are issues that haven't been sorted out in terms of how to look at weighting factors. I was very interested in Andy's approach, but I think that it requires some additional considerations, or at least we have to be cognizant of that issue.

If members of the subcommittee or people sitting around the table have some thoughts about that issue, I would certainly be interested in them.

DR. LEE: You heard the question. Any comments?

DR. MacGREGOR: I do think a statistical approach is necessary. I do like the idea of trying to tie it to a

clinical effect. It is probably not a requirement, but it is something that you do when you write a new drug application is you talk about where the receptors are.

This is the only way to be able to correlate clinical pharmacology from a molecular level all the way up to the clinical situation. So it is always a nice lead-in. That data is out there. It is always in the literature. We know where the receptors are. We know that cholinergic receptors are in one region, the beta sympathomimetics need to reach a different region.

When you make combinations of these two drugs, you actually have to justify your particle sizes and that. So I think that it is not on a drug-by-drug basis, as Dr. Hauck's fear is. It is more on a class system.

I think most of us know what the classes are and where the drugs should be deposited based upon the receptors where they are working. So I like the approach of trying to tie it more to a clinical stage of the impactor. Therefore, I think it becomes more that if you are going more for bioequivalence and you are slightly off in one of your stages, then you would go and justify why that stage is not really relevant to equivalence.

You have all the other parameters to go with it to back up your case. So I like the clinical approach.

DR. LEE: Thank you very much. It seems to me

that the statistical approach is preferred because it allows quantitation. I think a very interesting twist to this is to tie it in with the receptor distribution.

Also, I heard that we are not quite ready to comment on the chi-square comparison as yet. I think further work needs to be done. Is that all right?

MR. PAREKH: This is actually a continuation of the question, sort of a question on top of a question. When you talk about the bioequivalence and bioavailability, you just are referring more from if you are innovating a new product. What happens is, in the course of this life cycle of the product, the product changes. The components change. The formulation changes.

Is there an expectation that we use the statistical approach or a quality approach to compare as the product changes in the life cycle?

DR. ADAMS: If you talk about a formulation change during the life cycle of the product, that that may not be a bioequivalence issue. It may or may not be a bioequivalence issue, all depending upon what the objectives are. I don't have any response other than that.

DR. LEE: I think we have to move on to the next set of questions.

DR. HARRISON: May I make a closing comment? I am concerned that we can't really comment on the chi-square

analysis. The draft guidance is out there. Chi square is part of the guidance and is probably being used by the FDA right now as the deciding factor.

Do you have any comment, Wally, on how you see the appropriateness of that guidance right now in terms of using that for doing bioequivalence?

DR. ADAMS: On the appropriateness of the chi-square analysis, Lester?

DR. HARRISON: Yes; based on what you heard.

DR. ADAMS: I think that we have to consider what we have heard and discuss it within our technical committee. No; I don't have any comments other than that.

DR. LEE: I think the person to handle that question is not in this room.

We will move on to the final two questions concerning DPIs. This is a long question; "What design features of the device and formulation, and what parameters, should be considered in determining pharmaceutical equivalence?"

Did you hear the question?

DR. HARRISON: The answer is the hard part.

DR. DALBY: I will take a stab at it. The thing that bothers me a little bit about this question is that I think it misses the important thing which is how do people actually inhale. How the device responds to that and how

the formulation responds, to me, is a very secondary concern.

It should be important to define how people are likely to use the device and how the device responds when it is used in that way. But, to try and look at devices a priori and try and make determinations about what is important about the device and the formulations seems to me to be putting the cart before the horse.

So I think it is a very odd question.

DR. LEE: Would the framer of the question shed some light about what is being sought here?

DR. ADAMS: The genesis of the question has to do with approaches that firm would use for a second-entry dry-powder inhaler and how to best go about designing that product to assure the in vivo bioequivalence.

Our approach for metered-dose inhalers has been to try and recommend formulation equivalence and device equivalence as a way of providing additional assurance for a firm going into a study that, in fact, the product will be bioequivalent in the end.

So the intention of this question is along those same lines. As Dave Ganderton has talked about, product DPIs which have high flow resistance, low flow resistance, does that matter when a second-entry firm is designing its product? Maybe it doesn't matter? That is the intention,

to try and determine what factors in vitro matter.

Does the fact that one DPI may be a drug-only, but another DPI could be a drug-plus-lactose, for instance? Does that matter? What are the criteria that matter before going into the clinical study?

DR. DALBY: I never thought I would find myself saying this, but that seems to me a very academic question because most companies don't have the option of changing from one device to another device. So that, essentially, is to preclude entry into the market unless you essentially have a device that is functionally very similar to the innovative product.

I just don't see how you will ever see a bioequivalence issue even come to you to review.

DR. ADAMS: We haven't yet.

DR. DALBY: I don't think you will.

DR. LEE: So the answer to this question is yes?

DR. LI: I just want to make a brief comment. I would think that the operating characteristics of the equivalent devices ought to be as similar as possible. If one considers how these product will be used, essentially equivalent products will be considered interchangeable with the parent or the reference product so that a particular individual patient may get one product or another. It may actually be different at different times depending on what

pharmacy they use.

So the operating characteristics are different, if the inspiratory flow requirements are different; for example, one requiring a fast inhalation for maximum delivery and another product requiring a slow inhalation for maximal delivery. There really would not be an effective way to communicate that to the patient.

The instructions that providers give would differ depending on which equivalent product a patient was using. There are other operating characteristics having to do with the device, the timing and so on.

So just in general, I would think that equivalent devices really should have equivalent operating characteristics.

DR. ADAMS: Dr. Li, does that mean, then, that you are recommending that products have similar operating characteristics in terms of their flow resistance, for instance?

DR. LI: I would probably emphasize the instructions and the operating activities of the user rather than specifically identifying flow resistance. So, if the maneuver is similar, if the resistance is somewhat different and the delivery from in vitro studies is equivalent, then the resistance, as a particular parameter, would be, I think, probably secondary.

The are issues involving sameness of labeling which a generic firm has to meet.

DR. LI: First of all, help me with the terminology here. That does indicate something that is intended to be marketed as a generic equivalent, is it not?

DR. ADAMS: That is what I meant, it was generic.

DR. LI: I just wanted to confirm that. I guess I would disagree. It seems to me that, if that is the intent, what we very clearly know from things that were presented this morning and elsewhere, that flow-rate dependence of dose and dose delivered and particle-size distribution can certainly affect response.

Therefore, I think it needs to match with the two devices. It is hard for me to see how that would happen without having the resistance be similar and the flow rate generated, therefore, by the patient being similar as well. So I think do have to not only match resistance. You have to match flow-rate dependence of drug delivery which includes that resistance as a function.

I guess, taking Richard's point here a step further, that what happens in the hands of the patient is what is really important. There still could be some ergonomic differences in the device that, even though in vitro they could look very similar, and this may be stepping into the next question, but it seems to me that what kind of

flow rates patients actually generate with those devices in typical clinical circumstances would be a step that would be nice to add to that.

DR. LEE: Thank you.

Wally, do you have the input you needed?

DR. ADAMS: Did we get the input that we needed?

DR. LEE: The question seems to be ahead of its time.

DR. ADAMS: Just to elaborate a little further, the basis for the question is that we are in the process of drafting a orally inhaled BA/BE guidance. The Office of Generic Drugs has not approved any dry-powder inhalers at this time. It is an issue that, hopefully, we will be dealing with over time and so, therefore, bioequivalence issues will become something that we have to deal with.

So that was the purpose of these questions, was to look at what aspects of DPIs should be considered on a comparative basis.

DR. LEE: Apparently, no one around the table would like to take this on with specific answers.

DR. ADAMS: I think that Dr. Ahrens' comments were very helpful in terms of comparability.

DR. LEE: The final question for this morning is what comparative in vitro tests should be conducted to help support bioequivalence? I think this is a follow-up to

David Ganderton's plea. Any suggestions?

MR. PAREKH: Is the question intended, in addition to the test that you have already requested in the draft guidance? Are you validating whether those tests that are requested--are you asking are those valid tests?

DR. ADAMS: Basically, the intention of the question is to ask what additional tests may be needed such as drug delivery as a function of flow rate.

DR. DALBY: It does seem to me that the last system that Dr. Ganderton described is very powerful in terms of comparing DPI products for two reasons. One is that it addresses not only what is the peak flow rate that a patient would achieve at a particular pressure drop, the rate of rise of that flow, how it is generated, which, I believe, does have a strong effect.

The other thing is that I am generally a proponent of using gamma scintigraphy as a way of looking at product performance. But DPIs are the most difficult product with which to utilize that technology and, therefore, I think that this is a good secondary method. So I think that, while I know it is dangerous to recommend an additional test, I think the value of looking at the rate of rise of flow rather than just the flow rate is important.

DR. HARRISON: I think it is also valuable to look at multiple flow rates of the variability of the devices as

well as the regular tests, keep the Q1, Q2 about the same, collect the size distribution.

DR. LEE: So what we have heard is that some incorporation of flow rates' influence on the subject at hand would be appropriate.

DR. DERENDORF: I think the question is really only half a question because it asks what tests should be done but it really doesn't ask what should be the criteria after you do the test, if it is equivalent or not. So I think there it is very important that we focus on why we are doing this in the first place and that is to predict both local and systemic exposure.

I think that should be a criteria that we need to show that whatever we set as a goalpost has clinical meaning and this is relevant for either systemic or local exposure.

DR. LEE: So the word is clinically relevant in vitro tests.

DR. HARRISON: Absolutely.

DR. LEE: Thank you.

On that note, are there any other comments from around the table? If not, before we go into recess, I would turn it over to Nancy to say a few words.

MS. CHAMBERLIN: We will have to start at exactly 1:30 for the public session. We have eleven speakers during that time.

at

DR. LEE: I would like to remind the public speakers that you only have about five minutes to make your case.

MS. CHAMBERLIN: Four.

DR. LEE: Four minutes; I'm sorry.

[Whereupon, at 12:35 p.m., the proceedings were recessed to be resumed at 1:30 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:30 p.m.]

MS. CHAMBERLIN: We thank you for your patience. We have new mikes. You just need to be ten inches away from them.

Open Public Hearing

DR. LEE: I would like to invite these speakers to come to the platform. Instead of for me reading the title of your presentation, would you please do that for us.

Data Related to BE Testing of Nasal Sprays, and Comments on the BE Studies of Nasal Sprays for Systemic Action

DR. ZAHIR: Yes. I will just be presenting some bioequivalence testing that we do according to the draft guidance. I will just give some examples of the CMC sections, also.

[Slide.]

My main title, if I give it a title, will be "Do We Really Need These Numbers of Tests?" If you look at some of the tests I have given in this transparency, and if you see that, according to the bioequivalence guidance, we will be doing a minimum of 8100 laser-diffraction tests, because of three different distances, three different delay times, three life stages, then the precision number and 10 is the minimum size, and then we have three lots and then we have two products.

[Slide.]

Similarly, for spray pattern, we will be doing three different distances. For priming and repriming, we have to report the early pre-prime actuations also. If you read the draft guidance, you will see that the justification they give is that in order to see how the prime is developed.

Do we really need these numbers of tests, if I take just the simplest form solution nasal spray? I am sure you know my answer, that we don't. Why don't we? I have only four minutes. I have to rush.

If we do a method, once we do our product development, we do method development, we do method validations and we select the most optimum, the best distance, the optimum size, the optimum delay time, the optimum obscuration values. All these tests are done on the reference product so our goal post is the reference product.

So, for an ANDA nasal-spray solution, I don't think we need even three lots. I will show you why we don't need three lots. The lot-to-lot variability should never, ever be an issue of bioequivalence testing because this is well-controlled by the CMC sections.

[Slide.]

If you look at the CMC guidance, and please read it. I don't have the time to read this, but if you read

section IIIF(1), IIIG and IV, you will find that all these tests are done. According to the CMC guidance, these tests are done in order to make sure that the design reproducibility and performance characteristics of incoming lots of the components is maintained.

So the lot variability is an issue of the CMC section, not the bioequivalence section. If we have good method developments, good validation studies and then we have the CMC control, a very strong control component, I don't see how we need even three lots and we need all these tests.

[Slide.]

If we look at even the statistics part of it, and I am not going into statistics because the whole day, today, we were into it. But if you look at just two points, and all these questions were well-discussed before--if you look at the last two points, if you see if the reference variance is larger than the scaling variance, we are using reference scaling.

The idea is that if there is any variability among the reference three lots that we used in our BE testing, this will widen our limits and it won't punish us. But if the reference variance is less, then it is not shortening the limit. Rather, it is telling us to use a constant scaling.

So I don't think that if I buy three lots of reference product which are on the market, we all know that in most cases, all these components will be coming from the same lot of the components. Nobody wants to do these tests on a daily basis. If I am the manufacturer, I will buy all the components, the same lot, for five years.

So, in most cases, all these three lots of reference are anyhow from the same lot. So we are not looking at true variability of the reference, actually. Secondly, if I make a good product, I don't need the favor of this reference widening the limits.

I say I will compare just against one lot of brand and this is the manufacturer risk. I think the consumer will benefit from it a lot. Why? Because I am now assuming that the reference lots have the least variability without doing the test.

I will just summarize it. Even this is a summary, but I will further summarize it. I will say that if we have a strong CMC control, we have good method validation, method development, if I am using a constant-scale criteria for the statistic.

Please, let's not say, "Oh; how are we going to determine variability if we don't have three lots versus three lots?" I think we all know that statistics is used to define an objective. We don't develop our objective around

statistics. We develop our objective first and then we develop statistics.

So those things I am sure Dr. Hauck and the good statisticians that we have can take care of the statistical problem.

Now, I will just jump. In this case, if we have all these controls, and I am just touching them, but, please, look at them in detail, these two, the CMC guidance and the bioequivalence guidance should be read in conjunction with each other. They are not separate. They have separate objectives and development objectives should never be a part of the BE testing.

The second thing, and just finalizing it now, is that suppose, if I have a solution-dosage form, then, according to the CFR, we all know that solution-dosage forms don't have any problem with bioequivalence. So if there is no problem with the variability, then the solution-dosage form for systemic-solution nasal spray for systemic delivery, the only problem or concern we have is data of the components, the container-closure system, for which we do in vitro testing.

So I think maybe we missed it or what, but I think this nasal-solution spray for systemic action should also be added to this guidance.

[Slide.]

Lastly, I will say that what if I, and there is no mention of this in the guidance, but what if I have the same container-closure system as the reference product has.

It is up to me, or it is up to the agency, to give me a list of what do I need to prove that these are coming from the same lot of product? What if the manufacturer of the component is me, myself and I am making it for myself. So, if I have a solution nasal spray for systemic or local, when I am using the same components, is the brand product, the reference, should I get away for doing bioequivalence testing?

So, please, look into this also and add a statement to the guidance.

Thank you.

DR. LEE: Thank you very much. I think you made a very clear case.

DR. ZAHIR: Thank you.

DR. LEE: Dr. Dugger to address the issue of sublingual sprays.

MS. CHAMBERLIN: For those of you who did not get copies of the slides, they will be on the website. The way you get to it is on the handout.

Uniqueness of Lingual Spray Delivery

DR. DUGGER: Thank you.

[Slide.]

My name is Harry Dugger. I represent Flemington Pharmaceutical Corporation this morning. Our company specializes in the development of lingual or buckle sprays to be delivered into the mouth for systemic effect. These sprays are intended to reach a therapeutic blood level within three to ten minutes and usually at a much lower dose than the standard oral tablet or capsule and often, in many cases, the nasal spray.

[Slide.]

It is our feeling that this guidance should also include these products along with nasal sprays and inhalation products. There are many similarities between oral solutions and nasal solutions, and there are many places where this testing can be made more simple.

The present guidance tends to divide products along the lines of products that are solutions and products that have a phase difference within the product. Phase-different products, multiphase products with these things like suspensions, emulsions, micellular solutions which are really not true solutions but have a phase transition within the solution,.

Lingual sprays would fall into the area of solutions as would nasal solutions and inhalation solutions.

[Slide.]

True solutions are a much simpler system than

these others that we have been hearing about all morning. By their nature being homogenous, they can be approved with reduced testing. There are, really, basically three kinds of solutions. This is something we all learn in chemistry 101. There are unsaturated, saturated and supersaturated solutions.

Because the nature of the solution being homogenous, you don't have to worry about which you have. You can test this very easily by just adding a seed crystal, for those of you who are into your basic chemistry.

[Slide.]

There are some examples here. I don't have much time to go into all the differences and all the similarities between nasal solutions and buckle solutions, but here are some of them right here.

For instance, in a spray, for content uniformity, number one, there is no mouthpiece involved. It is sprayed directly into the mouth. Since they are homogenous, these products should be tested, in our opinion, by using the weight variation method of the USP. Every single unit of a solution has exactly the same content as every other unit of the same weight.

So, if you can deliver a certain weight, once you know the average amount of drug and that weight of solution, every time you deliver that weight, you are delivering that

amount of drug.

The weight-variation method in the USP for tablets and capsules makes the assumption that the drug product or the drug substance is uniformly distributed in the table or capsule matrix. In this case, we don't even have to make this assumption. It is a known fact that it will be homogenous.

SCU through a container life; again, solutions do not change. The only thing that would change in the case where container life would be a factor would be if ever there is leakage from the container or there was degradation of the product in the container. Otherwise, again, every weight of solution will deliver the same among of drug product.

[Slide.]

Temperature cycling, for instance; with solutions, this is not such a critical matter because what you are really looking at here, I would believe, is a chance for a phase separation. Many suspensions may aggregate and not resuspend on freezing and thawing, but for a solution, the contrasting event is crystallization of one of the components or, in the case where you have a liquid and a liquid, there may be a phase separation.

This could be very easily seen by just cooling it in an ice bath or a constant temperature bath. If you think

you have a supersaturated solution and you have a tendency towards crystallization, again, adding a seed crystal is all you need to find out whether that is the case.

If the crystal dissolves, you are unsaturated. If the crystal just sits there and looks at you, you are saturated. If crystallization is initiated, then you were supersaturated. It is as easy as that.

[Slide.]

Other examples are leachables. Lingual sprays often use very high boiling solvents. As a result, to use the formulation as an extraction medium for leachables is really not practical. The boiling point of some of these solvents is close to 200 degrees celsius and, in many cases, it requires vacuum distillation to remove the solvent.

Vacuum distillation, of course, impinges upon the integrity of the leachables test because they may also vacuum distil, along with everything else. I would propose, in a case like this, that the leachables be profiled using the USP tests A and B, which are water and isopropanol and that, in these cases, the actual solution to use for the formulation would not be used.

Orientation and resting for these solutions is also not a problem. Solutions do not settle out. Orientation doesn't play a role as long as the dip tube is underneath the solvent in the container. If the dip tube is

underneath the solvent, then the same weight of solvent will be delivered, the same weight of drug will be delivered.

If it is above the solvent, no drug will be delivered and if it is partially emerged, you can expect to get a partial dose. Things of this sort can be best addressed in the labeling of the product informing the patient that they have to keep the container in an upright position and that the dose has to be delivered into the mouth in a way so that the dip tube is under the solvent.

For stability testing, we would propose that only one set of conditions be used for solutions. Again, we are not so worried about settling out in the solution as we are probably worried about what happens when the solution comes in contact with the gasket.

We believe that the weight of test, the maximum test for this effect, is to have the solution upside-down or inverted so that you get the maximum contact between the solution and the gasket and valve components. If it will pass this test, it probably passes the other two, also.

"Solutions do not change on resting." There are many places where solutions--and this would be both buckle and nasal and probably respiratory, also, have a difference between that and the suspensions or phase-separated products.

I would like to see the guidance, if at all

possible, delineate between these two sets of formulations and make it very clear what testing is required for which one because our fear is that we come to the FDA and we are going to be expected to meet all the requirements for a nasal solution or a respiratory solution and they don't really apply to a buckle solution.

Thank you very much.

DR. LEE: Thank you.

Next comes a series of presentations by two groups that have been very active in this area. Dr. Cummings?

AAPS Inhalation Technology Focus Group (ITFG)/

International Pharmaceutical Aerosol Consortium (IPAC)

Collaboration Technology Teams

Overview of the ITFG/IPAC Collaboration

DR. CUMMINGS: Good afternoon. Thank you for the opportunity to speak today.

[Slide.]

My name is Harris Cummings. I am with Magellan Laboratories and Research at Triangle Park, North Carolina. In the next few minutes, four minutes, I believe, I would like to provide a brief overview of the collaboration between the Inhalation Technology Focus Group and the International Pharmaceutical Aerosol Consortium in addressing the recent draft guidances from the FDA and to express the extent of interest and commitment on the part of

industry to support the further development of these guidelines for inhaled products.

[Slide.]

Two groups are involved in this collaboration, the Inhalation Technology Focus Group which is the focus group of the AAPS is comprised of pharmaceutical scientists concerned with inhalation products.

[Slide.]

Also represented is the International Pharmaceutical Aerosol Consortium which is an association of manufacturers of aerosol products.

[Slide.]

Shown here are the three draft guidances which I think we are all pretty familiar with by now.

[Slide.]

As far as perspective of the two groups, both the ITFG and IPAC are in full agreement as to the value of the new guidance documents and welcome their issuance. In addition, we agree with the BA/BE and statistical issues including the questions surrounding dose content uniformity presented by the subcommittee today.

We do, however, believe that, in addition to these important questions, there are many significant CMC issues particularly related to testing and specifications that still need to be addressed. In addition, we believe that

these difference can and need to be resolved through a data-driven and science-based approach to achieve the best guidances possible, a process which IPAC and ITFG have started and are prepared to continue to support.

[Slide.]

The ITFG/IPAC collaboration was proposed in the IPAC statement at the June '99 workshop as a part of a consensus-building process involving collaboration with the ITFG. The collaborative work between the two groups began in September of 1999.

[Slide.]

The structure of the organization is as shown on the slide and it consists of the steering committee and five technical teams. The steering committee provides general oversight and review for the five technical teams which are shown in the slide and the technical teams are formed based on the general technical subjects found in the three guidances.

As you can see, CMC issues are the primary concern of the documents and of the technical teams.

[Slide.]

The significance of the concern and commitment on the part of industry is also reflected in the number of companies involved in this collaboration. Individuals for more than twenty companies representing a broad spectrum of

industry, including manufacturers, contract organizations and component suppliers participate in this collaboration.

In addition to the approximately 85 individuals who participate directly in the steering committee and technical teams are many times that number of scientists at member companies who work on collection and evaluation of data.

[Slide.]

In the presentations that follow mine, a representative of each of these technical teams will present the current activities of the team and future work which the team plans and the commitments that each team is willing to make to further the work of the subcommittee. This includes generation of data, technical papers and recommendations and even a willingness to meet with the subcommittee, if desired.

[Slide.]

Finally, the pharmaceutical industry, as represented by the IPAC/ITFG collaboration, is committed to a science-based and data-driven process of establishing best practices for the FDA guidances. Large amounts of work have already been completed in this process and even more has been committed to by the member companies of this collaboration.

Thank you very much for your consideration.

DR. LEE: Thank you very much.

The next presentation is on BA/BE by Steve Farr.

Presentation on the Work of the BA/BE Team

DR. FARR: Thank you, Dr. Lee. Good afternoon, ladies and gentlemen>

[Slide.]

I am Steven Farr. I am actually from Aradigm Corporation in Hayward, California. I am grateful for this opportunity to present to you today on behalf of the BA/BE in vitro and in vivo Test Team. Over the course of a number of meetings, the team is about through collection and evaluation of relevant information, a series of data-driven position statements that I wish to share with you today.

While the team used the current draft BA/BE guidance document pertaining to aerosol products for nasal application, it believes the findings are generally applicable to in vitro and in vivo testing of products that are both orally inhaled as well as nasal products.

[Slide.]

In the slide that you have in front of you, it really describes the team's work that has lead to the following propositions. And these were agreed to at the last meeting. With respect to in vitro testing, we strongly agree that it is essential for pharmaceutical product equivalence to have these tests and they should be included

as part of the BA/BE guidance for oral nasal and oral inhalation products.

But it is not currently sufficient for BE approval without establishing in vivo BE. In other words, in vitro testing is not sufficient to establish bioequivalence in the absence of in vivo testing.

Turning to in vivo tests for BE approval, in other words to establish product quality through the measurement of bioequivalence, the guidance documents for nasal and oral inhalation drug products should require the use of validated human models for testing for local and systemic exposure efficacy and safety.

[Slide.]

These working propositions are associated with certain assumptions that define their applicability. The team recognizes that its BA/BE recommendations apply to locally acting drugs only as per the current draft guidance for nasal aerosols and sprays. However, the team's comments apply to both orally inhaled and nasal drug products, but it is recommend that these dosage forms should be treated in separate guidances.

It is further recognized that the scientific and clinical bases for developing BA/BE guidance are evolving so the working propositions created by the team only reflect the state-of-the art knowledge.

[Slide.]

Based on currently available information, the team has reached the following conclusions. Current in vitro tests, namely dose-content uniformity and particle-size distribution, may be used to estimate lung deposition but their predictability with respect to bioequivalence has not yet been shown.

Furthermore, the in vitro tests described in the current draft guidance are not necessarily more relevant or discriminating than clinical studies for the measurement of bioequivalence. Systemic PK/PD studies will estimate local exposure which will contribute to safety but may not estimate local delivery which will contribute to efficacy and local tolerance.

In turn, efficacy studies alone of a locally-acting agent cannot establish bioequivalence since they will not assure comparable safety through systemic exposure. So, bearing in mind these preceding conclusions, the team believes that in vitro alone are not sufficient to assess product quality for bioequivalence.

Indeed, the guidance should not distinguish between testing requirements for nasal suspensions and solutions for in vivo BE.

[Slide.]

In closing, I just would like to inform the

subcommittee that the team is committed to prepare a technical paper by the end of June this year to support the conclusions described today. The purpose of the paper will be to highlight areas where there is sufficient data to draw conclusions and where there is not enough data at present, and also to review technical documentation related to BA/BE issues addressed by the team.

In addition, the team will be prepared to address the BA/BE questions which have been posed during today's meeting.

Thank you.

DR. LEE: Thank you.

The next up is Dr. Bo Olsson addressing the specifications.

Presentation of the Work of the Specifications Team (Dose Content Uniformity/Particle Size Distribution)

DR. OLSSON: Good morning. My name is Bo Olsson, AstraZeneca. I am grateful for this opportunity to present the statement of the CMC Specifications Technical Team.

[Slide.]

Our focus has been on dose-content uniformity and particle-size distribution as the key attributes. For the industry, internationally harmonized guidelines is the key component for timely and cost-effect development of safe and efficacious drug products. A tremendous amount of work has

gone into establishing a range of harmonized guidelines between the United States, Europe and Japan through the ICH process.

The Technical Team on CMC specifications believes that orally inhaled nasal drug products are amenable to the principles set forth by ICH. Particularly, the ICH Guideline Q6A on specifications provides a process for establishing specifications and the extended application to inhaled dosage forms is being encouraged by the document.

[Slide.]

The ICH Q6A recommends a data-driven process for specification setting. Based on pharmacopeial standards, results from development and from pivotal batches and a reasonable range of analytical and manufacturing variability. We concur with Q6A that it is important to consider all of this information an we don't believe it is justified to apply a single standard specification to the wide range of different products that are on the market and in development.

[Slide.]

Based on the collective experience, the Specifications Team has posed the hypothesis that the current state of OINDP technology may not allow general compliance with the DCU specifications in the draft guidances.

To address this question, to date more than twelve companies have initiated the process to collect a worldwide blinded database of more than 45 products to examine actual DCU capability of these products. Our target is to have an initial assessment of the database by the end of July.

It is our position that the format of specifications should be based on sound statistical practices such that they can be translated into quality requirements. We propose to work with the subcommittee and the agency to investigate using this database, alternate DCU specifications which may better serve this purpose.

This includes those approaches presented by Dr. Walter Hauck this morning.

[Slide.]

Also, for particle-size distribution data, we have initiated a process to collect a database. The target date for initial assessment is, again, by the end of July. The purpose of this survey is primarily to examine the relevancy of the mass balance criterion as a product specification versus a system-suitability requirement. But it may also be used for looking into profile comparison techniques as well.

[Slide.]

In summary, we believe that the achievements of ICH should be taken advantage of in the FDA guidances and we are collecting a wide database which we hope can provide

useful information for the subcommittee and the agency.

Thank you for your attention.

DR. LEE: Thank you.

The next subject is tests and methods. Carole Evans?

ITFG/IPAC Technology Team: CMC Tests and Methods

DR. EVANS: Good afternoon.

[Slide.]

My name is Carole Evans from Magellan Laboratories. My role in this series of presentations is to give an overview of the work and approach of the Test and Methods Team. The team has reviewed the draft CMC guidances and has identified areas where the FDA approach differs from that which we in industry feel is meaningful and scientific justified.

[Slide.]

As a result of this review, we have identified four general concerns. Firstly, while recognizing there are certain key tests which are required for all dosage forms, we feel that the requirement for certain other tests should be driven by a critical review of the data and that the guidance should, therefore, distinguish between these two categories of tests.

In some instances, the language used in the guidance was ambiguous. For example, we are uncertain of

the intent behind the requirement for a stability-indicating method of dose delivery of MDIs. We would recommend a change in wording to, for example, a validated method free from bias.

We feel that the guidances should be further edited to clarify the requirements for each dosage form possibly separating each dosage form into individual guidances. Finally, the team would like to strongly recommend further harmonization of requirements with other pharmacopeial and international standards; for example, the control of synthetic impurities should be aligned with ICH.

[Slide.]

The team has started its work by reviewing the diagram for metered-dose inhalers and has identified several areas for comment. These are shown here. The scope of the comments vary from simply requests for clarification of wording and calls for harmonization to suggestions for alternate approaches to testing.

For example, in some cases such as the requirement for moisture testing, the guidance should indicate that the need for this test should be driven largely by the development data. There are other tests such as plume geometry or spray pattern which did not offer meaningful performance characterization or redundant component controls. These, therefore, should not be required.

[Slide.]

Our approach has been to develop position statements on each of these areas and the outline of those is provided in our written statement. We plan to collect data with regard to most of these position statements. In cases where the request is simply for rewording or for further harmonization, we will not be collecting data.

[Slide.]

We are currently in the process of collecting the data. This data will allow us to evaluate and, where necessarily, refine our position statements. To date, we have only addressed the guidance with respect to metered-dose inhalers. It is our intent to repeat the process for other dosage forms.

[Slide.]

After we have completed this process, we would like the opportunity to share our recommendations with the subcommittee and the agency. We believe that data-driven recommendations will be helpful to the subcommittee and, ultimately the agency, in creating stronger guidances. We hope we can continue this discussion on critical CMC issues by providing these documents and welcome an opportunity for further dialogue.

Thank you.

DR. LEE: Thank you very much.

Next up is leachables and extractables. Dr. Dave?

Presentation on the Work

of the Leachables And Extractions Team

DR. DAVE: Thank you, Vincent. My name is Kaushik Dave. Actually work for Schering Plough. However, this afternoon, I represent the Extractable and the Leachable Team. What I will present is the opinion of the team based on reviewing the draft guidances.

[Slide.]

The team recognizes the importance of control of extractables and leachables from the point of view of patient safety and quality of these inhalation products. The team is committed to providing information in this area.

[Slide.]

Just to give you some background with regard to definitions, extractables is what one observes when one uses solvents. Leachables is what appears in the product. Just to put it in some other words here, I hope that you can extract as much as you can from this presentation and, from my perspective, I hope a lot of this leaches in.

[Slide.]

Just to share with you; the team has identified four particular areas of focus which are listed up there. The general approach which the team is taking is collecting data from several companies and what we plan to propose to

do is analyze the data and make some recommendations in these four areas.

I will, over the course of the next couple of minutes, just go over these four areas briefly.

[Slide.]

The first area of interest is what we have defined as analytical characterization of extractables. We feel that the guidelines are not particularly clear and, perhaps, it may be advantageous to propose slightly different language and clarification. For example, we feel that there is a need for clear definition of what a critical component is from an extractable point of view.

[Slide.]

The second area of interest is what we have defined as analytical characterization of leachables. The real question here is do we really need to be extractables and leachables testing commercially since we are looking at pretty much the same phenomenon.

The draft guidelines have identified this and has alluded to the fact that if a correlation can be established between the leachables and extractables, perhaps, there could be some reprieve from leachable testing. But, then, the question becomes what is a correlation here. The guidelines are not very forthcoming.

Keeping in mind that we are looking at trace

analysis here, firstly. Secondly, we are trying to compare extractables, which is a solvent-based phenomenon to leachables which is formulation-dependent. Can we really come up with a correlation and what kind of correlation should that be?

What the team proposes to do is, after reviewing data, come up with a working definition of a correlation.

[Slide.]

The third and most important area of discussion in the team is safety qualifications of leachables. We feel that this is an extremely important area where there is a need for discussion and understanding as to what are the requirements. Simple questions like, "What is the criterion for qualification? How do we determine the levels? Does ICH apply here? If it does, do we compare it to the active ingredient. They are not chemically related; does that make sense?"

Again, the team has formed a working group composed predominantly of toxicologists from the industry they will be reviewing this closely and making some recommendations.

[Slide.]

The fourth and final area of discussions in the team is is this the right way of approaching control of components, testing them at the end. Shouldn't we building

quality into components instead of looking for quality at the end? Again, there are a lot of systems out there, quality systems, which would insure that quality components are produced and also those quality systems will include change control and audit.

Actually, we have a technical team, the Supplier QC, which is looking into this.

[Slide.]

Finally, the team is committed to offer databased technical reports and recommendations to the agency and the subcommittee over the course of the next three to four months. Also, secondly, the team is available to evaluate any extractables or leachables issue which the subcommittee or the agency would like us to.

Thank you very much.

DR. LEE: Thank you.

The next issue concerns supplier quality control. Mr. Hansen?

Presentation on the Work

of the Supplier Quality Control Team

MR. HANSEN: Thank you and good afternoon.

[Slide.]

My name is Gordon Hansen from Boehringer Ingleheim Pharmaceuticals. I would like to take the next few minutes to present an overview of the work of the ITFG/IPAC Supplier

Quality Control Supplier Qualification Team. This collaboration has presented a unique opportunity for representatives from the pharma industry and component suppliers to collaborate on a review of the key issues in the draft CMC guidances which relate to the testing and qualification of inhalation-device components and excipients.

[Slide.]

The draft CMC guidances focus extensively on testing of components as well as excipients. A core theme of the CMC guidances with respect to these components is that tight standards and extensive testing by the pharma manufacturer are required in order to assure batch-to-batch quality of components and excipients.

[Slide.]

The team, in reviewing these guidances, has drafted a thesis or vision statement which may be described as follows. The qualification and control of critical components in the area of performance-related physical testing, extractables and leachables and excipients should be achieved by a combination of appropriate scientific practices, cGMP controls and supplier qualification systems.

[Slide.]

The first step for the team was to collect data on current GMP practices. A survey of suppliers was conducted

to evaluate quality and compliance practices at all stages of component, excipient, raw-material and active-substance manufacture. Information was obtained from fifty-three suppliers from raw materials through finished component manufacture.

[Slide.]

The results of the survey are shown on this slide. One is that the level of cGMP awareness and compliance in the component and raw-material supply chain is improving but improvement needs to continue. Secondly, there are specific cGMP program elements which remain to be generally accepted and implemented especially early in the supply chain.

[Slide.]

Some general observations were also made from the survey in that there are no generally accepted cGMP guidelines for the component supply chain but guidelines do exist for the control of bulk excipient manufacturers which have been drafted by IPEC, which is the International Pharmaceutical Excipients Council.

[Slide.]

The team proposes the following: the team endorses the IPEC guideline for the control and cGMP compliance of excipients and it encourages its broader acceptance. The team also proposes that an industry-wide initiative be established to develop a cGMP guideline for component

suppliers. This collaboration would be a unique, perhaps unprecedented, partnership between suppliers, the pharma industry and the agency in designing a system which assures product quality by building it in rather than by extensive testing by the end user.

[Slide.]

The team also requests that the agency partner with the pharma industry and component suppliers by first formally recognizing the value of the cGMP guideline for component suppliers by acknowledging in the guidance documents that if sufficient supplier mechanisms are in place, appropriate reductions in testing will be considered.

We also ask that the agency help establish key elements and expectations for the cGMP guideline for components and participates in reviewing and commenting on draft guidelines.

Thank you for your time.

DR. LEE: Thank you.

Now comes the concluding presentation by this group, Cynthia Flynn.

Concluding Presentation on ITFG/IPAC Collaboration

DR. FLYNN: Good afternoon.

[Slide.]

My name is Cynthia Flynn. I work for Aventis Pharmaceuticals. I would like to take this opportunity to

provide you the concluding remarks concerning the ITFG/IPAC collaboration.

[Slide.]

I trust that during the last six presentations, we were able to demonstrate the very high level of commitment and the massive amount of work that has been completed by more than 85 pharmaceutical scientists working in the foreground of this effort as well as the hundreds supporting them in the background which represent more than twenty companies to address key concerns in draft CMC and BA/BE guidance documents.

ITFG and IPAC is committed to collecting and assessing all relevant data which becomes available to this collaboration. More importantly, we are committed to sharing those findings in a very timely fashion with this subcommittee and the agency.

ITFG/IPAC anticipates that this information will be useful to the subcommittee in its deliberations and also to the agency in the preparation of the final CMC and BA/BE guidances. In addition, we believe that this information will assist in the creation of a very high-quality document which the industry and agency can use in designing the dosage forms of the future.

[Slide.]

I just would like to take the time, then, to

review very briefly the deliverables which the technical teams are committed to providing and the time frames associated with those deliverables. Firstly, the BA/BE team is committed to preparing a technical paper on BA/BE that have been highlighted in the previous presentation. This will be completed by the end of June.

In addition, that team will attempt to address as many questions as possible as have been raised during this meeting.

The Specifications Team is committed to completing, by the end of July, an initial statistical assessment of the actual DCU and particle-size database which is collected by this collaboration. We would very much like to share this initial assessment with you and with Dr. Hauck in order to help your endeavors.

The Test and Methods Team is committed to completing, within the next three to four months, the technology paper outlining the key MDI tests. In addition, in the future, we also plan to do similar work for other dosage forms, as was alluded to by Carole in the previous presentation.

The Leachables and Extractables Team is committed to also completing a technical report within the next three to four months as well as to making recommendations within the next three to four months concerning leachables and

extractables.

Lastly, the Supplier Quality-Control Technical Team is volunteering to ask as a co-leader with the agency in developing a cGMP guideline for component manufacturers.

[Slide.]

I would like to point out to the committee that it should be noted that the work of the collaboration deals with not only BA/BE issues, which have received substantial emphasis today, but also places a significant amount of emphasis on four critical CMC issues, not just the DUC issue.

[Slide.]

The collaboration of ITFG/IPAC is very convinced of the need for a science-based interactive dialogue and is requesting that the agency continue the subcommittee process. We are also requesting that the collaboration be given the opportunity to provide the deliverables that I just described in the next three to four months for the use of the subcommittee and agency in order to assist in the resolution of the various CMC, BA/BE issues.

[Slide.]

I would like, then, to conclude my remarks by acknowledging several groups. First of all, we would like to express our deep gratitude to the agency for holding this meeting and allowing us to present the work that has been

completed to date of the ITFG/IPAC collaboration.

We would also like to thank the members of the subcommittee for considering our comments and proposals and we look forward to working with them in the future. I would like last to acknowledge the very hard work of all of those people I was talking about, the 85 in the foreground and the hundreds in the background, for the commitment, constructive collaboration, that they have given to the ITFG/IPAC collaboration.

Thank you for your attention.

DR. LEE: Cynthia, may I ask you one quick question? What is the size of the team, how many members?

DR. FLYNN: The entire team? Or a specific technical team?

DR. LEE: A specific technical team.

DR. FLYNN: They vary, depending on the technical team. So you would have to tell me exactly which one. We have a total of 85 members when you add up all the steering committee and all the technical-team members. There are five technical teams.

DR. LEE: So divide by five. Ten or fifteen? Can someone be one several teams?

DR. FLYNN: In some cases, there are, but not in all cases; no.

DR. LEE: And then the position paper that you

will develop or deliver will be a consensus document?

DR. FLYNN: Correct.

DR. LEE: Thank you.

That concludes the presentations by those two groups. Now we have two more to go. Next up is on CMC issues by Dr. Neugebauer.

CMC Issues

DR. NEUGEBAUER: My name is Ken Neugebauer. I am the Director of Marketing for Solvay Fluorides responsible for the NAFTA region. I am speaking on behalf of and presenting the comments of Ms. Anja Pischtiak, Product Manager of Pharmaceutical Aerosols for Solvay Fluor based in Hanover, Germany.

[Slide.]

Solvay Fluor is a manufacturer of the propellants HFA227 and HVA134a used in inhalation drug products, marketed by Solvay under the trade name of Solkane, would like to make two comments on the major excipients and MDIs, the noncompendial propellants 227 and 134a. The comments relate to the draft guidance for industry, metered-dose inhaler and dry-powder inhaler drug products chemistry, manufacturing and controls documentation.

[Slide.]

The first point. Lines 288 to 295 identify a requirement for a toxicological qualification of the novel

excipients 134a and 227 but do not give directives of what comprises a toxicological qualification. The consortia IPACT I and II have submitted to the FDA extensive safety data on 134a and 227 intended for inhalation which may sufficiently demonstrate the toxicological suitability of the novel excipients 134a and 227 for use in medical products including MDIs.

Solvay believes that the uncertainty of the requirements for a toxicological qualification of the pure excipients strongly inhibits the pharmaceutical industry from reformulating its CFC-containing products to HFAs. Therefore, we propose that a definition for the toxicological qualification of the noncompendial propellants HFA134a and HFA227 be added to the draft.

The second point we want to make, lines 381 to 405 show impurity acceptance-criteria limits for 134a impurity by impurity, which are given in such detail, strictly process related. Solvay, for example, uses for the manufacturer of 134a pharma a process starting from trichlorethylene which is not mentioned in the FDA specification.

However, it is present in trace, but detectable, amounts in our product and, therefore, is specified by Solvay. While Solvay has four additional impurities not shown in the specification quoted by the FDA, sixteen other

impurities that are listed in the draft specifications are not contained in Solkane 124a as manufactured by Solvay.

Therefore, Solvay proposes to replace detailed impurity-by-impurity limits with acceptance criteria based on toxicological tests performed both for HFA134a and for HFA227.

[Slide.]

I submit, with these comments, Solvay's specification--that is impossible to read; I apologize. I will get a clearer copy for publication. Basically, this is our specification for 134a with detailed description of all of the impurities listed and comparison for what Solvay manufactures in the draft guidance.

[Slide.]

This slide is the specification for Solkane 227 pharma as filed currently with the FDA to be added to the draft guidance in case the 134a specification remains. The 227 specification is currently omitted.

Finally, I have included with my submission that we agree in principle with comments previously submitted by IPACT as published in the August 1999 Gold Sheet. Again, I am submitting them with the key points highlighted for the committee.

Thank you very much.

DR. LEE: Thank you very much.

The final speaker of this session is on growth effects of nasal steroids by Dr. Schenkel.

Growth Effects of Nasal Steroids in Children and Differences among the Steroid Preparations

DR. SCHENKEL: Good afternoon. I want to thank the committee for allowing me to speak about this issue.

[Slide.]

I am a practicing allergist. I am Director of Valley Clinical Research Center in Easton, Pennsylvania. I have been involved in a number of clinical trials looking at differences among the various nasal corticosteroids. What I am going to be talking about in the next few minutes is exactly that, the differences among the steroids in a clinical setting.

You have heard a lot today about trying to look at in vitro models and how to tell differences among the steroids. I am going to point out to you the fact that there are differences, not just in bioequivalence but in what I have called bioactivity, particularly in the pediatric population and particularly the effects on growth.

I would urge the subcommittee to look at this very carefully. It has already been looked at by the FDA in terms of acknowledging a new pediatric labeling for nasal corticosteroids.

It is well known that oral corticosteroids can

cause growth suppression in children. What was a surprise to the medical community was information that I was involved in that looked at the effect of certain nasal corticosteroids on growth in children. This prompted a joint meeting between the Endocrine Metabolism Group and the Allergy Pulmonary Group in July of 1998 to review proposed class labeling for both oral and intranasal corticosteroids regarding growth suppression.

In fact, in November, the FDA did announce new pediatric labeling along those lines.

[Slide.]

The FDA reviewed the literature at that time on both oral inhaled corticosteroids and intranasal corticosteroids. Two well-designed studies were reviewed regarding the nasal corticosteroids, one of which showed a growth-suppressive effect which I will show in just a minute. I am not going to deal with the issue of oral inhaled corticosteroids because that is not the issue we are talking about right now.

However, it was reviewed and four of the five studies did show a growth-suppression effect. It is interesting because the growth-suppression effect found in intranasal beclomethasone study, which I will review now, was separate from any effect on the HPI axis. As you all are aware, the HPI axis is sort of the gold standard of some

systemic activity of both nasal and oral inhaled corticosteroids.

But, as I will show in just a second, the growth-suppressive effect in this particular study, which is in a handout, also, involving intranasal beclomethasone, did not have any effect on the HPI axis. This study, which was a well-deigned, double-blind, placebo-controlled study which occurred over the course of a year in 100 prepubescent children, looked at growth effects of intranasal beclomethasone diproprionate, 168 micrograms BID in half the patients and placebo in the other half of the patients.

The patients all had allergic rhinitis and all were between the ages of 6 and 9-and-a-half.

At the end of the year, what surprised everyone was that there was a small but significant growth effect. The placebo group grew about 5.9 centimeters per year where as the BDP group grew only 5 centimeters per year. The conclusion was that the overall rate of growth was lower for the BDP group compared to the placebo group, about a centimeter over the course of a year.

This has been published now in Pediatrics on Line. What I did not show in this slide but is in the handout is that the HP axis was not affected in any of the groups. The conclusion was that a small, but statistically significant effect, of BDP on growth was observed separate from its

effect on the HPI axis.

Again, we have talked earlier this morning--I have heard a lot of really exciting talks on statistics and in vitro models--looking at ways in which you can compare, on an in vitro basis, certain nasal corticosteroids or corticosteroids in general. What I am going to show you, though, in an in vivo setting, the difference between beclomethasone and mometasone furoate nasal spray.

This study that I am going to talk about was not available to the FDA at their meeting and has recently been published in Pediatrics, the On Line version, in February of 2000. This was a study in which I was lead author and looked at, in the same fashion, the effect of mometasone furoate on the same group of children, ages 3 to 9, on the effects of growth and also HPI axis.

[Slide.]

The study design was essentially the same as the previous study, about 100 children, half receiving placebo or half receiving mometasone furoate. Standing height was assessed very carefully using stadiometric techniques.

With mometasone furoate, at the end of the year, children who received active drug did not have any suppression of growth in the group studied ages 3 to 9. The group that received mometasone furoate did not have any significant side effects and, very importantly for the

committee to understand, there was on effect on HPI axis.

So I think that this clearly shows that there are differences between these particular nasal corticosteroids. Can we translate this into other nasal corticosteroids? I believe we can based on bioavailability data. I think that if the committee is to consider other types of nasal corticosteroids, that they should all go through the rigorous growth studies as the currently available models have been done.

Thank you.

DR. LEE: Thank you very much.

I would like to thank all the speakers in the open public speaking session for being on time and informative.

Now we are going back to the form agenda which is a discussion on the in vivo BA/BE.

The first speaker in this session is Dr. Roman on clinical studies for local of nasal aerosols and sprays.

In Vivo BA and BE

Clinical Studies for Local Delivery

of Nasal Aerosols and Sprays

DR. ROMAN: Good afternoon. However, it feels more like "good evening" to me. My name is Izabela Roman and I am Medical Director and Founder of a contracting organization specializing in nasal study. I was involved in developing new drugs and studying generic products in nasal

allergy now for over twenty years, close to twenty years.

I would like to thank you very much for inviting me to help you with selection of a proper model of nasal study for the advisory board of FDA. I hope I will not disappoint you, that I will not present to you a novel, revolutionary model which will answer all the questions. We, as researchers of nasal allergy, are still struggling with the selection of the proper efficacy endpoints since we are still relying mostly on patients' reported symptoms and signs of nasal allergy which are very a variable and not very well standardized endpoint.

So, instead of presenting a completely new model, I will review the three proposed models in the draft guidance vis-a-vis their strengths, weaknesses and potential for bioequivalence studies.

[Slide.]

So, as you are all familiar, there are three well-studied models in nasal allergy; the so-called "park" study, the environment unit and traditional clinical study of seasonal allergic rhinitis. Each of them has their weaknesses and strengths and I will not go over, first of all, the detailed description of the basic principles that they can all be done double-blind, placebo-controlled, most of them parallel. That is all well known.

I also will not repeat the presentation of Dr.

Mary Fanning who did this overview in the June presentation to you in 1999. Again, I would like to present my opinion on the strengths and weaknesses.

[Slide.]

So the park study, so-called, which usually involves one or two days. It is a short duration of study which, of course, implies less weather variability and potentially better control evaluation of symptomatology and severity of symptoms over two days. However, of course, it does not allow us to study drugs with longer duration of action and drugs which will require, for a steady state, longer treatment than one or two doses.

It allows cohort enrollment, again potentially dealing with less environment variability and patient-to-patient variability since they are all exposed to the same concentration of allergens. Nonetheless, I believe this is not an easy way to deal when you talk about bioequivalence. It is too short a study.

Of course, it offers more control compliance. The drug is delivered by the medical staff, mostly by nurses or research associates, so we know how the patient took the drug, how it was delivered to the nose. It offers better compliance. It has a great potential for, of course, obtaining a greater number of time points for subjective and objective data, subjective, again, evaluation of symptoms of

patients' objective, potentially waiving the nasal tissues, collecting nasal washings, et cetera.

[Slide.]

However, it has a whole list of weaknesses. Again, it is restricted to seasons. Therefore, there are only three opportunities of conducting such trials in this country, at least; spring season, fall season and so-called cedar season in Texas.

I get mixed up a little bit, not looking at my slides. That is actually a weakness and I presented it previously as a strength that the drug does not reach effect. There is a weather risk. Frequently, it takes a long preparation to set up the studies, selection of patients and so on and so forth, and then rainy weather or stagnant weather does not permit you to conduct these trials.

There is a lack of site and population diversity. Again, it is done usually by one site--the other ones were done by two investigators--so it is less representative of geography and other sites in the United States. It is susceptible to single-investigator influence. Obviously systemic error done by one investigator carries through the whole study.

There is lower variability than the traditional study model--I'm sorry; that belongs to the strengths.

However, the next one is the potential for high incidence of sedation. It is a boring type study and if we study drugs which have a sedation potential, they are reporting in this type of study a lot of sedation.

Then it is not, of course, good for overall safety information.

[Slide.]

The type of study is most frequently used for pilot efficacy of new drugs, for onset of action, for dose-response or at least the approach of dose-response studies, and duration of the effect for single dose.

[Slide.]

In my opinion, as far as the bioequivalence potential of this, it is not very high particularly for the drugs which take more than two days to reach maximum effect. Usually, because of less variability in weather and between subjects, the treatment sizes are smaller than the traditional study, up to 50 to 100 patients per treatment group. 100 is pretty big in this model. And it is not inexpensive.

[Slide.]

The other proposed model is the environment unit. The strengths are very similar to the park model. Again, it is of very short duration so it is easy to conduct. It controls the environment. There is no environmental

variability. The concentration of allergen is controlled. It can be done all year around. It does not require seasons. It is also a good model for non-seasonal allergens such as cat dandruff.

[Slide.]

It is the farthest from reality. Of course, it is something completely artificial. It has a very limited number of center available. There are just a few in this country. The most well-known, actually, is Dr. Day in Canada. The whole duration is one day. The observations are over eight hours so it is just a single-dose type model.

The protocol is pretty complex. It requires priming of the patients for establishing baseline and severity of patients. Safety information is pretty limited from it.

[Slide.]

Again, it is more frequently used for onset of action, for pilot efficacy and for single-dose studies. However, this particular one offers a potential for the crossover studies. For short-acting drugs, which for bioequivalence purposes could be studied in crossover design, this is a model which potentially offers such a possibility for other drugs such as intranasal steroids which would require long-term treatment for maximum effect. It has rather low bioequivalence potential for using this

model.

Again, the treatment groups are much smaller than traditional, about 30 patients, and the cost is sky high.

[Slide.]

Finally, we are coming to the traditional clinical study. It is closest to reality. There are numerous sites around this country available to conduct such studies. It is well tested and quite well validated. It offers geographic diversification and, again, offers longer duration of observation versus the other models so we can observe steady-state efficacy and long-term safety.

[Slide.]

The weaknesses of this model is that it has high variability across sites, greater variability within a site due to the non-cohort enrollment. Some patients are enrolled at the peak season, others at the tail of the season, with different concentrations of pollens around. There is a lower sensitivity for detecting differences between the doses or vehicle or placebo inactive.

It is very much season-dependent. However, there is also a perennial rhinitis which could be potentially studied for bioequivalence. I don't think it will be a successful approach. And then, in this particular model, there is almost lack of total control over compliance since these intranasal drugs are very much technique dependent,

not to the same extent, of course, as an orally-inhaled drug, but still technique dependent.

The compliance in the study is in the hands of the patient and, very much, evaluations of efficacy depend on patient diaries and interpretation of the measurement used there which is severity of symptom scores with the best definitions from absent to more severe. Still it is patient dependent, how they evaluate themselves.

[Slide.]

It is most frequently used for efficacy and safety, for dose response and comparative studies.

[Slide.]

All of this is, of course, relative. But between the three models, I would suggest that this is the best model of all of the three for bioequivalence type studies.

[Slide.]

The problem with them is that, because of the endpoint insensitivity and variability, it requires large patient population size for treatment. Nowadays, it is about 130 and over per treatment arm and the cost is also substantial.

[Slide.]

So, in general, problems with in vivo bioequivalence studies, I would sort of summarize as follows; there is limited or lack of dose response. I do

not want to say that there isn't a dose response for nasal steroids or intranasal antihistamines. I believe that the limited way we can measure efficacy and variability and lack of sensitivity of this method does not allow for clear discrimination between the doses.

We have great difficulty in blinding. Obviously, all these products are delivered in devices which are patented specifically to the company producing them. In order to blind them, they have to be covered with something and there are a lot of problems with blinding them. The best way we can do it sometimes is just to have evaluator-blinded, not double-blind.

Vehicle and placebo responses make it quite difficult to distinguish between treatments. I just would like to bring to your attention that vehicle which is frequently used as a placebo for intranasal studies is a very effective treatment. In studies which we conducted in our group, we can prove a dose response to vehicle. Once-a-day vehicle is less effective than a twice-a-day vehicle.

So a vehicle is in higher doses, if you wish, or more frequent application, the efficacy is up to 35 percent change from baseline, which we usually use as an endpoint. Then, again, we are struggling with limited and non-standardized scales for efficacy measurements. Even with the best script, the interpretation of these scales by

patients that we are dealing with, and, of course, the sophistication of patient and user of such a method very much influences the results of the measurement.

[Slide.]

So, with this in mind, I would say that we have a changing nature of disease. We have a very variable environmental and mental conditions. We have subjective efficacy measurements and the spray-dose form is very much user-technique dependent, as I stated. So we have high variability and rather low sensitivity models.

[Slide.]

How I would suggest to improve this traditional study model; Again, as I stated before, the dose response is something which is quite difficult to establish with, particularly, intranasal steroids. So the requirements of doing two different doses to test the sensitivity of discriminating two doses is pretty hard. So vehicle control, which I suggested, is really an effective treatment and is, in my opinion, one of the arm of the dose-response treatments.

So, maybe just to make this more doable, vehicle control should serve as this noneffective dose, noneffective not in terms of active component but effective in terms of efficacy.

There are frequent designs using run-in period

with vehicle or placebo control sort of run-in period. We learned that this really decreases the baseline severity so, without run-in vehicle, we are increasing baseline severity and ability to discern differences in treatment groups. However, for a well-established baseline evaluation of symptomatology, some kind of just a collection of diaries and screening run-in is recommended.

[Slide.]

The last slide, which I will present, is real data. We conducted a study for a company with a generic intranasal steroid. The design of the study was traditional. What was done was a one-week run-in vehicle control, two weeks treatment, two doses of a reference product, two doses of the test drug and collection of the diary. Patients were evaluating their nasal symptoms scores and non-nasal symptom scores in a very classical way on a scale of 0 to 4.

We compared the overall results for two weeks to the baseline. So, in this particular study, the total nasal signs and symptoms expresses a percent mean change from baseline for the two weeks of treatment, for the lowest dose of tested drug, showed 21 percent improvement over baseline. The reference product showed 22 percent improvement. The high dose was 33 percent versus almost 31 percent for the reference product.

Now, for any physician looking at this, it will be quite sort of intuitive to say that, obviously, they are exchangeable or substitutable products since the efficacy there is quite close, or very close to each other. If they would be any closer, I would suspect that the data was cooked up. So I think that, in real life, that is exactly what we see.

As you see, the differences were not too big. However, because of variation of the methodology and so on, we have quite a bit standard error.

Now we applied, as requested by the FDA, the standards of bioequivalence for PK studies. So it was a 90 percent confidence interval as determined, and it is supposed to range 80 to 100 of target parameters, our normally distributed data.

[Slide.]

So, even with the therapeutic equivalence, the very close efficacy of this product, when compared, the confidence intervals were nicely distributed around 0, -8.3 to 6.2, but the at the 20 percent plus or minus as expressed as the delta 0.2 times reference product, the product did not make exchangeability criteria.

So the decision resulting from such a study--by the way, both of the doses showed statistically significant differences compared to vehicle or placebo. There was no

significant difference between the doses for most of the parameters. Still, this product would not, in some way, meet the exchangeability criteria.

My last suggestion is that the bioequivalence standards for PK studies should not be straightforwardly applied to in vivo trials and there should be some deliberation on what kind of standards should be developed for the in vivo trials.

Thank you very much for your attention.

DR. LEE: Thank you very much. At this point, I would like to announce a change in the program. Dr. Hartmut Derendorf also has to take an early exit, but I don't think he is going to Lubbock. He is going to talk about PK and PD studies for systemic exposure of locally acting drugs and, of course, the academic view.

Hartmut, I would like you to remain for a few moments after your presentation since you probably won't be here to participate in the discussion.

PK and PD Studies for Systemic Exposure

of Locally Acting Drugs

An Academic View

DR. DERENDORF: Good afternoon.

[Slide.]

It is a pleasure for me that I have the opportunity this afternoon to address some methods or some

thoughts on how pharmacokinetics and pharmacodynamics may help us to address bioavailability and bioequivalence issues of locally acting drugs. I want to point out that this presentation is jointly prepared by myself and my colleague, Gunther Hochhaus at the University of Florida.

[Slide.]

I would like, also, because of the limited time, only focus on inhaled corticosteroids and remind you of the scenario that we have. We administer the drug by inhalation. Our target site is the lung and this is where we have our local delivery. This is where we want to drug to go to. But we are all aware that then, after it has been active, it goes into the systemic circulation where it can cause systemic side effects. Of course, we have another entry via the GI tract where the drug can enter and we also have to address the issue of first-pass inactivation during absorption.

[Slide.]

So what we want to achieve in our treatment is a targeted activity with high local pulmonary activity and reduced systemic side effects. If you translate that into features of inhaled corticosteroid, that means we want to keep the drug in the lung as long as we can. We want to have low oral bioavailability so the portion that is swallowed shouldn't go in and what gets in should be cleared

quickly by high systemic clearance.

Furthermore, we want to have high plasma protein binding because only the unbound concentration will be systemically active. So these would be desirable features.

[Slide.]

I want to break down my talk into four parts to show you how we can use both PK and PD to assess both systemic and local exposure because when we talk about bioequivalence, what we want to achieve is equivalent rate and extent of both systemic and local exposure. That is our goal.

[Slide.]

So let's start out with PK as a measure of systemic exposure. This is really the easiest part of the talk because we can directly measure the plasma concentrations of our compounds. We have really benefitted from advances in improved analytical sensitivity recently so that we can, in most cases, measure our drug concentrations directly. For the assessment of systemic exposure, the route of absorption is irrelevant. It doesn't matter where it comes in through the lung or the gut. We are only interested in blood levels to assess safety.

[Slide.]

Just to show you some examples. This is one of our assays on fluticasone propionate where we now can

measure concentrations of 10 picagrams per milliliter in serum. As you can see, there is still room for improvements, that we can go to even lower concentrations. And it is possible today for all inhaled available corticosteroids to measure systemic levels.

These are some examples; fluticasone propionate, budesonide, triamcinolone acetonid and flunisolide resulting plasma concentrations after inhalation. I know that Les Harrison is going to show you some BDP data later on. So, really, that is pretty straightforward. We can measure the systemic concentrations directly.

[Slide.]

We can also do that, by the way, after nasal administration where the concentrations are lower. This is some of our data on fluticasone propionate, two different doses and the resulting concentrations that we observe.

[Slide.]

When we move on to pharmacodynamics as measure of systemic exposure, there are several methods that are used, most frequently cortisol. Cortisol is a good parameter because it is sort of the common currency of different corticosteroids so it allows us to compare systemic exposure from different steroids.

We have to watch out for the method that is used. It is very important that the correct method is 24-hour

serum cortisol at steady state has been proven as the most sensitive parameter whereas the other methods that are around, like 24-hour urinary cortisol or, particularly, 8:00 a.m. serum cortisol clearly are inferior in detecting the differences.

ACTH challenge is a different approach. It really doesn't measure the cortical suppression but it measures the responsiveness of the HPA access which really is not a major issue for the modern inhaled corticosteroids.

Other approaches are blood cells, which I will cover, and growth. Growth sometimes has been reported as being more sensitive than effects on the HPA axis. However, I am not convinced of that because it depends, again, on the method that is used for the assessment of the HPA axis. I believe, if it identify one correctly, then there will also be an effect on cortisol that can be observed in these situations.

[Slide.]

We need to keep in mind that a steroid is not a steroid, but that they have different receptor affinities. This is a comparison of the commonly used compounds. They are relative to dexamethasone which is 100. We can see that they vary quite a bit, keeping in mind that BDP, beclomethasone diproprionate, is an inactive pro-drug and is converting through the monoproprionate which, then, is a

very potent steroid, and fluticasone is about 18-fold more potent at the receptor site than dexamethasone.

So that needs to be taken into account.

[Slide.]

This is some recent data from our group comparing different treatments of budesonide and fluticasone in different doses. On the top, you have the single-dose administration. On the bottom, you have steady-state data after five days. And, in both cases, you have, in red, the placebo cortisol concentrations over 24 hours and, in white, the treatment group.

First of all, you see that, overall, the suppression of serum cortisol is relatively small. If you use the areas between the curves as a measure, we find, here, the respective percent suppression for the various treatment. They are statistically significant but, overall, they are relatively minor.

[Slide.]

One can, then, further go ahead and analyze these cortisol suppressions. We have developed a mathematical approach where we can model the circadian rhythm of cortisol. This is baseline data of healthy subjects; 1 day, 2 day, 3 day. Baseline, you see nicely the rhythm. And you see the line which is drawn by the equation that was modeled and fits quite well.