It can also be used to mathematically express the degree of suppression that we get with this equation and this model, then, allows us to predict how much cortisol suppression we would observe for various treatments.

[Slide.]

This is a study that we have done some time ago on triamcinolone acetonid after intravenous, oral and inhalative administration. We measured the kinetics and, based on the blood levels, then, model the effect on cortisol and just see, for all three treatments, that it works very nicely. The dashed line is the baseline pre-dose line and the other line is the suppressed curve measured and modeled.

[Slide.]

So this allows, us, then, then to make pretty good predictions, basically to translate the pharmacokinetics of the inhaled steroids, the serum concentrations, into the expected degree of cortisol suppression. Again, the best cumulative parameter to summarize this data is the AUC between baseline and treated group and express it in percent.

[Slide.]

We have developed a spreadsheet, an Excel spreadsheet, that puts all this information together and one location and one can, then, enter the drug, the dose, the

time of dose, which is important, and the device. Based on population average parameters, the program then will calculate an expected cortisol curve over 24 hours, calculate the percent cumulative suppression.

[Slide.]

We have, then, compared these predictions with a number of studies. All of these dots here represent major clinical studies that were not done by us. These are studies taken from the literature. We have shown a nice correlation between the predicted cumulative cortisol suppression based on the model that I have just shown you and the measured and reported data in the literature.

So, really, all we are doing is we are translating the kinetic information into the dynamic information and it is quite consistent. That makes sense because corticosteroids all work the same way. They have the same exact mechanism of action.

[Slide.]

Briefly, on other systemic-dynamic parameters, lymphocytes, the number of lymphocytes go down. This is from the same study that I had shown you earlier, 200 and 500 micrograms of fluticasone, single dose and multiple dose. You see, in red, placebo and, in black, the treatment group. Again, there is a significant decrease but of small magnitude.

[Slide.]

Only for the higher doses was it significant. The same was true for flunisolide, here.

[Slide.]

Similar results can be observed on the granulocytes, where we have the opposite effect. The number of granulocytes goes up, dose-dependent. This is flunisolide data here, 400 and 1000, single dose and multiple dose. In only this case, in the multiple dose situation, was it significantly different.

So, again, really, these parameters allow you to compare different compounds but they do not really improve the information that we get on systemic exposure if we compare two different formulations of the same compound.

[Slide.]

So, if we summarize this, if the issue is bioequivalence, we want to compare two formulations, we should simply take the plasma concentrations and no other data is really needed. Whereas, if we want to compare different steroids, that is a different question. And then 24-hour serum cortisol at steady state seems to be the parameter of choice.

[Slide.]

Now, let's move on the real hard question, and that is local exposure. How can we express local exposure.

How can we measure how much drug gets to the site of action in the lung. There are two different approaches. One is direct and one is indirect. Unfortunately, the direct measurements are limited to animal experiments.

Lung microdialysis is a very promising new technique where one can put a probe into the lung and measure directly the unbound concentrations. We are doing this right now in animal studies and getting very nice data but this is, unfortunately, not applicable to human studies.

Pulmonary-receptor occupancy; same issue. One can measure the steroid occupancy with binding assays. Again, unfortunately, this is only possible ex vivo and in animal studies.

The third direct way is gamma scintigraphy where one can follow the label. However, that has the downside that one would no longer study the original formulation but only after manipulation and introducing the label.

So we are really limited with indirect measurements but I hope that I can show that they may be of value. One way to go is to look at the pulmonary absorption profile after application of charcoal and deconvolution. So let's look at that a little more in detail.

[Slide.]

We have to keep in mind some basic pulmonary delivery concepts. First of all, before the drug is active

in the lung, and the steroid needs to be dissolved and get into the cell, the receptors on the cytosol. Also, only unbound fraction of the drug is active, so binding is an important factor.

Then, all of the drug that reaches the cytosolic steroid receptor then will be absorbed systemically. So, of all the components that are available so far, they will not magically disappear but, then, the next step is systemic absorption so one can really not have one without the other.

Thirdly, one should be very careful in looking at the literature not using total tissue concentrations, not using biopsy numbers, because they are hybrid numbers and reflect the sum of the drug in the tissue and are very difficult to interpret quantitatively.

[Slide.]

Furthermore, it is important to keep in mind that the delivery efficiency is a very important factor. This is a simulation to show that if you increase the percent of the drug that is delivered into the lung that, then, the targeting will be improved.

If you compare two compounds with an oral bioavailability of 10 percent, drug A, and an oral bioavailability of 0, drug B, then, if 10 percent gets into the lung by our device, that means, then, the systemic variability for compound A will be 19 percent, 10 percent

coming from the lung and 9 percent is 10 percent of the remaining 90 percent, so that adds to 19 percent, whereas for compound B, it is only the 10 percent that goes to the lung which is a ratio of 1.9.

If you improve, for the same compounds, the delivery to 30 percent and do the same calculations, you end up with 37 percent systemically and 30 percent, and that is a ratio of 1.2. So the oral bioavailability becomes less of an issue the more you deliver to the lung. That makes sense.

[Slide.]

So how can we differentiate, when we inhale, how much of the drug goes in through the lung versus the GI tract. There are three approaches. One is to simply use a drug that doesn't have any GI absorption. That is, of course, the easiest way. Or, if it is to block the GI absorption with charcoal, the third approach in the literature is utilize early time points where the pulmonary absorption is dominant and oral absorption is not yet very large.

[Slide.]

Fluticasone propionate will be an example for the first case where we have oral bioavailability of less than a percent, or around 1 percent, so one can assume that the vast majority of the drug that shows up systemically comes

from the lung.

[Slide.]

Charcoal has been used to separate the route of entry. This is a study on budesonide where two devices were compared, Turbuhaler MD-MDI, with and without charcoal, and, by calculation, then of the different profiles, one can show that the contribution from the lung and the GI is different.

[Slide.]

This is the Turbuhaler here and we see that the fraction that is coming through the lung is much, much larger than from the MDI by comparison of the absorption with and without charcoal. If one does it right, if the charcoal application is optimized, one can almost completely, or completely, block, the absorption.

[Slide.]

This is an example from not a steroid but terbutaline. Oral bioavailability with and without charcoal where it was possible to block the oral route almost completely.

[Slide.]

So, what one can do now is to really find out how the drug enters the body and also describe the time course of absorption and, thereby, the time course of pulmonary residence, is to use old-fashioned pharmacokinetics. What is needed for that is a good characterization of the

disposition which one only can get by an intravenous study.

So, if an intravenous study is done and the kinetic parameters are determined, like in this example of fluticasone propionate, and then a clearance of distribution is calculated after IV administration, then an inhalation experiment is made and, again, the kinetic parameters are calculated.

This is here an example from several studies from our group and others on the resulting profiles. And then you can use pharmacokinetic concepts such as deconvolution.

[Slide.]

This is one example, the so-called Loo-Riegelman method, allows then to calculate an absorption profile which is the rate of entry. If you block with charcoal, or have a drop that is not already absorbed, it is equal, then, to the pulmonary residence time--

[Slide.]

--you end up with a profile such as this absorption profile. It is percent absorbed versus time that allows you, then, to characterize and compare, in this case, different compounds but also different formulations of the same compound and would mirror, then, what is going on in the lung.

[Slide.]

One noncompartmental way to express the same data

is to use a mean-residence-time approach where, again, you need the intravenous data, calculate the mean-residence time after intravenous administration and after inhalation. If the inhalation is only through the lung, then the difference between the two will be equal to the mean absorption time or also equal to the mean pulmonary residence time. You would have a quantitative way of comparing.

[Slide.]

The fourth way, and the one that we have heard in the previous presentation, is to use pharmacodynamics as a measure of local exposure. I think the data that we have seen so far are very discouraging because, for the small differences that we want to detect, particularly in bioequivalence studies, the variability is very high and, therefore, the ability to discriminate between products is limited.

Another way to go would be to use surrogate endpoints. There is a lot of work that is being done right now to identify surrogate endpoints for steroid activity and it is the big hope that, one of these days, we will find one that is really reproducible and can, early on, tell us what we can expect after chronic use of the drug.

But, so far, unfortunately, there is none available that is really of that quality.

[Slide.]

So, I believe, right now, pharmacokinetics is our best bet and I believe that it is much more than just a measure of systemic exposure, that if you use kinetics correctly, that it is able to give us information about the local exposure as well so that one approach to tackle bioequivalence problems with inhaled corticosteroids is, first of all, of course, to have in vitro studies--and that was the discussion we had this morning--to come up with good criteria about in vitro equivalence.

After in vitro equivalence is shown, then follow up with in vivo studies where equivalent systemic exposure needs to be shown, and that can be done by just measuring plasma concentration, and equivalent pulmonary-absorption profiles that can be shown by showing equivalent absorption profiles using deconvolution methods.

Obviously, the details would need to e worked out and, very difficult, the goalposts need to be defined which will be quite a challenge.

[Slide.]

Would like to close by thanking all the people who have contributed to this data and thank you for your attention.

DR. LEE: Thank you, Harmut. I just wonder whether or not the subcommittee members have any questions.

I wonder whether or not you have looked at the

questions for discussion. Maybe, in a way, you have answered this question, which is, are there situations where the in vitro data plus systemic PK and PD data can be relied upon to assure local drug delivery for either nasal or inhaled drugs?

DR. DERENDORF: Yes; I believe that that may be possible, that if you use the data well, that we can make the conclusion that there will be sufficient--unfortunately, we don't have any better ways right now to approach this. If we would have a surrogate marker, a pharmacodynamic surrogate marker that would be easily quantifiable for the local activity, certainly that would be even better. But it is not out there.

So I think what we have right now, this seems to me the best approach.

DR. LEE: Were all the data you presented human data?

DR. DERENDORF: Yes.

DR. LEE: Thank you.

DR. BEHL: One quick comment. Even if you have some data that goes to the correlation of PK and PD, it is very hard for me to believe that PK can be used as a means to judge local effect.

DR. DERENDORF: What we are trying to do here is--we have two different issues here. If it comes to

bioequivalence, the traditional, or the approach that it used with bioequivalence for systemic drugs is if we show equal or equivalent exposure within a certain range with certain confidence, then we imply that the effects will be equivalent.

This is exactly the same approach that I would propose here. There is no need, in my opinion, for clinical studies. The systemic equivalency can be done just by traditional comparison of plasma concentrations. The more difficult part is the indirectly characterization of the local exposure that could be done by absorption profiles.

So, just as with any other bioequivalence, really, there is no need to measure any kind of pharmacodynamics if you follow the same logic that the same exposure profile will result in the same effect.

DR. AHRENS: You made the statement that systemic exposure, if you are using the same compound that you are inhaling, that you only need pharmacokinetics, which makes great sense to me, perhaps, except for beclomethasone because of the fact that there is more than one active species and the absorption profile, the plasma profile, for BDP may not be same as between products and BMP.

How would you handle that? Can you do that with kinetics alone?

DR. DERENDORF: Yes; I fully agree with you. I

think the concept still holds. It is more complicated to do because you have several players which you need to interpret and measure all of them and then add up the numbers.

Again, this is not new. There are other drugs for systemic use where you have active metabolites and the same issues exist there in bioequivalence situations. But, yes; of course, you would need to measure the active metabolites and interpret them correctly.

DR. LEE: I think that we ought to let him go. We will come back to this towards the end. Your taxi is waiting for you out there.

Let me talk about a few logistic changes because of the shift in the program. We will now take a break and I would like to come back at 3:25, about ten minute. When we come back from the break at 3:25, Dr. Richard Ahrens will be presenting his view on clinical studies for local delivery of orally inhaled corticosteroids. And then the surveillance will go into discussion. Then we will come back on line with the rest of the schedule.

Thank you.

[Break.]

DR. LEE: Before I turn the podium over to Dr. Ahrens, I would like to alert the clinician members of the committee to begin thinking about addressing the three questions in the upcoming sessions.

Dr. Ahrens will be talking about clinical studies for local delivery of orally inhaled corticosteroids.

In Vivo BA and BE:

Clinical Studies for Local Delivery

of Orally Inhaled Corticosteroids

DR. AHRENS: Thank you.

[Slide.]

This is the point where I am, of course, supposed to say I am happy to be here. It is particularly true this time because the topic I am talking about here is an area that I have been interested in for more than a decade in terms of the general issue of the assessment of bioequivalence of inhaled drugs used to treat asthma.

[Slide.]

The task of these clinical studies that I have been asked to address is, first of all, to address the issue, predominantly, of generic equivalence to determine whether the innovator and generic inhaled corticosteroid deliver bioequivalence quantities of drug to the site of action in the lungs. In other words, even if there is a difference in quantity delivered to the site of action, that that quantity is not large enough to make an important clinical difference.

The same approach to addressing this certainly could also be applied to reformulations that are not

intended to be pharmaceutically equivalent, although, there, it would be determining rather than proving bioequivalence, determining the ratio of doses that are required to deliver equivalent quantities of drug to the site of action.

For example, if an FHA inhaler delivered two or three times as much drug to the site of action as an innovator CFC preparation, that may well be okay and approvable but, still particularly important, at least in my opinion, that the clinician knows what that ratio is so that he or she can adjust the dosing strategy appropriately.

[Slide.]

So the concept of how to address this issue of bioequivalence. As we have heard earlier, there is a lot of variability in clinical studies, particularly with inhaled steroids, addressing the issue of bioequivalence.

The typical approach that I think is now reasonably well established in precedence, at least with beta agonists, is to look at formulations along the dose axis rather than the response axis; that is, rather than looking at a comparison or responses, are they equal or not to a given dose level, coming up with a ratio of doses that are likely to produce equal responses.

This is, in essence, using a pharmacodynamic response, in this case a clinical outcome, to bioassay the quantity of drug delivered to site of action. So, in a

sense, I have difficulty separating, in this context, the issue of clinical study from a pharmacodynamic study because they are getting after, in a sense, the same thing; are we delivering, within the realm of not making a bit clinical difference, an equivalent quantity of drug to the site of action.

[Slide.]

This issue of using the dose axis rather than the response axis is something that has a history relating to albuterol, generic albuterol inhalers. Albuterol, of course, went off patent in 1989. The initial studies that were done to try to address bioequivalence of inhaled albuterol, in fact, did look along the response axis figuring that if you showed equivalent response to two different inhalers at the same dose that they must be bioequivalent, looking, in this case, at bronchodilitation.

At the prompting of some people, including myself, a control was put in these studies where the innovator product had more than one dose level. Then, in 1992, when everybody got back together to look at the results of those studies, in horror--Wally, I hope you agree with this history; this is at least my interpretation of the history--to everyone's horror, they discovered that the studies couldn't discriminate between different dose levels of the same product. And, if they couldn't do that, then how could

they be expected to differentiate different doses delivered by different products.

That led to a search, more advisory committee meetings and a search over the next several years for acceptable and valid methodologies to accomplish this and, ultimately, to the approval of the first generic inhaled albuterol, at least in terms of the in vivo study, a bioassay study, demonstrating bioequivalence.

[Slide.]

So the concept here, in essence, is to perform more than one dose level to at least on preparation, preferably both. In this case, this is a so-called two-by-two bioassay because there are two doses of each preparation. And then, instead of looking at a comparison of responses, to look, essentially, at the distance between the dose-response curves.

This is the ratio of doses that will produce an equal level of effect. If it takes twice as much to produce the same effect, that test preparation would, therefore, be half as potent.

This is an old concept dating back, probably, to the forties. With well-established validity criteria, you have to have a significant dose-response curve, dose-response relationship, to act as a standard curve. If you don't, you don't have a valid bioassay. You need to have

responses that are in the same region--that is what this means--and the response curves, of course, need to be parallel.

With two inhalers delivering the same product, at least, hopefully, you would expect that to be the case.

[Slide.]

We applied this approach, in my laboratory, to Baker Norton's product. This is the product, the first generic albuterol that was approved, using these data as the in vivo demonstration of bioequivalence.

We looked at a response to histamine bronchial provocation, PC20 FEV 1 versus dose, down here. As you can see, the curves largely coincide. And then we applied bioassay statistical methodology to come up with a confidence interval. As you can see here, that was 0.69 1.40. This met the concurrently established bioequivalence criteria of being between 0.67 and 1.5, essentially between two-thirds and one-and-a-half times as potent since the entire confidence interval was within that range.

[Slide.]

That was the analysis that we did using so-called Finney bioassay. The FDA, I think for very good reasons, chose a somewhat different statistical approach which they called a dose-scale approach. We used two doses of each preparation. They, instead, chose to use the reference as a

standard curve and then compare one dose of the test preparation at a time.

The curve-fitting methodology was a little bit different. The method for establishing the confidence interval, we used Fieller's theorem as part of Finney bioassay which relies on normal theory whereas they chose to use the somewhat more robust methodology of bootstrap which doesn't require normality.

It was comforting to find that the results by these two methodologies were virtually the same.

[Slide.]

So that is the concept, at least as it was developed in addressing inhaled albuterol. Now the problem at hand is that this kind of bioassay approach has rarely been applied to inhaled corticosteroids because it is not very easy to do.

Furthermore, when it has been applied, it has really met with very limited success. On the next slide, I will give you an example of that.

[Slide.]

This is, in my humble opinion, the best bioassay study, if you will, comparing inhaled corticosteroids. It was a study done by 3M in the approval process of their HFT BDP product comparing it to CFC BDP. This was an exceeding rigorous clinical trial, clinical study, which involved

hundreds of subjects each of which came to the clinic at least five days a week to perform lung functions in many ways that are beyond that. It was an extremely rigorous, carefully done study, not a typical study.

They did succeed in estimating a potency, a dose ratio, that each microgram of HFA is equivalent to 2.6 micrograms of the CFC product. However, if you look at the confidence interval, it stretched from 1.1 to over 11.0, essentially, not a very clinically meaningful confidence interval if it is over a ten-fold range.

The fact that it didn't encompass one indicates that, at a statistically significant level, these two preparations are not equivalent. It does not, even with the best study that has been done to date, give you a clear answer as to exactly what that potency ratio is, what the bioequivalent dose is.

[Slide.]

This issue has been addressed by a number of people, but, in this recent review by Peter Barnes and Bill Busse and Soren Pedersen, first of all, they noted that this was true that, in spite of dozens of studies that are in the literature, it is very difficult to draw firm conclusions comparing comparative efficacy.

It is hard to say that anything is different from anything else in the way studies have been done and relate

that to things like study designs, control over important confounding variables and, last but not least, the lack of a strong dose response relationship for inhaled corticosteroids.

[Slide.]

That leads to the common wisdom that the problem with inhaled corticosteroids is that the dose-response curve is just so darned flat that you really can't detect any differences.

If this is really true, that the dose-response curve is that flat then, first of all, the dose delivered really doesn't seem to matter much, clinically. If you can't tell a difference in dose, that may mean that the dose doesn't really matter.

If that is true, then you don't need to, and, in fact, can't really do a valid bioassay using the concept that I just described simply because you don't have a valid significant dose-response curve. Therefore, you don't have a valid bioassay.

[Slide.]

You could, therefore, simply rely on clinical trials going back to the concept of comparing responses. By the way, this "no" doesn't belong there. My apologies. Cross that out. You could use a clinical trial showing that two formulations yield similar responses.

That is in fact what was done. This is a recent publication which was presenting data that was at least part of the basis on which a Baker Norton HFA product was approved in the U.K. You can see, they studied morning peak flows here in a group of mild, not so well-controlled, asthmatics and more severe asthmatics. These are actually two different studies, hence the different doses of BDP.

You can see that there are no significant differences in response. Unfortunately, failure to show a significant difference in response is not at all the same as proving the two things are the same. This has lead to a good deal of consternation, I am told, by Dr. Ganderton and others in the U.K. as well as what I understand is a record number of letters to the editor to respiratory medicine particularly when this study and the fact that the Baker Norton product was approved on a one-to-one, a one inhalation equals one inhalation basis, with the next study.

[Slide.]

This will be familiar to you. This is the 3M study I showed you earlier which shows a difference, a significant difference, in potency. I have it on good authority, although I could not vouch for it myself, based on what was in those letters to the editor and other discussions that have taken place, that these two inhalers are very close to being pharmaceutically equivalent.

If that is true, that is what has led to the consternation in that how could one be approved on a one-to-one basis and this one be approved in the U.K. on a two-to-one basis, two inhalations of CFC is equivalent to one inhalation of the HFA.

[Slide.]

That leads me to the following question. That is all based, by the way, on the fact that the dose-response curve must be just so darned flat. That is what the letters to the editor really addressed, that you really can't do what the Baker Norton study did but there isn't, necessarily, a good way to get around this problem.

I might just stop here at this point and say what everybody says, it is just really hard to deal with inhaled steroids so clinical studies may be not that useful.

I would like to now ask the question is it really true that inhaled steroid dose-response curves are just that flat.

[Slide.]

What has got me originally thinking about this is what I will label here as the asthma clinician's paradox. That is, in clinical studies, multiple clinical studies, with hundreds of patients, it has been very difficult to show anything but a very flat--dose-response curves that are flat to nonexistent.

On the other hand, clinicians think they see inhaled dose-response relationships in the clinic every day in individual patients. Both of these cannot be true. One says there is no dose-response relationship. The other says, at least in some patients, there is an important, clinically important, dose-response relationship that we all see.

[Slide.]

So the question is, which is allusion and which is reality. I would like to make a modest proposal here, for the remainder of my talk, as to what the answer to this may be. I will start out with this quote: "Good judgement comes from experience. Experience comes from bad judgement." I think we have all experienced that from time to time.

"Furthermore, experience teaches you to recognize a mistake when you have made it again."

[Slide.]

What I would like to propose to you here is the that the typical inhaled corticosteroid study design which has been used over and over again with various modifications but the same basic theme, in dozens of studies, is a mistake that we keep repeating over and over again.

The typical study, as most all of you will recall, is a parallel group study lasting varying lengths of time but at least for a month or two. The general approach is

that you take baseline data in poorly controlled asthmatics and then do something that none of us really do very often as clinicians, is just place those poorly controlled asthmatics on a inhaled steroid and wait for them to get better of subsequent weeks, and then measure their response.

This is marked by very high variability in response, the very shallow dose-response curves that we have talked about and a tremendous reluctance to do crossover studies because of the prolonged treatment time potential carryover.

[Slide.]

Let's take a little further look at just what it would take to do a good bioassay study using this kind of methodology. I am not going to go into detail at all here although, perhaps, Dr. Hauck and others would like me to as to what methodology we use to do sample size, statistical power and sample-size calculations.

For here, it is not a straightforward matter but something that there have been some recent publications on and my biostatistitican, Dr. Singh Ho Hahn and I, have done some work with. But, I will suffice it here to say that it is not related simply to the variability of the response. It is also related to the steepness of the dose-response curve and, in fact, those two things do not function independently. They function as a ratio.

The smaller that ratio, the more powerful and discriminative the study.

[Slide.]

So we did some sample-size calculations with assumptions that we were going to try to demonstrate using two one-sided hypothesis testing, that a generic between 0.5 and 2.0 times as potent as the innovator, typical alpha and power level using a two-by-two bioassay study design, two doses of each preparation.

[Slide.]

Here is the S over B ratio that I talked about earlier. Sample size calculated--this is using the data from that 3M Busse study--looking like it would take in the neighborhood of a thousand patients to really fulfill that goal. This was an exceeding rigorous and difficult study to do. I don't know for sure where typical studies are, but they are probably--most other studies are up here someplace.

That is not a very practical number of patients to do, particularly if you are a generic company trying to get a product approved.

[Slide.]

Because of this problem, we launched into a pilot--well, actually, we did a number of pilot studies searching for the holy grail of a better outcome measure that would give us greater reproducibility. This was part of that

series. It was a study that we did in collaboration with 3M using their HFA preparation.

We did it as a crossover study and we justified that in terms of dealing with carryover by the following, by giving a prednisone burst at the beginning of the study to essentially maximize carryover in patients, give everybody, as near as we could, maximal steroid effect by maximally improving their asthma.

That, in fact, models what clinicians do all the time. If we see a patient who is in trouble with their asthma, we generally give them a course of oral steroids and then start them on their inhaled steroid to maintain that control.

We then looked at the stability of asthma over the subsequent three weeks, looked at virtually every outcome measure, again, in search of that holy grail, that we could think of expressed in every way we could think of for a total of 58 different outcome variables searching for the lowest S over B ratio.

[Slide.]

What we found was that, in this model, some outcomes were terrible. There are some that are even up here further, but look at the computed sample size here over S over B ratio. We are up in the thousands.

I had this great idea that if patients got up at

4 a.m. routinely, set their alarm and did their peak flow meters, that that would model morning dipping and that would give us a good response. Not only did it not work, it got a lot of patients angry with me. That wasn't a very good idea.

Here, you can see maybe your other favorite outcome, and there are others on this list, that didn't work very well. I would now like to zoom in, down on this corner down here.

[Slide.]

Computed sample size; now, we are dropping down to 100 or under. To my surprise, the best outcome measure was, essentially, morning home spirometry. We had a portable electric spirometer that gave us FEV 1, FEF 25, 75, as well as peak flow. I am not sure that those differences are so really important as the fact that it was upon-awakening morning spirometry that turned out to give us the best power.

But the remarkable thing is that it appears, in contrast to that Busse study I showed you earlier, you could achieve this sort of thing with 100 subjects or under.

[Slide.]

Now, I think, the most important issue with this. Here are those same points that I just showed you down here with the best outcome measures. Here are the same outcome

measures using the same pilot data but now doing sample-size calculations for a parallel study, as if we had done this as a parallel study rather than a crossover study.

It become apparent to me that these data suggest, at least, that the problem with the traditional study that we have done--there is the Busse study right in the middle of it--of the outcome measures that turned out pretty good in a crossover study.

The real study is not the outcome measures. The problem is the study design. It is a parallel versus a crossover study design.

[Slide.]

We are not the only ones to have stumbled upon this although I think the implication has not been quite so clear. This is a study done by Soren Pedersen a few years ago looking at exercise-induced asthma in children, again, a small number of children, yet got a highly significant dose-response relationship.

By the way, in that study I just showed you with those best outcome measures, the dose-response relationship is with only twelve subjects. It was less than 0.0001.

There is nothing new under the sun. It is not exactly a great revelation to Dr. Hauck that crossover studies are more powerful than parallel studies. That is old as the sun. So that is not exactly a revelation and yet

I think what is a revelation is that, in no place does it seem to be more true than in dealing with inhaled-steroid dose-response relationships and comparison of preparations.

I think this may be the answer to this asthma clinician's paradox that I showed you earlier. It may well be that there are very real dose-response relationships in individual patients, that we are not deluding ourselves when we think we see that. What these data suggest is that that very real response, in at least some patients, gets lost in a great deal of interpatient variability between asthmatics which we, as clinicians, also, all know is there.

[Slide.]

So, in summary, the task has been to develop a capable method of demonstrating in vivo bioequivalence for inhaled steroids. The concept I have presented is to use a clinical bioassay dose-axis comparison. The common wisdom is that the dose-response curve is just too darned flat to really do this. I am presenting an iconoclastic potential alternative that the real problem may just be that you can't do this if you are going to persist in doing parallel studies.

[Slide.]

The solution may be to not say we can't do crossover studies because of carryover. For heaven's sake, most parallel studies have to deal with carryover because

many of the subjects came into those studies already on inhaled corticosteroids. There is carryover there to begin with. So it is not a matter of getting rid of carryover so you don't have to worry about it. It is a matter of how to control it.

We presented at least one method by starting each treatment period now with a wash-out but with a wash-in, with a burst of oral steroids to minimize the potential for carryover to be able to do these crossover studies.

This should allow accurate assessment of bioequivalence if it really works with tens to hundreds rather than thousands of patients. However, the proof of the pudding is in the eating. This is just a pilot study.

There hasn't been a study that actually has accomplished this yet. You will have to wait for that, this is the commercial message, it is no great surprise that I continue to look for additional opportunities, collaborative opportunities, to address this issue.

Thanks for your attention.

DR. LEE: Thank you very much, Dr. Ahrens. I invite you to take the hot seat and maybe entertain some questions.

Subcommittee Discussion

DR. LEE: We now go into the discussion period. There are two major groups of questions to be addressed

following the two presentations, one on nasal aerosols and sprays and the other one on orally inhaled corticosteroids.

In order to keep the momentum, let me propose that we take on the second group of questions first which is, "Clinical studies for local delivery of orally inhaled corticosteroids, ICS." These are two questions that the agency would like to get input on.

The first one is, "A number of approaches have been proposed to assess bioequivalence of ICS." You have heard some of those. The question is, "Are any of these study designs proven to offer better discrimination in terms of dose-response sensitivity?"

Here, we will look to the clinician colleagues on the committee to guide us.

DR. LI: I will make a comment. I appreciate the discussion that we have had so far. I think that one of the issues with the dose-response for inhaled corticosteroids has to do with the usual doses at which we conduct our studies and the usual doses that we use in clinical practice. Those doses tend to be on the high end where we get a maximal or a near maximal benefit. That may be clinically appropriate.

But I think that the differences between preparations or formulations may be more apparent at the lower end of the scale. So one of the suggestions that I

have heard that makes some sense is when conducting a dose-response study to use lower than usual doses to see if differences can be apparent at the lower doses rather than at usual doses.

DR. SZEFLER: This is an area Richard and I and a number of people have discussed for a number of years. The markers that seem to be attractive are exercise-induced asthma, exhaled nitric oxide and then I would toss in a third one which would be bronchodilator reversibility.

We are in a process now with the Asthma Clinical Research Network of testing these in kind of a different model. It is a little bit different than what Richard proposed and we are trying to match up efficacy measures with levels of cortisol suppression because, I think as you pointed out earlier, you could do one measure and compare it to another.

We kind of took the position of trying to assess each of the individual steroids for levels of cortisol suppression and then take those doses for given levels of cortisol suppression and look at efficacy. We are now kind of ending the third phase of that trial and we will have some answers on that. But at least looking at the literature, the things that seem to be appealing are the study that Richard mentioned in terms of exercise-induced asthma.

Exhaled nitric oxide, there are a few studies on that, but people don't look at that as kind of a--it is not acceptable yet as a surrogate marker of inflammation. It is a nice bioassay, maybe.

The third one that I am kind of intrigued with looking at that seems to be surfacing as a potential marker of response is beta-agonist reversibility. So there are three that I think I would look at. The other ones, like FEV 1 and peak flow, the changes appear to be small.

John Toogood, early on, had identified that very low doses can achieve your maximal effect but you need higher doses to get more at the exercise-induced areas.

If you look at other levels of reactivity like methacholine and histamine, you just can't differentiate changes. That is probably because they are very slowly reversible.

DR. AHRENS: The fact that, in what I just said here, I emphasized the basic study design, parallel versus crossover studies, doesn't diminish the importance of selecting the right patients and choosing the right outcome. In terms of the issue that was just brought up about patients being often at the top of the dose-response curve in typically clinically used doses.

For many patients, that is clearly true, even at the very lowest dose. There are certain patients that it

takes almost--the biggest step in the dose-response curve goes from nothing to something. Once you get to that, anyplace else you go in the dose-response curve doesn't have much effect.

For those patients, probably the dose-response curve is very flat and the dose probably doesn't make a big difference. A broad difference in dose delivered probably wouldn't hurt those patients. But there are other patients where the dose-response curve really is steeper. For sake of time, I didn't go into the details for this pilot study, for example, what patients we selected. But they clearly were steroid-dependent patients in the sense that they were not well-controlled unless they were on substantial doses of inhaled steroids.

There are clues in other studies that have been done that those patients are not a tiny minority, though, that there is a substantial percentage of those patients around. It is those patients we need to protect by having properly done bioequivalence studies and, therefore, it is those patients who really ought to be the subjects for those studies.

So it isn't a matter of--what you said, James, I think is correct that, for some patients, even at typical clinical doses, they are at the top of the dose-response relationship. But I don't think it is true for all subjects

and we ought to be able to develop entrance criteria to studies to identify those patients during run-in periods.

DR. SZEFLER: There is some appeal, in terms of your model from the ethics standpoint and the availability. We try to recruit those patients and they are a challenge to find because now of the extensive use of inhaled steroids and also because of some of the problems we run into with institutional review boards in terms of delaying treatment and observation period.

So the attractiveness of your model is that you can treat that right away and you can even take patients who are in inhaled steroids because you are escalating the treatment and then you are withdrawing and watching carefully. So there are some ethical and, also, some availability in terms of numbers of patients to look at that offer some attractiveness in terms of your model.

DR. AHRENS: Stanley, you brought up the issue of what outcome measures to choose. I think that is also an important issue, that there are some outcome measures that are clearly much less discriminative than others.

For what it is worth, it was only a small pilot study, but bronchodilator reversibility was one of the things that we looked at in the study and it didn't come out very well. I was amazed that one of the simplest things, just doing morning peak flows, is what turned out to be as

discriminative as anything. We didn't do exercise in the study. It is certainly more cumbersome to do, but, based on Pedersen's data, that also is right if you use his data to do the same sample-sized calculations. It is right in there with the morning spirometry, the peak flows that we looked at.

It is not a lot better, but it is not worse either. I think it is an alternative kind of model.

DR. SZEFLER: In our studies, we were really trying to answer the question, are steroids different. I think the question we have facing us today is, given a steroid with a different delivery device, is it equivalent. So it is kind of the opposite end of the spectrum.

So then you get into setting the goal posts with the model in terms of what is acceptable, tight goal posts or wide goal posts and everybody can kick a field goal.

DR. AHRENS: I guess I would respond to that by saying the handling of those two situations is slightly clinically different but not that much. In one, you want to make sure, based on two one-sided hypothesis testing, that the confidence intervals are inside the goal posts. For the other, you don't have goals posts. You just want to know what the truth is. If something is three times a potent, you want to know that but there, again, you need to have the same kind of confidence limits.

If you wanted to know between half and twice as potent in terms of proving bioequivalence, if something is three times as potent, you really want to know, okay, my estimate is three times. Is it 1.5 to 6.0 or where? You want to narrow the confidence interval on that estimate, wherever it is, to the point where it is clinically useful and not tenfold or more wide that isn't clinically useful.

DR. LEE: Let me interject here and ask the question, is there any discriminatory study design known today?

DR. AHRENS: Based on what I have presented here, It should be obvious my opinion is, in terms of things that have been done and proven and used in this kind of-- validated by having actually been used and been successful, no. What I have been holding out here is that I think there may be some promise looking at things a bit differently than in the past.

But that still may be entirely doable. But it has not been done yet, to the best of my knowledge, in a way that would be truly usable for bioequivalence.

DR. LEE: So would question B2 be a logical follow up to that, looking for surrogate markers that might be sufficiently sensitive?

DR. AHRENS: As I think I was just saying, my opinion to that is that that is an important thing to do

but, in itself, insufficient. We did a grand total of, I believe it was six pilot studies searching for that holy grail of what is the best outcome measure to make this problem go away. It was in the sixth study, the sixth pilot study, that we finally came around to the idea that the problem really may not be the marker. It is the basics of the study design.

That is important, but I think you are going to have to come up with a way to do a crossover study or you are never going to be able to use this in a bioequivalence kind of approach, in a bioassay kind of approach, like was done with albuterol, and apply that to inhaled steroids.

You can decide that you don't really want to do that, that it is more trouble than it is worth. But if you want to do it, then I think that is what it is going to take.

DR. LEE: Other points or opinions? Could it be because we don't understand the disease stage well enough?

DR. AHRENS: Stanley, do you want to respond to that?

DR. SZEFLER: I think we understand its manifestation. We don't understand totally its etiology. But I think the variability is a problem. We would like to think it is not product related and so we trust that the products that we are working with would limit that

variability. But I think it is the disease variability that makes it statistically hard to sort out.

DR. AHRENS: An asthmatic is not an asthmatic is not an asthmatic even if you bring them into the study like is often done within the same FEV1. Their FEV1 is between 50 and 70 percent of predicted, or whatever the criteria are. You still, even though you do that, get some very different people in terms of their characteristics of their asthma and what apparently is the case in terms of their responsiveness of inhaled steroids in that kind of study.

DR. LEE: Thank you.

Lester?

DR. HARRISON: We certainly support the crossover study design as well. It is very appealing to us and, based on our knowledge with BDP, it seems the way to go. We would be very encouraged if you would--somebody would--actually do the real definitive study and prove the point.

We were involved in the pilot study but that needs to be taken the next step. It did seem like it has the potential to actually discriminate.

DR. LEE: Very good. Wally, do you have the information you need?

DR. ADAMS: Yes. I think that is helpful.

DR. LEE: Okay; great. Let's move on and talk about question A1 and A2 which are similar to the ICS

situation. You may recall Dr. Roman's presentation about the three models and the same question was posed to see whether or not is it feasible to demonstrate a dose response for locally acting drugs using any one of these designs.

Let me see what the committee has to say.

DR. BEHL: From what I have seen so far, and it is for question B1, B2 questions also on the steroids, the dynamics of locally acting compounds in the nose and in the lung are such that I don't see how one could replace the need of, if not a full-scale clinical trial, then at least a bridging clinical trial to show that, after showing all the pharmaceutical equivalence of the product and other equivalence that can be easily shown, that the results of therapeutically equivalent.

I don't see what we know today, in terms of valid approaches which can be used in lieu of, if not a full-scale, then a bridging clinical trial.

DR. LEE: Any opinion? Dr. Roman, you would like to respond?

DR. ROMAN: Yes. I agree, actually, that the crossover is a much better design in terms of controlling some of the variability. However, I cannot, at the moment, imagine any crossover design for nasal-allergy studies which are very much depending on season and shortness of it, if you wish.

Of course, the fact that the endpoint measurement is not so reliable as the pulmonary-function test, the rhinomometries. I don't know if it is in infancy or agony. I am not quite sure which phase of this we are observing, but it is not a very reliable method so far.

So I would be very hard-pressed to come with a design which will be as elegant and interesting as Dr. Ahrens. Another thing if, if I may ask and think here, will this--you see, the problem is that most of the reference drugs do not show much of the dose response in their full development programs.

So the companies will have to do the reference-drug study tests as well as the dose responses in addition to the tested drugs.

DR. DALBY: In the hierarchy of acceptable testing, you have the clinical test and, if that is found to be nondiscriminating, you drop down to the in vitro tests. It seems to me, although, again, it is not, perhaps, a population thought that the intermediate ground is the scintigraphic study of deposition which at least incorporates the anatomy of the nose, and it is not such a big stretch, in my opinion, to go from if the drug is depositing equivalently in two formulations, that it will act equivalent and it is not necessary to fall straight down to the in vitro tests.

I fully accept the difficulty of validating the labeling technique, but, by the same token, if we are going to develop criteria that can find two products to be bioequivalent, as Andy said, that is no different than finding an innovator product to be the same as the labeled innovative product.

So, putting those things together and accepting that a nasal solution is probably the easiest type of dosage form to reliably radiolabel with a deposition marker, it would seem to me at least appropriate to consider scintigraphy as a measure of equivalence.

DR. BEHL: It might be a case of trying to prove the impossible. If the original innovator product in two different dose strengths was approved, of course, there is no burden on their part to show the equivalence or a good inherent dose response, for example, that has just been on the market.

If they go back and do them again, and prove the dose response and prove that a 2-mg dose is better than a 1-mg dose on the market, they might fail in doing that now. It depends on what the suggestion is how we are going to show the bioequivalence of the same dose but different formulations, or same formulations and maybe a different company.

Maybe we are asking to do something that is not

doable.

DR. MacGREGOR: I guess I have a couple of comments on what you said and that is to get a nasal product on the market, you had to run it against placebo. We all know that the placebo response is 35 percent, is a typical number. The response of the active drug is typically 45 or 50 percent.

So that is why you needed 400, 600, patients. So there is a problem right there, if you had a three-way study, parallel-group study, where you had placebo, the innovator and the test, I guess what you are worried about is that you ended up with going in the opposite direction from the placebo or that you are just the same as the placebo.

But it took a lot to get there so that is where I see there is a problem studying. As far as your comment about solutions, it is my understanding, in reading the guidance, that solution formulations, there is no request for bioequivalence of solutions. There is a request for suspensions for multiphase products but not for a solution.

I have looked as hard as possible to see why you would need a study for bioequivalence of a solution being an innovator with a solution on the market, I am asked to look at that and say, come up with a reason why someone has to do bioequivalence, and I can't. Clinically, I just don't see--

once you show you have the same solution and the same droplet size and plume pattern met, I don't see why there is a need for a clinical trial.

I agree with the guidance from that point of view. As far as a suspension, then you have other things going about. The problem is, in the clinical trial, it took 600 patients to show that difference from 35 to, say, 45 or 50. That is where I look for more innovation in the design. I think we are too often going back to what it took to get the innovator on the market.

That is why I am interesting in seeing alternatives where we do crossovers or something along that line, one nostril for this one, one nostril for that, and go in and look for inflammation. What is there that we can do?

DR. DALBY: I am just concerned that, in the drop-down from a clinical study to the in vitro testing, that it is possible to design tests that are so discriminating but completely irrelevant that you can falsely keep an appropriate product from the market.

DR. MacGREGOR: I just think that scintigraphy in a multiphase product, having done that in the past, is one of the most difficult things, even going back and making--in the case of the drug that we had, we made a hot bromine into the molecule so that we could study it. I remember that, because it was a multiphase system, it was just so difficult

to get it to be identical to what was on the manufacturing line, because you are only making ten or fifteen of these devices, it is technologically--if we walked in here, there would be so many questions about the data that we would lose sight of any clinical benefit that we had seen from it.

DR. HAUCK: I just wanted to take the discussion back to a little bit of basics again. A key, really a requirement, of anything to show bioequivalence is that it be able to show differences. If you have a test that comes back and says 7 all the time, then everything is equivalent and it is real easy to show equivalence.

So I kind of had problems when we were hearing Dr. Roman earlier, the note I wrote down is, "Why are we doing these?" They didn't seem like they are going to discriminate against anything so, showing equivalence out of at least the parallel-design clinical studies that she was discussing, don't seem terribly relevant.

I would much rather be, and now back to Dr. Dalby's comments--I would much rather be in the overly discriminating case because that is a goalpost question. You just don't have to set a tight goalpost if it is discriminating things that--if something is very tightly discriminating, you just set a wider goalpost. But you have to have the discrimination or you just can't do equivalence at all.

Where that puts your labeling, that I can't help you with.

DR. LEE: It seems to me, based on what I have heard, it is not feasible to demonstrate dose response for a locally acting drug; is that correct?

DR. HAUCK: That's what I hear.

DR. LEE: At the present time. And, if not, what other approaches may we rely upon. I don't think we have the answer.

DR. HAUCK: Wait a minute. That sounded like too general a statement. I mean, it is an issue of the type of study and the type of drug. We just saw a dose-response study.

DR. LEE: That is for nasally acting drugs.

DR. HAUCK: He said locally acting.

DR. LEE: I'm sorry; for locally acting nasal drugs.

DR. HAUCK: Is that a true statement for all types, antihistamines as well, steroids? I just don't know, but I raise that question.

DR. AHRENS: I am tempted to say it is true, but I don't really know for sure.

DR. BEHL: From the dynamics of how they act and the mechanics of what has to happen for them to show the effect, I would say that that statement, even though not

shown for all compounds, is probably very close to be true.

DR. LEE: I think back to the old question again; we need more data.

DR. HAUCK: I think it is hard for us to say that such a thing can't exist. It is sort of the absence of data is not the data for its absence, or something. Other than saying we have not been shown it today.

DR. LEE: I guess a more prudent way to say it is that we need to explore this further.

DR. DALBY: One thing I think would be worth considering is, since, if I understand Harmut's presentation correctly, for every known steroid that is now on the market, it is possible to detect it in plasma. I wasn't sure what his method was. If you have an equivalent plasma time-profile, must that have resulted from an equivalent deposition and an equivalent local concentration?

Could we not extrapolate that to equivalency because pharmacokinetic profiling is the number-one acceptable criteria that the age says it prefers.

DR. LEE: I think, along the same lines, Richard, is basically discomfort about the scintigraphy studies is that we are not certain what has been deposited is available and, therefore, maybe some sort of sophisticated techniques like receptor imaging is the way to go.

DR. AHRENS: It would seem to me, though, in

reference to that, that we are in a bit different ball game here than with inhaled drugs intended to go to the lung. Inhaled drugs intended to go to the lung, there can be some real questions about aerosol particle behavior and where they wind up in the lungs.

While there may be some of the same issues about distribution in the nose, it has got to be a lot less problematic in terms of knowing the total percentage of what you spray in nose that winds up staying there. Maybe that is the kind of thing--that could easily be done with scintigraphy or, perhaps, other methodologies, so there is a while issue about delivering something that is a long distance away with chances for particles to misbehave versus spraying it essentially directly on a topical surface.

So it seems to me that, if that is true, then it may be that you could just go plasma pharmacokinetics for a drug that is actively absorbed from the nose. If the time profile is the same, and perhaps you could maybe combine it with a charcoal block so you knew if it is orally absorbable drug.

Therefore, what went in, must have gone in through the nose. Wouldn't that reflect the dissolution-time profile which is really the issue, isn't it? Isn't that the reason that solutions, you wouldn't need to do all this, but, suspensions, yes? It is because of the issue of the

dissolution profile of the particles.

DR. DALBY: I think, for most nasal products, that criterion is met. You generally see, from an aqueous nasal spray, a very small percentage getting through into the lung, and there is support for that. So I think that it is possible that it as least worth investigating.

DR. LEE: Dr. Szefler, the last word?

DR. SZEFLER: I was just going to say you could combine this two-dose analysis in kind of a different way. I think each drug has to be defined by a lowest effective dose and a maximal safe dose, but you kind of work with ranges with these drugs. I don't know the nasal literature as well as I know the inhaled steroid literature, but it would seem to me that you would have to define that your lowest dose would be equivalent in terms of efficacy with your lowest dose of the reference product, and that your highest dose should not be any more toxic in terms of systemic measures, whether you use blood levels or cortisol suppression than your highest labeled dose of your reference product.

So if you took those two and kind of set your standards in terms of looking at comparative efficacy at the low range, comparative systemic effect at the high range, then you would kind of be able to pinpoint where the product fits in in terms of equivalency, I think.

DR. DALBY: I just think it is important not to mix up a safety study with an equivalency study although we sometimes derive safety inferences from an equivalence study.

DR. LEE: There is one more question to be addressed, and that question might even be equally challenging which is, what we have talked about so far is based on the so-called seasonal allergic rhinitis. "How much can bioequivalence, established based on that endpoint, assure bioequivalence for other indications such as recurrence of nasal polyps or other non-SAR conditions?" This is question A2.

Wally, is that your territory?

DR. ADAMS: Yes. The concern here is that, in our draft nasal BA/BE guidance, we have recommended that the studies to document bioequivalence use the seasonal allergic rhinitis model for all of the drugs, whether it be antihistamine or cortical steroids or anticholinergic.

The question that we are asking here is is there any reason to suspect that bioequivalence based upon the SAR model does not establish bioequivalence for perennial allergic rhinitis or for nasal polyps for the one drug, beclomethasone, for which nasal polyps is an indication.

DR. LEE: Is that clear to the committee members? Richard, do you want to take this on?

DR. AHRENS: I think we are all hesitating to answer because any answer we give is likely to be right out of the air. We have been saying all day we need more data, but, in this area, I know of no correlations between those two. If you went Richard's route with a drug that was well-absorbed and you showed similar time plasma profiles that must have to do with a similar dissolution pattern in the nose, and, therefore, absorption across that mucosa, you could be reasonably comfortable in that setting that, if they behave the same, they would dissolve the same, and they probably would act the same. It is the same compound.

DR. LEE: You can argue that the dose requirements will be different.

DR. AHRENS: But the dose requirement will be different for both preparations. So the issue is bioequivalence between the two.

DR. LEE: Right.

DR. AHRENS: I think that is all you can do is kind of reason it out of how it might be. But I know of no way to really nail it down.

DR. DALBY: If you don't like it for the simple case, you definitely wouldn't like it for this more complicated case.

DR. ADAMS: Dick, are you suggesting, then, a slightly different question, that if you have in vitro data

and PK data for nasal drug products that that would assure bioequivalence?

DR. AHRENS: Assuming that that PK data was discriminatory, we all know that there are some nasally deposited products which are absorbed very little into the systemic circulation that, obviously, isn't going to work very well for those. For other products, where there is substantial absorption from the nose and that is measurable and is discriminative, I, personally--I haven't spent a lot of time thinking about it, but, at least where I am sitting here now, to me, that sounds reasonable. It is a very different ball game, I think, from drugs that are inhaled into the lung.

DR. ADAMS: And this would be a case where, with charcoal block, you could prevent the drug coming in from the GI tract or for a drug with low oral bioavailability.

DR. SZEFLER: A quick comment. I think you could reverse the question by asking does that disease pathology change the toxicity of the drug or the dynamics of the delivery. I am not aware of any studies that would suggest that the absorption is different in terms of allergic rhinitis versus nonallergic rhinitis or polyps.

With polyps, it could be more but I don't know of any data that suggests that it is changed in any way. So I think you have to look at the question the reverse way, too,

in terms of--

DR. BEHL: My question to Wally is, given that the PK can show that, then it is something very difficult to show for even nasal products. The in vitro pharmaceutical equivalence, for example, in my opinion is not sufficient to show the therapeutic equivalence of locally acting compounds intranasally. Having talked to a lot of others over the years, I don't see how we can escape the need to do at least a small bridging clinical trial to show the therapeutic equivalence along with a need to show other equivalence that can be shown very easily.

DR. DALBY: I guess I would turn the question around and ask what phenomenon do you think could get in the way of a finding that if you saw the same plasm concentration time profile, you would not have had the same profile of drug deposition and absorption in the nose.

DR. BEHL: One is the way a compound would travel, through ciliary movement in the nasal tissue, the surface area to cover from the spray, for example. The spray patterns become very important. By changing them, you could maybe still get the same PK information or the same PK data, but not the same coverage of the same surface in the nose.

The rate of ciliary currents in the back of the throat may be different from formasin(?) formation, may not show much of a difference in the absorption depending on how

it is deposited in the nose; a number of factors. If we have particles in the formulation, it makes it more difficult.

[Slide.]

I think I need to move on. Obviously, Wally has posed some very interesting questions which require some educated guesses. I think that is the best that we can offer.

We now move into the final session of today dealing with PK and PD for systemic exposure of locally acting drugs. Dr. Uppoor from the agency is going to provide us with the FDA practices.

PK and PD Studies for Systemic Exposure of Locally Acting Drugs

Current FDA PK Practices

DR. UPPOOR: Good afternoon, everyone.

[Slide.]

We have heard from Dr. Derendorf as to some of the systemic PK studies that are done and some of the reasons--what we can rely on and what we cannot. Let me go through my presentation and I will talk about the current FDA practices primarily for new oral inhalation and nasal aerosol products.

During the course, I will actually point out the level of systemic exposure.

[Slide.]

During my presentation today, I will be dealing with the general pharmacokinetics and bioequivalence studies that are needed for new molecular entities at the same time they are developed as new inhalation or nasal-spray products; as we have heard this morning from Dr. Adams, the different steps or different approaches we can use to generally assess bioavailability and bioequivalence; and then go through the methods and some of the issues. Some of these have been discussed in the previous discussion as well.

Finally, I will go through something that we also want to get your input on, is the role of systemic pharmacokinetic and pharmacodynamic studies not only for a generic product--that comes in--but even when product changes are made for an innovative product. We want to hear that from you.

[Slide.]

For a new molecular entity, from a pharmacokinetics and biopharmaceutics perspective, we want to know the fate of the drug. Obviously, we want to know the mass-balance studies. We want to know the single dose, the multiple dose pharmacokinetics. We would like to know the absolute bioavailability and relative bioavailability of the drug.

Dose proportionality is one of the key issues. As we have been deliberating all day, bioequivalence studies made between the product that was tested in the clinical trials versus what is to be marketed.

[Slide.]

From a clinical pharmacological perspective, of course we would like to know what the pharmacokinetics are in the target population, especially if there are differences in delivery in healthy volunteers versus the target population.

Additional studies that are necessary to understand and label the drug; the age, gender and race effects; of course, special populations, what would happen in the renal- and hepatic-impairment patients. One of the things which is, of course, very important is to know what kinds of drug interactions might be expected, so from a pharmacokinetics perspective, we would like to see appropriate drug-interaction studies conducted.

In addition, we would also like to see pharmacokinetic and pharmacodynamic correlations established wherever possible. For inhalation and nasal products intended for local action, the pharmacodynamics that I am going to focus on and talk about are from a systemic safety perspective.

[Slide.]

So, as we have discussed, we know bioavailability is an important factor, but from a product-quality perspective as well as from a clinical pharmacology perspective to understand the in vivo characteristics of the drugs. However, with all the discussion, we still do not believe that in vitro testing alone is sufficient for all kinds of drug products. There may be some cases where in vitro testing is sufficient.

[Slide.]

Knowing the sensitivity and accuracy of the pharmacokinetic data, the CFR outlines clearly the different approaches that can be used for bioavailability and bioequivalence. Pharmacokinetic studies are, obviously, preferred. However, there are issues with the products intended for local delivery.

[Slide.]

I won't really go into detail today because Dr. Derendorf talked about why we cannot rely solely on pharmacokinetics, systemic plasma concentrations, for bioequivalence and bioavailability purposes.

[Slide.]

Because systemic-exposure data helps characterize the systemic safety for these locally acting drug products, and to address the local delivery and efficacy issues.

At this point, we definitely request that clinical

data be submitted to look at the efficacy.

[Slide.]

So, recapping, for a locally acting, orally inhaled drug product is what I am focussing on now, but even for an inhaled product, the general, conventional clinical pharmacology and biopharmaceutic studies are needed. If it is not a totally new drug, from the new product, we request single dose, multiple dose, dose proportionality and relative bioavailability as well, where as appropriate, and PK/PD studies.

Generally, pharmacokinetic studies are done in healthy volunteers. However, we have been sensitized with several of the new dosage forms that are being developed. These studies may be needed in the appropriate target patient population if the drug delivery is expected to be different.

[Slide.]

The two aspects that we have been touching upon a couple of times today are--the first one is the inhalation pharmacokinetics with the charcoal block. We really do not require that this study be done. However, I think that it does have merits that can be useful in the drug-development perspective.

It is helpful in comparing relative dose delivery to the lung from different formulations. The concern that I

have is that it really does not address the delivery to the relevant biospace. It also doesn't really point out what is the oropharyngeal deposition.

[Slide.]

Similarly, with the gamma scintigraphy studies, we have been seeing a lot of activity in this area. It is very useful. However, again, as concerns were expressed today, we have concerns about possible lab-to-lab variation. Obviously, the labeled drugs may have different aerodynamic characteristics or even a modification to the original product.

There is significant activity in terms of standardization of these tests, but still, at this point, we are not comfortable to use it from a regulatory perspective.

[Slide.]

So for new oral inhalation, and probably it could even apply to the nasal products, in addition to the pharmacokinetic studies, we do require clinical studies for efficacy and safety. Some of the pharmacokinetic data can be acquired through population pharmacokinetic and pharmacodynamic studies. One other thing that I would like to point out is when a specific topical claim is sought for that drug and drug product, the special topical versus systemic-effect studies may be necessary.

[Slide.]

Knowing this three-pronged approach of using the in vitro data, and the in vivo data from efficacy as well as pharmacokinetics or systemic pharmacodynamic data, I want to actually discuss a little bit on where we might be able to use the systemic pharmacokinetic and pharmacodynamic data, especially for new drug products. When minor changes are made to a well-characterized product, in vitro data as well as systemic PK/PD may sufficient in those cases.

However, when major changes are made to the product, either to the formulation or to the device, additional clinical data is necessary in those cases and, at this point, it has been a case-by-case scenario and it is a consultation with the division. We would really like your help to clarify some of these and where the comfort factor lies.

We also know the pharmacokinetic studies are recommended. But other pharmacokinetics data needs to be collected when a product is being changed or, for example, from a CFC to a non-CFC-based inhalation or nasal-dosage form. We do our guidance points-to-consider document that requests pharmacokinetic studies.

So I think, in summary, we have been talking about use of pharmacokinetic studies all along. It is a sensitive approach. There are some restrictions on how we can use this for a locally acting drug product. However, the

sensitive assays that are being developed, we do have an ability to measure or detect plasma concentrations after oral inhalation in nasal products although we do have some cases where we are still struggling with the measurement of these plasma concentrations, or detecting and quantifying these concentrations.

So I would actually say that we do require that pharmacokinetic-based bioavailability studies be conducted, both to understand from a clinical pharmacology perspective as well as the product-quality perspective. However, for orally inhaled and nasal drug products intended for local action, it is multiple aspects that have to be address. Bioavailability and bioequivalence cannot be solely addressed based on pharmacokinetics.

But, because of the accuracy and, wherever possible, we say pharmacokinetic studies are the first choice to characterize the systemic exposure. However, that alone is not sufficient. You need additional pharmacodynamic data from a safety perspective as well as clinical efficacy data where appropriate.

Thank you.

DR. LEE: Thank you very much.

Dr. Harrison, you have the last words, but you only have twenty minutes.

Industry View

DR. HARRISON: Good afternoon. I want to thank you for allowing me to be the last presenter.

[Slide.]

My topic is PK and PD studies for systemic exposure of locally acting drugs. I am giving an industry viewpoint.

[Slide.]

The value of PK for OINDP is that it measures systemic absorption or systemic exposure. Both terms are used in the guidance. I look at them as interchangeable. Really, what they are doing is measuring systemic safety. PK is an established bioequivalence metric. It can be standardized. It can be validated. It is discriminating. So certainly it has an awful lot of pluses for it.

[Slide.]

There are some concerns, however, with PK that were raised. One is the low doses that are given nasally and by inhalation, what limitations that imposes. The assay lower limit of quantitation; there is quite a bit of variability that is encountered in PK studies for the nose. There could be draining of excess dose so that you really don't get a good dose response. And, for oral inhalation, the dosing technique is quite critical.

[Slide.]

What I want to do is address those concerns up

front. The first one is low doses. That really is not so important anymore. The bottom line is can you quantitate. With the new advances in analytical techniques, you can usually do it. Low dose is not a big issue, I think, especially when you have a therapeutic dose range, as has been proposed in the new guidance--the nasal guidance, that is--you can go, say, one puff, two puffs or even up to four puffs. Whatever is recommended in the dosing recommendations, it is fair game to use in the PK study. That also will help in analytical sensitivity.

So that gives you a lot more dose options than doing a PK study. To me, that is a good idea. The nasal route, you may be limited by drainage on how much you can give but, again, there is sensitivity there even for that.

[Slide.]

Looking at the assay lower limit of quantitation, with LC mass spec/mass spec, now, you have got tremendous capabilities to go into the peak of gram per ml range. In many cases, you can get down to about 10 to 20.

What I have listed there are commercial assays that are actually available. Say, if you were a generic firm, you could find those assays available right now. For BDP that is important because it has got a 17 monoproprionate metabolite that is really the primary material in plasma and it is the most active and there are

assays for that as well as BDP.

So you can do a good kinetic analysis of BDP as well. Again, because the equipment is so pervasive, you could get an analytical lab to help you out with whatever assay you wanted, I believe. So that is not a big issue anymore, either.

[Slide.]

Variability is a concern. There is large intersubject variability. There is large intrasubject variability. There is also variability with the dosing technique. That needs to be addressed.

[Slide.]

This is just a slide showing, in one of the treatments given nasal formoterol, perhaps an example of a beta agonist, the variability you are seeing here with about an N of 27 is roughly on the order of about 40 or so percent. That is fairly typical. It is also, say, typical of a topical product or a variable oral product and it is something that would could live with.

DR. HAUCK: Here, with a N of 12, the variability is a little bit higher. This is nasal triamcinolone. This variation, by the way, was somewhat similar to what was presented earlier by Dr. Derendorf or nasal fluticasone.

[Slide.]

Here, budesonide. Again, very similar. These are

standard errors but, again, it is coming out to be 40 to 50 percent variability that you are encountering in plasma levels.

[Slide.]

This is oral fluticasone. Again, you can see the range that you get in the plasma levels in these twelve individuals. So they vary broadly, but the curve pretty much is established by the mean. It is something I think that we can live with. We can reduce variability. There are various possibilities.

Replicate study designs is an interesting possibility that I have not seen anybody, at least approach in the literature. It is something that could be investigated.

[Slide.]

What people have looked at, what we have looked at, is increasing the subject number. With the nasal route, you may need to reduce the dose.

What we have looked at for oral inhalation is training the individuals to use proper technique. A criticism there; it is not the real world and there are actually even little computer machines that could teach a person exactly how to inhale the product properly. Certainly, we have used that in the past and with good results as well.

[Slide.]

So what are the limitations of, then, doing pharmacokinetics? There really is no correlation with efficacy right now. That has been seen. I will show you some examples of that for the corticosteroids. And it does represent only a fraction of the dose, usually less than 30 percent.

As we talked about for nasal, it could be just a few percent. Again, if you compare the nasal PK, you may be working hard to get equivalence of an extremely small part of the real dose and what is being positive in the nose, where your efficacy is, may be completely different than what you are focussing on.

Again, there are even concerns with the fine-particle fraction. That is debatable. What are the right ranges? So there is still some confusion there. That is, again, a limitation of how you interpret it.

Really, when you look at it, PK is the summary parameter. It represents absorption through many different routes; the mouth, the GI tract and, on first pass, going to the liver, the lungs. Actually, the appearances really have different rates into the blood. We have seen some sensitivities there. In terms of depending on how much goes in the mouth versus the lungs, you actually can get some confusion in your datasets.

[Slide.]

Here is an example of what I want to get at now is that there is no good relationship between efficacy and blood levels. This is a study with fluticasone given nasally. C1 represents the concentration at one hour and the symptom scare represents your efficacy.

What you see here is that, for the oral products and the placebo, you saw no difference in the symptom score but the nasal administration, you did whereas, in the blood levels, you had detectable levels only orally but not nasally. So, again, they were separated. Blood levels were seen orally. Efficacy was only seen nasally.

[Slide.]

The same thing was done through the oral-inhalation route, again with fluticasone. Again, what you are seeing is a very similar type of design where now you are looking at your efficacy parameters, AM FEV1 and symptom score and you are seeing activity with the inhaled route but not the oral route.

Then, if you look at the Cmax and AUC as your pharmacokinetic parameters, what you are seeing there are your highest levels orally. They are easily twice that of what is seen by your higher inhaled dose and yet you are not seeing any activity associated with that.

So, once again, what you have is really a

dissociation between pharmacokinetics and efficacy. So that is a limitation as well.

[Slide.]

The conclusions are that PK is useful to establish systemic absorption. It really is not a surrogate for local efficacy but it is doable. Right now, the assays are out there. You can measure the levels, even nasally, and you can reduce the variability to make it worthwhile and doable.

The next question to ask is can you actually do systemic bioequivalence.

[Slide.]

We have got some examples there. We have done a lot of work with BDP. What I want to talk about first, when we are comparing two formulations. Formulations; we will call them MDI-A, MDI-B. The study designs that we used were single dose but multiple inhalations. They were asthmatics with a crossover design and good inhalation technique.

So that will be common to the studies.

[Slide.]

In terms of the devices, if you look at the draft nasal bioequivalence guidance, what you could say is Q1 and Q2 were the same and identical, those two devices. The particle-size distribution, the spray pattern, would meet the criteria were essentially similar. The route size was the same and the actuator, again, dimensions were

essentially the same.

So there wasn't a lot of difference between the two.

[Slide.]

When we did the first study, it was in 18 asthmatics. The objective was comparability. What we found was that we came close to matching confidence intervals but we did not make it. You can see Cmax was on the low side of the accepted 0.1 to 1.25. AUC was on the high side.

Coefficients of variability, about 50 percent for Cmax, again, similar to what was seen in the earlier slides I showed you with others. AUC also was variable.

[Slide.]

Another study was done, again with the exact same MDIs, MDI-A, MDI-B. Here, the objective was systemic bioequivalence. So, what we did is we increased in N number to 45 and we actually looked at two doses, a low dose and a high dose in this study.

[Slide.]

You can see here coefficients of variation were reduced for the most part with a higher N number and now, essentially, all the parameters did actually meet strict bioequivalence criteria.

So we concluded from this that we could actually show systemic equivalence but we also did local delivery

studies for efficacy. We did not stop there.

[Slide.]

Another example we have got is now looking at MDI-C versus MDI-D. In this case, we actually had just different strength products. So, it is the same dose. The only thing different here to give the same dose is different numbers of puffs because you had a different valve size.

So one MDI may require twice as much as the other to get the same dose delivered. The study designs that we looked at to analyze C versus D again were single-dose asthmatics, crossover, and a good inhalation technique. Similar to what we found in the previous examples, you have everything matched identical in this case except for the valve size.

So, again it was very similar, such as the same formulation but different valve sizes and we did a study with that. We are looking at systemic comparability here in 18 asthmatics and we came very close to getting bioequivalence with an N of 18. It was just outside, 7.6 for Cmax. If you want to use a more liberal criteria of 7.5, it actually would make it.

CV wasn't that great in this case.

[Slide.]

If you look at the next study, when we went to 30, we actually met the criteria. We could include equivalence

as the conclusion, therefore. We, again, had equivalence, in this case with a reduced N number but we did run a local delivery study to demonstrate efficacy as well. We did not stop there.

[Slide.]

Looking at other PK options, we have talked about charcoal block. It certainly allows differentiation of the pulmonary or non-pulmonary absorbed drug. It has got a lot of appeal there. The nice thing is it utilizes the same drug assays and metrics so there is little added time or cost. You really don't have to alter the reference or the test formulations as you would have to do for, like, gamma scintigraphy. So it has got a certain appeal to it.

[Slide.]

However, the limitations that I see with the charcoal block is that there is no evidence that pulmonary absorbed drug correlates, again, with efficacy. It is true, it gets into lungs, but that is where the real correlation stops. And it does not discriminate potentially important product differences such as oropharyngeal deposition or regional lung deposition.

I look at it as a very useful laboratory took to get at the pulmonary drug absorbed but I don't see it, really as adding very much more to PK. It could be looked at as a potential surrogate for local delivery, again if we

can establish that link between what is put in the lungs and absorbed versus efficacy.

[Slide.]

Another option is urinary excretion. Supposedly, when PK is not doable, that is a possibility. There are examples of that in the literature. It has been reported for the various products up there. There are references for each one of them.

[Slide.]

Here is one, for instance, in nasal ipratropium. It is highly variable. You can see the CV was 84 percent and the dose excreted also was 89 percent. So, although you can do it, it really doesn't seem to have a lot of added value. So I look at it--it has got high variability. It has got low sensitivity. And, therefore, it is unlikely to be a reliable surrogate of what we are trying to do here.

[Slide.]

PD has been suggested as a surrogate when PK is not doable. Now, the PD that I am considering is only systemic PD. So you are looking at cortisol, markers of bone growth, of demineralization, things like that. I am not talking about FEV1s at all here. And, again, that requires an appropriate study design.

You usually need a dose-response curve to show that your PD measures are sensitive. It requires repeat

administration.

[Slide.]

Frankly, it is highly variable. It has got low sensitivity. It requires, again, multiple dose levels. I don't see that as being very valuable. If you can't do pharmacokinetics, the likelihood of doing PD is very low. If you are looking at, say, what is out there published with nasal products, if you cannot do pharmacokinetics, I don't know how you are going to deal with, say, urinary cortisol or 24-hour cortisols. It just doesn't have the same sensitivity.

You get the best results when you can do PK as well so, therefore, I don't see that as a great surrogate either.

[Slide.]

PK/PD. That is a very nice thing. There has been a lot of work done there. It, again, allows correlation of PK with PD. PK is linear. PD has got a dose-response curve. It certainly offers increased understanding of what is happening for systemic exposure and safety.

So it has got, again, a lot of appeal in helping the understanding.

[Slide.]

It is sophisticated work, though. It requires several dose levels, additional analyses and I don't think

it really increases the ability to discriminate which is the bottom line for doing bioequivalence. So I look at as a very useful laboratory tool but I don't see it as needed for bioequivalence either.

[Slide.]

So, in summary, systemic PK assessment really is what is needed to assure systemic safety and it really is doable for most drugs. The state of the art is you can do it, even nasally.

The other possibilities, PD, urine levels, are not likely surrogates. Charcoal block and PK/PD, again, are nice development tools but I don't really see them making the leap, either.

[Slide.]

So my input into the last question, are there situations where in vitro data plus PK, and, again, even PD, can be relied upon to show assure local efficacy, they can be relied on is the key thing. It really does imply predictability and the list of drugs. It has not been established, really, for any of them.

Certainly, there are a lot of questions there. Until we can get better information, I think we need to have caution and err on the side of caution and not really look for situations where you can just do PK without having some type of local delivery component.

DR. LEE: Thank you, Lester.

Subcommittee Discussion

DR. LEE: Wally, would you like to provide some background for your question?

DR. ADAMS: Yes. I would like to ask Lester a question concerning his last slide. Lester, you were talking about in vitro data plus PK plus systemic absorption PD in that case.

DR. HARRISON: Yes; that is correct.

DR. ADAMS: Our question was a general one related to whether in vitro data plus PK data would be able to assure bioequivalence. Lester, you are saying no; that is your answer to this question?

DR. HARRISON: That's correct.

DR. ADAMS: Yet there are cases where you are indicating if PK data are not doable, then you feel that the PD is not going to contribute.

DR. HARRISON: That is my position. Based on what I have experienced in the literature, I have never been convinced that, if you can't do one, you can do the other. It is a nice objective but, in reality, I have not seen it done.

DR. ADAMS: You could have situations where neither a test product nor a reference product may inhibit the adrenal axis.

DR. HARRISON: Exactly; that is more likely to happen. That is why going up in doses may be an absolute necessity in cases like that. But, even for fluticasone, you can do nasal fluticasone now and the assays are so good that I think that it is getting to the point where we can measure almost anything.

DR. LEE: Are there members of the committee who can shed some light on this question?

DR. LI: I think, from the standpoint of orally inhaled drugs, that are sufficient variables in regional lung deposition, particle-size distribution, that the sort of in vitro assessment along with pharmacokinetic data without any clinical types of evaluation is probably not going to be enough.

I would say that the orally inhaled products should have an in vivo assessment.

If we kind of look back to some of the cascade data that we saw and our attempts to use the chi square to get a numerical handle on comparability, chances are that any in vitro assessment for a new product is not going to be exactly the same as the reference product. There are going to be some differences, and the differences may be at various stages of cascade or may be differences in particle size and different ranges.

So it is going to be really impossible to predict

precisely the biological activity of that orally inhaled product. So I, basically, would agree, at least certainly in the area of orally inhaled products, that in vitro assessment is important but not sufficient. Pharmacokinetic data is also important but not sufficient. Some in vivo assessment would be necessary.

DR. ADAMS: Just for clarity, Dr. Li, you are talking about efficacy.

DR. LI: That's correct; for orally inhaled products.

DR. BEHL: Which could be a bridging study also as opposed to a full-scale study.

DR. LEE: Is Steve Forrester here? He left? Okay.

DR. ADAMS: Just to follow up further on this question, Dr. Uppoor, did you wish to ask the subcommittee any question with regard to that last question?

DR. UPPOOR: I actually just want to find out, even if you have an innovative product, for example, and that has been shown to be clinically safe and efficacious and you have done all these trials that have been approved, and some minor, some type of change is made to that product and it is the same product, you have a handle on what goes on with that product, you have some understanding or, hopefully, a reasonable understanding of the product, and

some minor changes are made, even in those cases, what I am hearing is it doesn't matter what the change is, but if it is an orally inhaled drug product, we would like some kind of efficacy data in addition to in vitro and PK.

DR. LI: If you are addressing that question to me, that would be a question that would, in my view, be extremely focused. I did not, in fact, say that, in that particular set of circumstances, one would necessarily need to go through clinical studies and even to specify what kind of in vitro studies would be necessary.

I think, in a very narrow sense, depending on what those changes were, say, in the development of the product, if they were such change where one might not expect any significant, really, change in delivery, then probably I would say how things are handled now, case-by-case, would be the way to go.

If there are major changes in the formulation and the production and changes in propellent, for example, that would be an example. A change in propellent is probably enough of a change that you would really need to do more extensive testing.

DR. GORE: Just a comment from the perspective of those of us in product quality that have a lot of experience with cascade impactors, rather minor changes in the formulation of the composition of the material can, in fact,

change what you are, in reality, measuring in the individual stages of the cascade impactor.

So, because of formulation and what is deposited on the cascade-impactor stage is a combination of excipients as well as active ingredient. That is something that would require a lot of validation if you were trying to make a crossover between two different formulations.

DR. LEE: Are there any comments? I think we are kind of supersaturated.

DR. LAGANIERE: I would just add that the experience of Dr. Harrison concerning nasal drug administration, he seems to be alluding to the fact that you can increase the dose if you are not able to see it at the small doses that are usually administered in therapeutics.

But, in the context of safety or exposure, I would like to have maybe the opinion of physicians regarding the relevance of using a so much higher dose that would be usually higher than the recommended daily dose.

DR. HARRISON: Let me just clarify that before you ask an opinion. I meant within the therapeutic dose range. You increase the dose. As long as it is in the therapeutic dose range, say up to four puffs per nostril, you can do that much.

DR. LAGANIERE: Okay. So that would be a limit in establishing whether a pre-case exposure study is feasible

or not.

DR. HARRISON: Yes. I went fast through my slides, but what I did show is pharmacokinetically, you can get a nice dose response with pharmacokinetics in the nose. It has easily been shown by inhalation, but nasal as well.

DR. LEE: Wally, the short answer to your question is that, apparently, nobody around this table has any situations that would respond to your question.

DR. ADAMS: I hear that. Thank you, Vincent.

DR. LEE: Guirag and Wally, are there any other questions for the committee before we adjourn the meeting? Anybody else?

DR. GORE: May I ask more of a procedural question because there was actually a comment made earlier about the need for another meeting. I would like to say I think there is a need for another meeting. There is a huge amount of information, particularly in the CMC area, that was brought forward in the afternoon that we did not have an opportunity to discuss and also some proposals for ways to bring more data into the discussion.

That is just my proposal. I think we need another meeting.

DR. LEE: If there are no further comments, I would like to thank everybody for participating openly. I am surprised that I am still alive. I thank you for your

at

input and have a safe journey home. Thank you.

[Whereupon, at 5:08 p.m., the meeting was adjourned.]

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CERTIFICATE

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