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CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT  
PULMONARY ALLERGY DRUGS ADVISORY COMMITTEE  
ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

ORALLY INHALED/INTRANASAL  
CORTICOSTEROIDS AND  
GROWTH IN CHILDREN

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P R O C E E D I N G S

(8:03 a.m.)

**Agenda Item: Call to Order, Introductions,  
Opening Comments - Henry G. Bone, III, M.D., Chair,  
Endocrinologic and Metabolic Drugs Advisory Committee**

DR. BONE: I'm Dr. Henry Bone. I'm the chairman of the Endocrinologic and Metabolic Drugs Advisory Committee. I'm calling the second half of this joint meeting with the Pulmonary Committee, which was chaired yesterday by Dr. Li, to order.

We'll begin with the introductions, I believe starting with Dr. Purucker at the far corner, and going around the table.

[Introductions were made.]

Thank you all.

We are continuing today with the discussion of some proposed class labeling for the use of intranasal and inhaled glucocorticosteroids for treatment of rhinitis and asthma. The meeting statement will be read by the executive secretary, Kathleen Reedy.

**Agenda Item: Meeting Statement - Kathleen R.  
Reedy, Executive Secretary, Endocrinologic and Metabolic  
Drugs Advisory Committee**

MS. REEDY: The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made a part of the record to preclude even

the appearance of such at this meeting.

Based on the submitted agenda for the meeting, and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting with the following exceptions:

Since the issues to be discussed by the committee at this meeting will not have a unique impact on any particular firm or product, but rather may have widespread implications with respect to the entire class of products, in accordance with 18USC208B each participant has been granted a waiver which permits them to participate in today's discussion.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or

previous financial involvement with any firm whose products they may wish to comment upon.

DR. BONE: Thank you, Ms. Reedy. I should note for the transcript that we also have Drs. Cross and Hintz, and Dr. Bilstad of the FDA.

The next step on our agenda is the series of presentations by FDA staff, and the first presentation will be an introduction by Dr. Purucker.

**Agenda Item: FDA Presentations - Introduction:  
Mary E. Purucker, M.D., Ph.D., Medical Officer, Division of  
Pulmonary Drug Products, CDER**

DR. PURUCKER: Thank you, Dr. Bone.

Good morning and welcome to day two of this joint meeting of the Pulmonary and Endocrine Advisory Committees. I would like to take this opportunity to acknowledge our four invited speakers for their truly outstanding presentations yesterday morning. These talks were not only scholarly, but very clear and very relevant to the issue of class labeling. They certainly set a very high standard for the rest of us for the remainder of the meeting.

Yesterday the companies offered their perspective on inhaled and intranasal corticosteroids in growth in children. We also heard from the community at large in the open public forum, where we were fortunate to have so many distinguished academicians.

Today we will open the meeting with the agency's review of the scientific evidence as it pertains to the growth effects of the corticosteroid products, and we will end with a second presentation of a class label by Dr. John Jenkins. This will be followed by the committee consideration of the questions or points for discussion.

There will be a total of five agency presentations this morning. Please hold your questions until the end, when we can reconvene all the speakers, and each question may be directed to the person most suited to answer it.

I'd like to remind you that the class label proposed for the intranasal and the orally inhaled corticosteroids was written by a multidisciplinary working group, which included individuals from five separate divisions of the Center for Drugs. The home division is Pulmonary Allergy, whose products are involved, followed by the primary consulting division, Metabolic Endocrine, whose advisory committee and scientific expertise we're also fortunate enough to borrow today.

The other three divisions who contributed their expertise include: Epidemiology and Pharmacovigilance, who researched the pediatric adverse event database for us; Biometrics, who dealt with the many complex statistical issues; and Biopharmaceuticals, who provided the support to the notion of a class effect of these products.

The program is organized so that the most general information is presented first, pediatric use data and the adverse event database. It proceeds to a general assessment of the peer reviewed medical literature, and ends with proprietary growth studies, including a discussion of the unique statistical issues encountered in the design and analysis of the so-called growth studies.

The first speaker this morning is Dr. David Graham, who is a physician in the Division of Epidemiology and Pharmacovigilance. Dr. Graham will give us a perspective on the frequency of use of the intranasal and orally inhaled corticosteroids among children in the various age groups, both on label and off label, as well as a sample of the adverse events reported to the agency as growth suppression, which have been associated with the use of these products.

David.

**Agenda Item: Epidemiologic Background and Actual Use Data - David Graham, M.D., MPH, Medical Officer, Division of Pharmacovigilance and Epidemiology, CDER**

DR. GRAHAM: Good morning. Over the next several minutes I'll briefly discuss three distinct types of information relating to the issue of growth suppression and the use of intranasal or inhaled corticosteroid products. The purpose is to provide a sense of the magnitude of

exposure, and to begin to explore some of the factors which we believe may be important to consider.

I'll present data on patterns of corticosteroid use in children, and summarize case reports of growth suppression which have been submitted to FDA. After this, I'll discuss briefly the concept of meta-analysis, and why we believe that this approach cannot provide a reliable answer the question, "Does the use of intranasal or inhaled corticosteroid products have an adverse effect on final adult height?"

We'll begin with a description of the drug use data on these products. FDA has access to two commercially available drug use databases, both provided by IMS Health. The first is the National Prescription Audit, and the other is the National Disease and Therapeutic Index.

The National Prescription Audit or NPA, is commercially available. It provides information on outpatient prescriptions from over 20,000 computerized pharmacies nationwide. The sampling that occurs from these pharmacies is used to generate national projections, and this information is useful for trending of drug use information, comparing one product to another.

The other database that we're presenting data from today is the National Disease and Therapeutic Index, which presents information on patient demographics, the

indications for use, as well as information on the prescription size, duration of use, and information about the prescribing physicians.

These data are obtained from a panel of about 2,900 office-based physicians nationwide who are representative with respect to geography, geographic location, as well as subspecialty distribution, however, it is not a random sample of physicians. The data from this panel of physicians is used to general national projections for the information that will be presented.

The unit of measure that NDTI relies upon is something called a mention. A mention is not exactly a prescription. It's actually a prescription or dispensing of the product, or a situation where the physician recommends the use of the product, or just discusses the use of a product. So it's not exactly a prescription, but it can be used to give one a general sense of the overall use of a product, and the types of patients the product is being used in.

This first slide presents prescription data from the National Prescription Audit. Along the X axis we have the years from 1993 to the first quarter of 1998, and the Y axis, prescriptions in millions. The lighter blue are the intranasal products, and the green are the orally inhaled corticosteroid products.

We can see over the time period that we have the data presented here, there has been a steady increase in the use of both the intranasal and the inhaled oral corticosteroid products. In 1998, we have data for the first quarter. If we project this for the full year, the upward trend in use will continue.

I think it's important to mention in light of yesterday's presentations that with an increase in the prevalence of diagnosis and treatment of asthma, that the increase in the use of these products may be due to the increase in the overall prevalence of disease, and not to an increased treatment of the existing population.

This slide is from the NDTI, and shows the use of intranasal steroid products by age group. We can see that about 12 percent of intranasal steroid products are used in children under the age of 12.

On the Y axis we have the mentions in millions. Remember that mentions are not exactly prescriptions, but they give us a sense of how these products are used.

This is another slide from NDTI for the intranasal products. We show the indications for use stratified by age group. We can see that with increasing age, that there is an increase in the use of the intranasal products for the indication of rhinitis, and a decreasing use for the indication of sinusitis. Overall, about 13 percent of

intranasal steroid products in children were used for the indication of asthma. The category "other" included a grab bag of various indications for use including hypertrophy of the adenoids, conjunctivitis, and then primarily unspecified complaints.

We present similar data from NDTI for the inhaled corticosteroid products. We have mentions in millions along the Y axis, and overall there is about 10 percent or so of use of the inhaled corticosteroid products that are used in children under the age of 12.

From NDTI again, stratified by age group, we have the proportional distribution of indications for use. We can see that the overwhelming indication for use of the inhaled corticosteroid products in children is for the indication of asthma. And overall for the children ages 0-11, about 84 percent of use is for this indication. Another 3 percent was for bronchitis, and then the remaining 13 percent was for a grab bag of indications, primarily unspecified respiratory complaints.

We'll shift gears now and talk a little bit about spontaneous reporting of adverse reactions of growth suppression reported to FDA. The FDA maintains an adverse event reporting system which has been in operation since 1969. It covers all marketed products in the United States. What it consists of is case reports of adverse events

submitted by health professionals, drug companies, or consumers to the FDA.

The FDA computerizes these data in a database, and currently we have about 1.6 million reports in the database. Each report is systematically coded to facilitate retrieval of adverse events that might share common features. This database is useful for generation of case series, and for signaling functions of potentially unrecognized adverse events.

This slide summarizes the cases which have been reported of growth suppression with intranasal steroid products. Since 1988, which is the first year that a report was received, we have received eight reports, seven from the U.S., one foreign report relating to six different intranasal products in which the complaint was one of growth suppression. The ages range from 2-15 in the children who were affected, and the gender was equally distributed between boys and girls.

This portion of the slide highlights one of the deficiencies of case reporting as it is received by FDA in which it is incomplete information. Although there are eight cases, gender was available in only six of them.

The duration of use of the products where growth suppression was reported ranged from six months to two years. In half of the cases, the duration was greater than

or equal to one year. Where the dose was noted, it was in the recommended range in five.

This slide summaries cases of growth suppression reported with the inhaled corticosteroid products. We had 12 case reports, 2 from the U.S. and 10 foreign, relating to 5 different products. The ages of children range from 5-14, with roughly comparable distribution between boys and girls. The duration of use ranged from 6 months to 4 years, with two-thirds of the cases having durations of use greater than or equal to 2 years. In 5 of the cases, the dose was on the high side considering the age of the child.

One might be tempted to conclude that since there are so few cases reported, that the problem of growth suppression with the use of the inhaled corticosteroid products or the intranasal products is not really something to be concerned about. The purpose of this slide is to caution you against jumping to such a conclusion hastily.

There are a number of barriers to reporting, and this is probably the chief problem with case reporting to FDA, and that is the issue of underreporting. Basically, the majority of adverse events aren't reported. One can conceptualize the reporting process as a series of barriers or hurdles, each of which has to be overcome in order for a report to be received by the agency.

Each barrier has a probability of success

associated with it. The final product of these success probabilities results in the probability of a report actually being received. So one can look at diagnosis, attribution, and registration as these barriers.

With diagnosis, we are talking about arriving at the conclusion that, yes, this child has growth suppression. As we saw yesterday, it is quite likely that in this situation that it might not be recognized, especially if growth suppression is mild. If someone dropped from the 50th to the 25th percentile, that might not be noted, because physicians, as we learned yesterday, aren't monitoring the growth of children in a sort of systematic fashion once they are out of the infant or toddler age ranges.

After diagnosis occurs, one has to attribute the adverse event to the particular drug product in question. That would require that after diagnosis growth suppression, that the physician attributed it to the intranasal or the inhaled corticosteroid product.

Then finally, having done diagnosis and attribution, registering the event with the drug company or with FDA. That would involve filing a report. There has been very little systematic study of this problem, except as it relates to registration. What has been noted here in a series of studies is that for very serious adverse events,

those resulting in death or hospitalization because of a life threatening adverse event, that the reporting is generally in the range of about 10-15 percent.

So the success rate of the final hurdle in the reporting has a success rate of about 10 percent. In the issue of growth suppression with inhaled steroid products, the rate of diagnosis might be very low, especially if we are talking for milder in degrees of growth suppression. So you can sort of think in your own minds what you think the reporting rate might be, but we believe it to be very low.

Finally, I'll talk briefly now about meta-analytic approaches to answering the question, "Does growth suppression occur with the use of these products?" The most robust types of meta-analyses would involve patient-specific data that was obtained from randomized and blinded trials. The data would be comprehensive with respect to exposure, and to the outcomes of interest, and would include data on the confounders that are viewed to be important in the study of this issue.

Among the confounders that would be most important would be duration of use, the timing of puberty, and the relationship between the use and the onset of puberty. Other factors which might be important would include the use of oral steroids, systemic steroids, and steroid burst treatment, and a number of factors that were talked about

yesterday in presentations by Dr. Allen.

If we look at the meta-analyses that have been done to date in studying this issue, most of them did not use patient-specific data. Rather, they relied on means as reported in the literature. The meta-analysis included trials and studies from all types of backgrounds, ranging from case series, to convenience samples, to randomized trials. And the data was not comprehensive with respect to exposure, or to the duration of use, or to the pattern of use with respect to the age of the children.

Finally, over time there has been a shift, if you will, in the way these products are used in the treatment of children with asthma. This was described yesterday, that in more recent years there has been a shift towards the treatment of children with asthma earlier, and on a chronic basis with these products. Studies which came from earlier time periods where the style of usage is different than that would be expected to give us information that really doesn't relate to the current way the products are used.

This final slide is intended to illustrate five hypothetical patterns of use of inhaled corticosteroid products to try to illustrate some of the issues which we believe are important with respect to confounders. We have age along the X axis, and this is the age of the child, their chronologic age, and then five hypothetical patterns

of use.

One could use the inhaled products sort of for short periods of time, with longer periods where they are drug free, and have this occur over a series of years. Or one could use it for longer periods of time, and then stop, and not continue it.

We here sort of between 11 and maybe 13, the onset of puberty. The question comes up, well, would a pattern of use that comes closer to the timing of puberty have a differential effect with respect to growth than a pattern of use which was for a roughly similar duration of time, but was more remote from the time when puberty occurred?

Then would the impact of such product use in either of these situations differ from that where the use was continuous, and went through the period of time when puberty occurred?

I think these are important factors to consider. In looking over the issue of meta-analysis, and listening to the discussions yesterday about how one might want to analyze these data, from an epidemiologic perspective, it appears to me at least, that the issue of growth suppression with these products is a multi-variate process, which means that regression techniques might be appropriate where one could adjust for the effects of multiple different factors simultaneously.

What I'm particularly interested in has to do with the timing relationships if you will, between puberty and when the product is used, and hope that the committee will be able to consider sort of the time dependency issue in a discussion of methodologies and ways to analyze these data.

So this concludes my remarks. Now I will introduce Dr. Alex Worobec, who will discuss her review of the medical literature with respect to growth suppression.

**Agenda Item: Review of the Medical Literature -  
Alexandra Worobec, M.D., Medical Officer, Division of  
Pulmonary Drug Products, CDER**

DR. WOROBEK: Well, in our last presentation, Dr. David Graham delineated some of the important epidemiologic issues that need to be taken into consideration when looking at the whole topic of growth suppression and intranasal and in orally inhaled corticosteroid use in children. He also brought up some important study design issues that should be looked at when evaluating these types of studies.

Nonetheless, I'd like to turn your attention right now to a review of what is currently available in the literature with regard to corticosteroids and growth suppression. In the next 20 minutes or so, I would like to focus on four main points: basically, our rationale for evaluating the published literature; how we approached evaluating these articles; the results that were found in

these studies; and our conclusions based on the data.

We evaluated the peer reviewed published literature primarily for three reasons. First, to evaluate the extent of published literature, essentially, what is available out there as with respect to each intranasal and oral inhaled corticosteroid active moiety that is currently marketed in the United States.

Furthermore, we sought to review and to critique the different study designs that were employed in evaluating growth suppression. And finally, and perhaps most importantly, we sought to look for signals, or lack thereof, of growth retardation in association with intranasal and/or inhaled corticosteroid use in children.

Now we approached evaluating these publications in the following manner. Obviously, we looked at the pediatric population. This included prepubescent and pubescent patients. We assessed the corticosteroids by their active moiety, and also how they were delivered, meaning either the intranasal route, or the oral inhaled route. And using this approach, we were able to identify five different active moieties.

We searched a number of library databases, which spanned about a 30 year time period, from 1966 until May 1998. This included: the Medline, Grateful Med, Embase, SciSearch, and Biosis databases. We looked at all

languages, and where warranted, had the appropriate translations.

The types of publications, however, that we did exclude included meta-analysis for some of the reasons that Dr. Graham had talked about earlier. And in particular, studies in which there was no identification of either the corticosteroid active moiety, or the doses that were employed. This is primarily because we had no way of knowing whether patients were receiving perhaps higher than the recommended doses, which could confound our interpretations of the results.

Of course we didn't consider abstracts. So therefore, we were able to identify a total of 55 unique, evaluable articles for both the intranasal and oral inhaled corticosteroids.

We also noticed when we were doing our search that there was essentially a bimodal distribution of the time periods when these studies were published. And there two main peaks. One was in the 1970s, and the others were in the 1980s, and 1990s. What we found was that the studies that were performed earlier had clearly some different study design differences. So we sought to also look at these publications that were published prior to 1980 -- this was nine studies -- and those that were published during and after 1980, and this was 46 studies.

Now the types of studies that we had encountered included: case reports and case series; randomized, double-blind, placebo controlled, parallel group and crossover studies; open label studies; and retrospective chart reviews.

In addition, we looked at studies based on the duration that patients received treatment with their respective corticosteroid. We defined short-term studies as being those in which a patient received less than six months of treatment, and longer-term studies, those in which patients received every six months of treatment, but generally much longer.

Studies were analyzed by their authors, and we also took into account how patients had their growth measured. In some of the older studies, really all it stated was that routine height was measured through a standard pediatric scale. But in some of the newer studies it was clearly stated that patients had their heights measured by stadiometry or knemometry.

Finally, determination of growth suppression in a given study was based on the presence or absence of statistically significant growth suppression in corticosteroid-treated patients, or in the underpowered studies by the authors own conclusions.

Now I would like to focus your attention on some

of these study design flaws that were encountered in the literature, and there were actually quite a few. First of all, there were different study designs encountered, and a substantial number of these were open label or retrospective studies.

Furthermore, most studies failed to acquire pre-entrance or baseline growth velocity data. Additionally, most studies also failed to acquire post-treatment growth velocity data, nor did they provide bone age data. A large number of studies were of a short duration.

For some studies, both pre- and pubescent patients were analyzed together, or there was no assessment of pubertal status altogether. In some of the studies there was also inclusion in the safety analysis of only study evaluable patients, and not the intent-to-treat population. This was generally due to a fairly large number of patient drop outs during the trials.

Concluding, use of growth assessment techniques of varying sensitivity were seen in the different studies. And inadequate statistical power was sometimes found in some of the studies whereby it was very difficult to detect a specific change in growth velocity or height. Again, this was generally due to small numbers of patients.

Now specifically, with regard to the asthma studies, there were two study design flaws that were

encountered, and these were generally in the earlier trials that we reviewed: enrollment of severe or steroid-dependent asthmatics in some of the trials; and allowance for the use of intermittent oral corticosteroids during the trial for asthma exacerbations.

Now turning to the results of these studies, and the important point I would like to make is that despite these study flaws, there were a number of studies that did show growth suppressive effects. I think that needs to be taken into account.

But when we look at all studies that we were reviewing -- that's a total of 55 studies for both the intranasal and oral inhaled corticosteroids -- for the intranasal corticosteroids we were able to find two peer reviewed publications, and one of these showed a growth suppressive effect. Now for the oral inhaled corticosteroids, we were able to identify 53 publications, and 24 of these showed a growth suppressive effect.

Now when we look at the well designed studies, and by that I mean studies which were randomized, double-blind, placebo controlled, parallel group studies, there were two intranasal corticosteroid growth studies, and both of these were considered to be well designed. Of these two studies, one of them showed a growth suppressive effect.

When we turn our attention to the asthma studies,

of the 53 growth studies that were reviewed, 5 were considered to be well designed studies. Of these studies, four showed a growth suppressive effect.

So in summary, at least for the oral inhaled corticosteroids, those studies that were actually better designed, a majority of these studies did show a growth suppressive effect with corticosteroid use.

Now those studies that were negative or inconclusive, these were actually characterized by number of characteristics, and I'll just run through these: generally, a shorter duration of treatment; an open label design or a retrospective chart review; inclusion of prepubescent and pubescent patients in the same patient database; inclusion of severe steroid-dependent asthmatics, or the allowance of use of oral corticosteroids; powering of the study for efficacy endpoints, and not for the change in growth velocity endpoint; enrollment of small numbers of patients into the trial; and growth assessment that were performed as post hoc analyses, in which there was no prespecification of height and/or growth velocity of the safety endpoint.

Conversely, the positive studies were more commonly characterized by these features: again, a randomized, double-blind, placebo controlled, parallel group study design, which often included an active comparator,

either another steroid, or a non-steroid asthma treatment; a longer duration of treatment, and this was generally at least one year, to perhaps more than five years of treatment; a general tendency to exclusively study prepubescent children; and enrollment of a larger number of patients in each treatment arm, for example, 50 patients, or powering of the study to detect a specific change in growth velocity or height.

Now with respect to the positive asthma studies, these were more commonly characterized by enrollment of mild to moderate asthmatics, and that's by the 1997 National Heart, Lung, Blood Institute definition of mild to moderate asthma.

Now I'd like to focus on one issue which I think is very important, which was brought up yesterday, and that is if you find growth suppression with corticosteroid use, so what? What is really the clinical relevance of this? And really, how big of an effect are we seeing in these studies?

So in terms of the magnitude of the growth velocity effect that was seen in our positive studies -- and for this I mean all of the studies that we looked at, both the well controlled, and the less better designed studies for both the intranasal and oral inhaled corticosteroids -- in the shorter studies in which growth velocity was

expressed in millimeters per week, the magnitude of effect on growth velocity decrement was found to range anywhere from -0.11 to -0.74 millimeters for week for those studies that performed comparisons with placebo, or had performed comparisons with the pretreatment run in period.

Now in those studies that were longer studies, and in which growth was expressed in centimeters per year, the magnitude of the effect on growth velocity was found to range from about -0.5 centimeter, to -1.5 centimeters per year decrement. So this is actually consistent with some of the messages we were getting from yesterday's discussion.

The important other point I would like to make is one cannot extrapolate short-term data from these short-term studies to long-term studies, because of significant study design issues.

There is also a third type of a measurement, which is a little confusing, but has been found in a smaller number of the studies, and that is called the SDS, or sometimes referred to as the height velocity standard deviation score. In these studies, this score, which is actually a ratio, was calculated by taking the patient's growth velocity, subtracting the mean growth velocity for their age, and dividing this whole sum by the standard deviation of growth velocity for age.

When this measurement was used, the magnitude of

effect on growth velocity -- and actually, this was primarily for the oral inhaled corticosteroids -- was found to range from approximately -0.28 to -0.88.

One other feature we have identified in looking at some of the studies was a possible dose response effect in terms of growth suppression. That is, in one of the two allergic rhinitis studies, and in three of the six asthma studies which compared different doses of the same corticosteroid active moiety, there was a greater decrement noted in growth velocity with the higher dose.

I'm not going to discuss the actual active moieties or the doses, but to say that generally there was a doubling of the dose with the higher dose. The growth velocity decrement that was seen here, was actually very small. It was ranging from -0.03 to -0.17 millimeters per week.

Now I would like to turn your attention to an example of one better designed study. I would like to present one. We don't have time to discuss more than one. But this is a study that will be discussed in greater detail by Dr. Saul Malozowski in an upcoming presenting, as it was received as a proprietary study from the sponsor, but was also published in the New England Journal of Medicine in 1997 by Dr. Simon Goodall(?).

This was a comparison of beclomethasone,

salmeterol, and placebo in children with asthma. The study design was a randomized, double-blind, placebo controlled, parallel group study which was one year in duration, with a two week run in period, and upon completion of treatment was followed by a two week follow-up period.

The patient study consisted of 241 mild persistent asthmatics that ranged from 6-14 years of age, and they were randomized to one of three treatment arms: beclomethasone, 200 milligrams twice a day, given for one year; salmeterol, 50 micrograms twice a day, given for one year; and placebo given for one year.

Growth was assessed by monthly stadiometry, although height was not measured after medications were discontinued. The statistically analysis that was employed in this study consisted of a growth rate, which was calculated for each child as the regression co-efficient of height over time, expressed in centimeters per month, and analyzed by analysis of co-variants. The model included effects of sex, study site, and assigned treatment. Age and height at baseline were co-variants.

Unfortunately, powering was not described in the methods section of this study. In addition to this potential study flaw, there were a couple of others that were identified, and that is that the study had approximately a 25 percent drop out rate. It didn't adjust

for the puberty status of patients, meaning the Tanner stage, and growth was not a primary endpoint. This was an efficacy study.

Nevertheless, there were some interesting results seen in this study. During months 1-12 height in the beclomethasone group was noted to increase less than in either the placebo or salmeterol group, and in the beclomethasone group the height increased by 3.96 centimeters, whereas in the other two groups the height had increased over that year by over 5 centimeters. By the author's own statistical analysis, this was found to be statistically significant differences between the beclomethasone group and the other two comparators.

So in summary, I would like to discuss some points about the well designed corticosteroid trials. This is for the both the intranasal and the oral inhaled products. First, these studies were generally randomized, double-blind, placebo controlled, parallel group studies, and they were unfortunately only found for two corticosteroid active moieties.

Nevertheless, when well designed trials were examined, generally at least 50 percent of the studies did show a positive growth suppressive effect, although the actual number of trials was quite small.

Now when we turn to the intranasal

corticosteroids, some conclusions I think we can make is that there were really very few peer reviewed studies that addressed growth suppressions with intranasal corticosteroid use. Now in the two published articles, both of which were short-term studies, one did demonstrate a decrease in growth velocity in children using the intranasal corticosteroid. Furthermore, a result of this growth effect on final adult height is not known at present.

Now for the oral inhaled corticosteroid products we had noted many design flaws and confounders, particularly with the older studies. In these older studies no placebos or active controls were often used as comparators. Many of the study subjects were severe asthmas on oral corticosteroids.

Nonetheless, we did note signals of decreased growth velocity in children that were seen across different inhaled corticosteroids; again, were commonly in the longer-term studies, in the better designed trials, and in patients with mild to moderate asthma.

As my final point, I'd like to leave you with this food for thought. The magnitude of this effect might not be similar across all doses of an given corticosteroid, as shown in some of the studies that we had reviewed, as it does appear to increase with increasing dose of corticosteroid.

Thank you for your attention.

[Applause.]

DR. BONE: Thank you. The next speaker will be Barbara Elashoff.

**Agenda Item: Statistical Issues in the Design and Analysis of Growth Studies - Barbara Elashoff, MS, Biostatistics Reviewer, Division of Biometrics, CDER**

MS. ELASHOFF: Good morning. Dr. Worobec talked about the literature data, and the next discussant, Dr. Malozowski will be presenting the proprietary data from the company. We feel that this is an appropriate time to discuss the problems that appear to be inherent in the design and analysis of the growth studies we have reviewed, and to think about the contrast between the evaluation of the literature studies, and those submitted to the agency by the companies participating in this meeting.

My presentation is intended to provide a brief, critical overview of this information, and to encourage us to use an appropriate level of caution in evaluating the estimates and treatment differences reported for these studies.

Even though some studies in the literature, as Dr. Worobec pointed out, are better than others, and some of the company studies were relatively high quality growth studies, producing perhaps the best data we have, I think we would

all agree that we haven't yet seen that elusive ideal growth study.

The ideal design of the growth study in the asthma population would be one with a very large sample size, perhaps 1,000 patients randomized to each arm.

[Laughter.]

The randomization would be stratified by every relevant demographic and baseline factor. Subjects' growth velocity would be assessed during a run in period of substantial length. Subjects would be followed for a long time, say 20 years. There would be complete data for all 2,000 patient. Subjects would receive constant doses of study medications, and of course subjects would not be allowed to take other medications, or be allowed to go through puberty.

Perhaps then we would have study results that could analyzed in a straightforward fashion. We would not be concerned with lack of power, baseline imbalances, complicating factors arising during the study, or dealing with missing data.

Obviously, the literature studies and the company studies that we have reviewed fall short of this mark. We don't have ideal data. In particular, there may be differences in baseline factors, a large variety of treatment period events, and high drop out rates. I'll

discuss each of these factors in turn now.

As discussed yesterday by Dr. Hintz and others, there are numerous baseline factors that are important in asthma growth studies. As growth is a long-term process, the treatment effects in the one year or shorter duration studies may be difficult to isolate, especially in the presence of other factors that affect growth such as baseline height, baseline growth velocity, age, and bone age, and puberty status.

The studies we reviewed are a mixed bag. Some important factors such as for example, baseline growth velocity, were not included in all the studies. Without consistent data, we can't adjust the analyses to account for differences in treatment groups. We can't be completely confident that the estimates are accurate, and therefore cross-study comparisons may be compromised by caveats and assumptions.

In theory, randomization should produce treatment groups with similar baseline factors, however, as we all know, this doesn't always happen. A general difficulty with evaluating literature studies is that we don't have the data, and at times, we are not always certain how baseline factors are handled in the analysis.

There were a few examples from the literature and from the company studies in which the mean height

percentiles or the mean growth velocity percentiles or the mean ages for the treatment groups were different at baseline. The authors of the studies in the literature did always report whether the estimate of the treatment effect was adjusted for these differences. In contrast, the company studies thoroughly examined any differences they found, and the potential effects on the analyses.

Most of the growth studies we have discussed allowed for the use of systemic corticosteroids during the treatment period. Some of these studies even allowed use during the run in period, complicating the assessment of baseline growth velocity.

Though systemic corticosteroids appear to have growth effects of their own, some authors of the literature studies did not fully investigate the bias that these effects may have had on estimates of treatment difference. This was because they considered that the use of the systemic corticosteroid was balanced across treatment groups, however, dose and frequency of use are potentially important factors on growth, and can be measured and analyzed in different ways.

For example, the mean total dose of the systemic rescue corticosteroid could be similar across treatment groups, while the number and frequency of patients who had say at least one course of treatment could be different.

Therefore, it is difficult to evaluate potential bias introduced by the differential use of rescue systemic corticosteroids in these studies.

In addition, even if we assume, as some of the authors did, that no bias is introduced, the use of rescue systemic corticosteroids in these studies potentially introduced extra noise or variability, thereby making it more difficult to demonstrate statistically significant differences in growth velocity between treatment groups.

Related to issues associated with the use of rescue medications is the potential impact of drop outs and missing data on the analysis. As growth studies in the asthma population were generally of longer duration than typical asthma efficacy studies, there was more missing data.

Some of the analyses of the asthma growth studies reported in the literature excluded greater than 25 percent of the patients who were randomized. In some cases the exclusion rates varied widely across treatment groups. The primary reason for exclusion was drop out.

An extreme example of this was one study from the group of well design studies that Dr. Worobec discussed in which the analysis excluded approximately 35 percent of the patients in the steroid groups, and about 47 percent of the placebo patients.

The effects of drop outs are a problem in growth studies, particularly in the asthma population, because the reason for drop out is usually related to efficacy, which in turn may be related to growth velocity, as we discussed yesterday. For example, non-steroid patients who drop out due to lack of effect may be growing slower due to disease severity, therefore, excluding these patients might magnify the estimate of the treatment difference.

Drop outs complicate the analyses of these studies. Whether drop outs are included or excluded, we need to make assumptions about the growth velocity of the drop outs after they have dropped out. The assumptions we make may be incorrect. It is difficult to include the drop outs in our analyses by extrapolating the growth velocity, because growth may not necessarily be linear, and because the estimates of treatment effects may differ by duration of use.

Therefore, it is difficult to know what the effect of excluding the drop outs may have on the analyses, minimizing or magnifying the difference in treatments, or whether it varies from study to study.

Further, it is difficult to know what the effect of excluding the drop outs may have on the variability of the estimate of the treatment differences, increasing it due to decreased sample size, or decreasing it due to performing

analyses on a subset of patients with similar characteristics. Even the highly selected subset of studies we considered good designs based on our criteria, suffered from most of these problems to a lesser or greater extent.

Having gone through the general problems of asthma growth studies, I would now like to briefly discuss the specific issues of the five company studies we received in the context of these problems. The company were in general, large, randomized, controlled trials. Three of the studies were specifically designed as growth studies, that is, they were powered to show a difference in growth velocity across treatment groups.

Two of the studies were safety extensions of efficacy studies. After the 12 weeks of the efficacy assessment in these two studies, the patients were re-randomized to either non-steroid or the inhaled corticosteroid. There was no wash out in between. The studies were not blinded, and they were not designed to show a difference in growth velocity. They were designed as safety studies in which height was one of many endpoints.

The companies attempted to address some of the problems I have discussed, that is, adjusting for baseline differences between treatment groups, however, as I mentioned previously, one important baseline factor, growth velocity, was assessed in only one of the five studies. In

that study, it was found that the percentile growth velocity at baseline did explain some of the variability observed in growth velocity during the treatment period. It was unfortunate that the analyses of the other studies could not adjust for this baseline factor.

Pubertal stage was almost always assessed at baseline, but only in a couple of the studies was it assessed during the year long treatment period. In two of the studies, the dose of the inhaled corticosteroid was titrated to meet the individual patient's needs. The dose adjustments were recorded and summarized, however, the estimate of the treatment effect was not adjusted for mean dose of inhaled corticosteroid.

Similarly, systemic corticosteroid rescue medication use was recorded and summarized, but the estimate of the treatment effect was not adjusted for this factor. In addition, even these carefully designed, expensive company trials experienced problems related to drop outs.

The major difference between the results reported in the literature and the results from the companies was that the companies thoroughly analyzed the data and submitted full reports describing the sensitivity of the results to the type of analysis used to the patients included in the analyses, and to the relationships between drop outs, age, and puberty status when it was recorded.

Additionally, from the perspective of a reviewer, it was a great advantage for us to be able to independently analyze these data to carry out appropriate descriptive analyses not performed by the company.

In addition, the company data alerted us to a problem that the studies in the literature had not revealed, that is, the potential variability in the measurements recorded for individual patient data. These are some example graphs of individual patients from longitudinal studies we received from the companies. On these graphs patients had changes of up to 10 centimeters in one month. This phenomenon was not limited to a single study, but instead was present in most of the studies we received.

The causes may have been incorrect recording of height, incorrect measuring techniques, or natural growth peculiarities, or a combination of these factors. Some companies attempted to control for this error by measuring the children several times in a single visit. This aspect of the study design did appear to reduce, but did not completely eliminate these questionable data.

The companies also attempted to validate some of these unusual data points with results that further complicated the issue. For example, illustrating how difficult it can be to capture these data accurately, one company detecting a problem during their edits contacted the

investigative site about this female patient who grew 10 centimeters within 2 months, then grew another 40 centimeters or approximately 16 inches in the next 2 months, to final height of 166 centimeters, or 5 1/2 feet. This patient was 4 years old.

[Laughter.]

The investigative site verified that this information was correct, however, the company did not use this patient's data in their analysis, as the data were thought to be unreliable. We concurred.

But where do you make the cuts on these data? Where do you draw the line? Inclusion or exclusion of the unusual values may have a striking effect on the statistical analysis of these data.

In one of the companies' studies an analysis on the growth velocity calculated using the slopes of all of the patients who had greater than two measurements did not yield a statistically significant difference, however, when two patients were excluded, one from the control group, who appeared to be shorter at the end of the study than at the beginning, and one from the active treatment group who appeared to grow at a rate of 28 centimeters per year, the difference in growth velocity became statistically significant.

This illustrates how sensitive the analysis may be

to decisions concerning patient inclusion. It also illustrates how difficult it is to critically assess the results reported in the literature when we have summaries of it and not the data, as we do from the company studies.

Therefore, in addition to all the variability between patients introduced by baseline and treatment period event differences, there is variability within patient, that can be an order of magnitude larger than the purported treatment effects. We have seen that the estimate and statistical significance of the treatment effects are sensitive to the inclusion or exclusion of patients with unusual data points.

The estimate and statistical significance of the treatment effect are dependent largely upon the statistical methodology, the variables included in the model, and the patients selected for analysis, for example, drop outs versus completers, patients with or without unusual data points, et cetera. Comparing the treatment effects across studies is difficult precisely because the estimate and statistical significance of the treatment differences are dependent upon these factors.

The trials had differences in design, entrance requirements regarding inhaled steroid use, baseline demographics, numbers of drop outs, and prevalence of on-study factors. As I have discussed, all of these factors

make it difficult enough to compare treatment and control within a study, let alone compare treatments across studies. For this reason, we feel that cross-study comparisons are not appropriate.

Though it is apparent that my ideal growth study may not be a practical instrument, there are ways to minimize the variability and problems I have discussed. To collect better data in the future, we need to discuss and establish standards for the design and analysis of growth studies.

We would like input from the committees on what is a clinically relevant difference in growth velocity, and for how long do patients need to be studied to detect this difference? Perhaps the difference only occurs in the first year of treatment, or perhaps the difference increases with every year.

What baseline factors are most important to assess, and by which factors should the randomization be stratified? Is it necessary to require patients to be prepubescent at randomization? Or perhaps should we include pubescent patients in order to study whether the treatment effect is different between prepubescent and pubescent patients.

Should the dose of the inhaled corticosteroid be kept constant, or should the dose be titrated according to

the individual patient needs, as it may be in the real world?

How should we control for systemic corticosteroid rescue medication use, by mean dose or by numbers of patients who took at least one course, at least two courses, at least three courses, or by some other method?

Finally, how can we decrease measurement error?

In the next presentation, Dr. Malozowski will be showing you data from five company studies, the same studies that the companies presented yesterday. Instead of focusing on the analyses that suffer from so many potential problems, we thought we would present descriptive analyses, including graphical displays of the data, to give you more of the sense of the results at an individual patient level.

We will be showing you standard growth velocity charts. In this manner, we are able to account for some baseline factors such as age and gender. These descriptive analyses, you will see, did not account for problems such as oral steroid use during the trial, and most importantly, drop outs. We will not be showing the patients who dropped out of the studies. These are completers analyses.

Therefore, we consider these graphical displays as exploratory, and we ask that you view them keeping in mind the problems that I discussed.

Thank you. I would like to introduce Dr.

Malozowski.

[Applause.]

**Agenda Item: Review of Proprietary Growth Studies  
- Saul Malozowski, M.D., Ph.D., Medical Officer, Division of  
Metabolic and Endocrine Drug Products, CDER**

DR. MALOZOWSKI: I was given the responsibility of reviewing the studies that were presented yesterday. As we just heard, most of the analyses were done in very close collaboration with the previous speaker, that was instrumental in the results that we will be presenting today.

The goal of my presentation is to assess the impact of orally inhaled and intranasal corticosteroids on growth velocity in children. It is not to compare outcomes among several studies involving different drugs. These comparisons cannot be made, because each study included only a single drug, and study designs differ among the studies.

Why did we come together in this meeting? Because we found signals from adverse event databases that raised our concerns as presented by David, because the peer reviewed literature suggested an affect on these drugs on growth, but we felt that inadequate study designed tended to obscure these effects, and because the growth studies recently submitted by pharmaceutical sponsors allowed us to do so.

We have to keep in mind several considerations. First, the growth velocity tends to plateau before puberty, and that's the reason we decided to limit our analyses to this age group. We focused in the prepuberty age ranges, and these are the ages of the girls and the boys at the beginning of the studies. Also because children less than four tend to grow more rapidly, we decided when data was available, to look at these data separately.

Here you have a growth chart. I'm sure you cannot see this from the back of the room. But clearly, to show how growth velocity is quite constant during the prepubertal stage. This the reason we decided to focus on this age. You see the 50th percentile. This is the growth velocity for a child at different ages. Here at age 8, and the 97th percentile, and the 3rd percentile.

This curve indicates how a child is moving through childhood. For example, a patient at age 4 growing 5 centimeter. If she will continue to grow in the 3rd percentile, you see that she will be growing less and less until she reaches the prepubertal age, in which she will accelerate. Similarly, somebody growing at the 50th percentile will decrease from 4 to 6, and they will plateau until they increase again. We will be using this chart to show each one of the patients that we analyzed plotted against normal kids.

It is important to emphasize that some caveats need to be taken into consideration when looking at our analysis. The P values are not adjusted for baseline or demographic factors. These are post hoc analyses, and not intent-to-treat analysis. Also, we are not accounting for drop outs.

Most importantly, when we are labeling safety parameters, we look at trends. Statistically significant differences are not required. Trends, especially in smaller studies, suffice for safety labeling. You will see that in most of the studies we have statistically significant differences in growth velocities.

What did we do? As Barbara stated before, we looked at the raw data that were sent by the sponsors. The patients were excluded if the growth rates were listed as negative, and we have plenty of those in different studies. If the prepubertal growth rates exceeded 12 centimeters per year, that means a standard deviation of about the 50 percentile. We used this number to exclude patients both in the control and the active groups, and we did not choose this number after looking at the data. We decided that this number was quite generous.

Also, we used girls less than 11 years old, and boys less than 12. Some of them may have been already in early puberty. Also, as stated before, children less than 4

were analyzed in a separate group. Therefore, the re-analysis is not based on an intent-to-treat population.

A different study is the ability of the inhaled beclomethasone, is the study that was mentioned by the two previous speakers. This was a randomized, double-blind, parallel, and placebo controlled. It was well designed. The children were between 6-14, but we excluded, as stated before, the children that were if boys, older than 12, and girls older than 11. The mean age for this group was 8.8.

It had three arms, the placebo, the BDP, and the salmeterol, but I will focus only on the first two. Again, let me show you what was published in the literature. We are focusing on only in 46 kids in the placebo group, and 54 in the active group.

These are the results. The patients that received the drug were growing at approximately 4.2 centimeters per year, while the patients on the placebo, 6.2 centimeters per year. The standard deviations are quite similar. The difference approximately is exactly 2 centimeters per year, with a  $P = 2.002$ .

The difference in growth velocity of 2 centimeters in a child of this mean age corresponds to 2.5 standard deviations. What does it mean? It means that if a child was growing at the 50th percentile growth velocity before, or was expected to grow, it would have been growing at the

3rd or below the 3rd percentile while on treatment as a group. That's the magnitude of the effect. If the patient would have been growing at the 97th percentile at the beginning, it would have shifted to the 50th percentile.

Let's look at the data in another manner. We are showing here the median growth velocity, and the 95 confidence intervals. The median line is the median, and the external lines are the 95 confidence intervals. Let's focus on the bottom left corner.

Here we have the growth velocity in centimeters per year of the change from baseline. We have different growth velocities. Here we have always in black dots, patients in the control group, in this case, females. We see that the median growth velocity for girls was 6, while the median growth velocity for girls on treatment was substantially less.

The same pattern can be seen in males, in which the median growth velocity was approximately 6, and the median growth velocity on the treated growth expressed in these red triangles was less than the median in the control group.

This also allows us to look at outliers. We see that some patients in the active drug were growing quite fast, and the same here in the control group. Similarly, here you have two patients in the control group, males, that

did not grow in one year, 0 growth velocity.

This is to refer the growth velocities we have seen in the previous slide to what is happening in the normal population. Again, the black dots are the controls, and the triangles are the patients receiving in this case, beclomethasone. These are for girls. You can see here again that there is a trend that these patients tend to be overrepresented in the lower growth velocity percentiles.

In boys we see exactly the same trend. Remember, there were two patients that were not growing. They are here. At the same time, you see the overrepresentation of these patients below the curve, the 3rd percentile. Similarly, a lot of patients are below the 50th percentile.

In summary, we can look at these data in the following manner. We can either compare one against the other, or we can compare each one against what is suspected in the normal population. We will compare one against each other. We see that patients in the beclomethasone group were growing slower as a group in every single percentile depicted in this slide, while 17 percent of the patients in the placebo group were growing at or below the 3rd percentile, 59 percent of the patients on the beclomethasone group were doing so, and this trend repeats itself across the study.

What happened with the triamcinolone, acetonide

study? The design was also randomized, but was open label placebo control. It was also one year duration, and the patients were stratified by asthma severity. I will be presenting only the data on prepubertal with moderate to severe asthma. These are the age groups that we will see. The mean age is 8.5 years. I'm looking only at two arms, the non-steroidal, 94 patients, and the patients treated with TAA.

The patients treated with active drug grew at 5.3 centimeters per year, while the patients in the control group grew at 6.1 centimeters, a difference of 0.8 centimeters per year, also statistically significant. This was approximately one standard deviation below, meaning that this group was growing one standard deviation slower as a mean than the control group.

This a bar chart that is similar to the previous one. In the bottom we have the girls in the control group, and in the top we have the girls in the active group. In the bottom we have the boys in the control group, and the boys in the active drug. Also, we see a similar trend in which the distribution is shifted in the active drug to the left, suggesting that these patients are growing slower.

I think that it is important now to think about the usefulness or lack of it of the mean and standard deviation. What are we missing when we look at these data

that are statistically significant, and we'll only look at mean and standard deviation? What we are missing when we do that are these patients that are really probably the patients that are mostly affected by this medication.

What should be done with a patient like this? When a patient comes and is growing this slow, probably we have to measure her again to make sure that this number is correct. This is the first thing.

The second thing, to make sure that this patient is taking the medication in way in which it is indicated. Maybe the patient is taking more medication than we have indicated. If this is not the case, and the patient is taking the dose that is indicated, maybe we have to reconsider in adjusting the dose.

Going back to this patient, really when looking at the slow growth velocity, maybe this patient, if we have a previous growth velocity, the medication is helping this particular patient to move up. But if we look at the trends in the group, I think that it is clear that these patients are growing slower.

The similar trend here with the boys. Patients receiving the active drug are overrepresented in the lower percentiles. This is summarized in this table, in which there were 5 percent of patients in the control were growing at or below the 3rd percentile, 16 percent of patients in

the active drug were doing so. These trends occur also at the 10th, 25th, and 50th percentiles. The means are small, but the trends are big.

The design of this particular study was with budesonide. It's also a randomized, placebo control. It's also open label. It's an extension trial. Eventually patients were treated for 12 weeks. The age range was very large, from 9 months to 8 years. For this reason, we decided to divide this into two separate analyses, from 4 to 8 year, and less than 4. Patients were either treated with non-steroidal medication, 81, or with inhaled budesonide at this dose.

For the age range of 4-8, the mean age was 6.1 years. The results showed that patients on the active drug grew at 5.9 centimeters per year, and patients in the non-steroidal group grew at 6.2. The difference is not statistically significant, 0.3 centimeters. It's approximately one-third of a standard deviation.

The randomization was such that there is an overrepresentation of patients treated, but also I think there is a slight indication again that some patients receiving the active drug may be growing slower than the patients receiving the control. I think you can visualize here, but because the randomization was three to one, this is a little bit deceptive, because one patient in this group

may represent three in the other, but we are not sure about that. The same in here; look at the boys. It's a similar trend.

I think that this summarizes what we are seeing in the previous three figures, and we see that again, the trend of overrepresentation in patients in the lower percentiles is clearly seen in the active drug.

If we look at the smaller group, and this is the only slide I have to show, this is the age range from 9 months to 3.9 years, with a mean age of approximately 2.3 years. The patients on budesonide grew at 7.8 centimeters per year, while the patients in the control group grew at 9.5 centimeters per year.

Here the difference is statistically significant, and this difference is approximately one standard deviation. Remember that these patients are growing faster, and here the magnitude of the standard deviation is much larger than in the previous studies.

The last drug that was orally inhaled was fluticasone(?). This study was randomized, double blind, placebo controlled, one year duration. Prepubertal children with moderate asthma were treated, and the age range for boys was 4-11, and girls, 4-9. The mean age was 8.4 years. It had three different arms: a placebo arm; a 50 micrograms twice a day, and a 100 microgram twice a day.

This is a little bit busy, but it has to do with the assignment of the study. The patients on the placebo grew at 6.3 centimeters per year. The patients in the 50 BID, 6.1; and the patients in the 100 dose, 5.7. The difference between the placebo and the 50 was 0.2, statistically significant. The difference between the placebo and the 100 was 0.6, and the difference between these two doses, you see the numbers here.

The differences in growth velocity were less than one standard deviation for both doses. There is some indication that there is a dose response effect on growth.

Let's see how these patients were distributed. We have a new group here that is the intermediate dose, that is square green symbols. We see the girls in the control group, the girls in the 50, and the girls in the 100. We see again, the median shifting to the left. A same trend is seen in the boys, in which you see again the median shifting slightly to the left.

When we look at each one of these individuals, we see that most of these kids fit in the normal growth curve. I'm showing here only the control and the 100, because it would have been too busy. Although most of them fit between the normal ranges, if you look at the distribution, you see that there is an overrepresentation of these red triangles.

In the boys, a similar trend with some outliers

here, patients that were growing at slower growth velocities, and also a group of patients that probably were undergoing early signs of puberty if they were properly measured.

The same again, I think if we look at the red triangles, there is a large number of red triangles here. When we look at confounding results, we see that there is not too much difference at the 3rd percentile. There is not too much difference on the 10th percentile. But when we start to move up to the higher percentiles -- remember, I told you that this group is overrepresented below the 50 percentile -- we see that it seems that the patients either with 50 or 100 have some affects.

The last study is a randomized, double blind study on BDP in intranasal beclomethasone that was a well designed, controlled, parallel group study of one year duration. Prepubertal children with allergic rhinitis were studied, and these are the ages. The mean age is 8.1 years.

There were only two arms. The BDP, this is the dose, 49 kids, and the placebo, 48 children. The results are as follows. Children treated with the active moiety grew at 5.1 centimeters per year. Children treated with the placebo, 5.8 centimeters. The difference was 0.7 centimeters. This was statistically significant, and was approximately one standard deviation between the groups.

That was the difference.

Again, there is a trend in this group to move to the left when compared with the controls here in the girls. In the boys we see almost a normal distribution, with some outliers. Here we see the overrepresentation of patients that are growing at slower growth velocities.

Going back to the growth curves, remember that here the randomization was one-to-one. Some patients are clearly growing slower. In the boys this is very much apparent.

The reason I'm trying to emphasize that means and standard deviation may not give the full picture, look here. We calculated these patients as part of the active drug. This is shifting all these groups substantially up, and doesn't give us an idea that these patients are affected. When we look at means and standard deviation, we might be missing the patients that are really affected, because maybe not all the patients are affected in the same manner.

As a synthesis of the previous study, again, the patients on placebo, 4 percent of this group was growing at 3 or less than 3 percentile, while the patients on the beclomethasone was 22 percent. Five times more patients were growing below the 10th percentile, 13 percent of the patients in the placebo group were growing at the 10th percentile. Here, 31 percent of the patients, and the trend

continues.

In summary, when compared to controls all studies show growth suppression in some children receiving corticosteroids. This suggests that all these products are systemically absorbed, and some patients' growth may be negatively affected by corticosteroids. The depiction of growth data as the mean and standard deviation fails to convey the observation that some patients' growth may be negatively affected by corticosteroids.

During the weekend we were fortunate to receive further information from one of the sponsors, Glaxco, that was generous enough to share with us information regarding growth velocities before patients were treated with these drugs. So far the only thing that we are able to show is a comparison between active drugs and placebo, but I think that the company that gave us this information that can illustrate a little bit what is happening with the patients before they are started on the medication, and what is happening with the patients when they are enrolled into the studies.

What I will show now is a growth velocity distribution in percentages before and after the drug. In the left column you have each one of the percentiles; the percentage of patients equal or below the 3rd percentile, and so on. The second column shows the distribution of

these patients before they were enrolled into the study, the BIS, 50. The same thing, the growth velocity of these children before they started on the drug, and the BAS, 100, the same in the group that was after enrolled in the 100 dose.

We see the first two columns, BAS-CT(?), and BAS-50, the distribution is quite similar. In BAS-100, especially between the 25th and 50th percentile, there is a slight overrepresentation of patients that were growing a little bit slower.

Then if we look at post-exposure either to placebo or to the drugs, we see how the picture slightly changes. We see in the first two columns how the patients in the control group almost did not change in growth velocity during the study. Therefore, all the data we showed before, at least in this study, we can assume that the patients that were depicted at the growth velocity of 8, was very similar at the age velocity of 7.

This trend is not the same in the patients that were treated with the drugs, because either at the 10th, 25th, or 50th percentile we see a change of overrepresentation of patients in the slower growth percentile. I think that this clearly indicates that the patients during treatment are growing at slower rates when exposed to the drugs, than they were growing before

treatment.

This also shows what happens before and after corticosteroid use in the completers. We see below or equal the 50th percentile, and above the 50th percentile. In the control, 32 percent of the patients were growing below the 30th percentile; and after, 36; 68 were growing above the 50th percentile, while 64 during the study. Therefore, no change was seen.

If you look at 50, while 33 percent of the patients were growing below the 50th percentile, during treatment 10 percent more patients moved in that direction, while of course 10 more patients decreased about the 50th percentile. This trend also is seen in the higher dose, and this trend seems to be more important, and is strongly suggesting a dose response relationship.

Thank you very much.

[Applause.]

DR. BONE: Dr. Purucker will be making some summary remarks, and then we'll have an opportunity for the committee members to ask questions and discuss some of the points raised in these presentations.

**Agenda Item: Summary and Conclusions - Mary E. Purucker, M.D., Ph.D., Medical Officer, Division of Pulmonary Drug Products, CDER**

DR. PURUCKER: Thank you, Dr. Malozowski. As I'm

certain everyone can appreciate, we have attempted to cover a lot of material during these presentations this morning, but we must have spoken very quickly, because we're about a half hour ahead of schedule.

During the next 15 minutes or so I'll try to summarize as succinctly as possible, the major elements of each presentation, and the conclusion that the working group has arrived at in their review of the scientific evidence supporting class labeling of the inhaled and the intranasal corticosteroids for potential growth effects in children.

The next slides you have seen before. They summarize the pulmonary allergy products in question, which are proposed for the class label. The first of these two slides lists the intranasal corticosteroids, including the active corticosteroid moieties, the trade name of the product, and the youngest age for which a nasal product containing the indicated corticosteroid moiety is presently approved.

Let me remind you that there are a total of six corticosteroid entities represented in these products, excluding dexamethasone, and that five of them carry a pediatric indication down to the age of 6 years, and in one case, down to age 4. There are different formulations of each moiety to include aqueous pump sprays and pressurized MDIs, and not all of them carry the same pediatric

indication.

Similarly, with the orally inhaled corticosteroids, a total of five active moieties are represented, again, excluding dexamethasone, and all carry an approval for use by children down to age 6, or again in one case, down to age 4. Again, each moiety may have more than one formulation, including inspiratory(?) -driven, dry powder inhalers, and pressured MDIs, or metered dose inhalers. And in some cases, different formulations may contain different actuated doses of each active ingredient. Not all of these products carry identical pediatric age range approval.

The next slide summarized the pediatric use data, and adverse events reported as growth suppression to the agency, which was covered by our first speaker, Dr. David Graham. The use of the orally inhaled and intranasal corticosteroids has increased in a linear fashion over the past decade, which appears to reflect both the increasing prevalence of disease, asthma in particular, and the current guidelines recommending treatment of the underlying inflammation, which is characteristic of both allergic rhinitis and asthma.

Children under the age of 12 are estimated to account for approximately 10 percent of all prescriptions written for these products. Based on the data presented

earlier, this would suggest that 2.4 million units of intranasal corticosteroids were dispensed for use by children last year. If we assume one prescription per child per year, and a disease of allergic rhinitis of 20-30 million children, that would suggest that something under 10 percent of children who carry the diagnosis of allergic rhinitis received intranasal corticosteroids as part of their management.

Similarly, for the orally inhaled product 1.3 million units were dispensed for use by children last year. Note that this is half the total reported for the nasal products on a by prescription basis. Assuming a disease prevalence of 4.8 million children with asthma, these data support the notion that a very small minority of pediatric asthmatics actually receive inhaled corticosteroids as part of their management.

Even if one child accounted for one prescription per year, which of course is unlikely, considering that each device only contains about one or two month's supply of corticosteroid, even then only 30 percent of the population would have received corticosteroids. Assuming a more realistic number of devices per child per year, an estimate of about 5 percent or under of asthmatic children actually receive inhaled corticosteroids. This is consistent with the data that was presented by Dr. Shapiro yesterday.

With regard to the adverse events database, growth suppression is rarely reported to agency in association with these products. For the reasons stated previously, there is likely to be underreporting.

The next slide summarizes the peer reviewed medical literature as presented by Dr. Alexandra Worobec. The database consisted of case reports, case theories, and clinical trials which spanned over three decades. Over 50 of the clinical trials retrieved by the search were included in the review. Although many trials were negative or inconclusive, serious design flaws were apparent -- retrospective chart reviews, open label, brief duration, and so forth.

It was notable that the trials which met the criteria which are generally accepted as well designed, randomized, double blind, parallel group, placebo, larger scale, and so forth, did tend to demonstrate decreased growth velocity among the treated patients.

The next slide shows the effect on growth velocity when detected varied from about a  $-.05$  centimeter to a  $-1.8$  centimeters per year. Overall, conclusions drawn from the clinical trials reported in the peer reviewed medical literature suffer from a number of limitations, one of which I just alluded to, design, and to which I will return on a subsequent slide.

Other limitations include they are almost exclusive representation of the orally inhaled products, rarely the intranasal, and the preponderance of a very few of the currently available corticosteroid moieties. BDP or beclomethasone was the most prominently studied of course, followed by budesonide, and fluticisone. Very few studies in the published literature included either triamcinolone or flunisolide.

Other limitations include the fact that these studies represent different practice patterns, and different uses of corticosteroid products.

The contribution of the underlying disease to growth suppression is still somewhat unclear. That is, uncontrolled asthma itself may impair growth. The studies on the whole did not address the long-term effects of these products. In particular, caution is warranted in concluding that there is no effect on final adult height, or that there is an effect. Conclusions based on a meta-analysis, which is in turn based upon flawed studies will only have a compounding of error as described by Dr. David Graham.

The next slide summarizes several of the major statistical issues which arise in the design and interpretation of growth studies as presented by our third speaker, Barbara Elashoff. Although issues are numerous, I would like to focus on the three listed here. In the vast

majority of studies cited from the peer reviewed literature, growth was not a primary endpoint. In addition, there were serious baseline heterogeneities in the populations studied, age range, growth velocity, disease severity, pubertal status, and prior systemic corticosteroid use.

The durations of the studies tended to be inadequate, with a baseline treatment period itself, or in the follow-up. Many of the proprietary studies, in addition to the well designed studies from the peer reviewed literature, attempted to address these problems. In particular, some representation of growth was often selected as the primary endpoint, and the study was then powered to detect a prespecified change.

Attempts were made to control for baseline heterogeneity, either by inclusion or exclusion criteria or by stratification. Attempts were made to study patients for as long as feasible, at least one year in most of the proprietary studies. For the most part, the proprietary studies or the better designed literature studies were randomized, controlled, parallel in design. They used label doses, and they were at least one year in duration.

With regard to the results, these proprietary studies did demonstrate a consistent direction of change. Mean growth velocity decreased in active treatment in all of these studies. Generally, the change in mean growth

velocity was of the same order of magnitude as seen in the positive studies in the peer reviewed literature. That is, a 0.3 centimeters to a -2 centimeters per year. A trend toward a dose response was seen in the one trial where it was examined.

Finally, although we did not deal with this observation in depth, the impact on growth was often seen very early in the treatment, after as little as one month out of a 12 month study.

The finding of growth inhibition was robust. The effect was observed despite differing analyses, whether there was a comparison of the mean change in growth velocity between treated and untreated, or whether the data was analyzed and displayed as a growth velocity distribution on a scatter plot, or as a growth velocity distribution on a growth curve.

There is a shift of the corticosteroid treated patients as a group toward lower growth velocity, and lower percentiles of growth by age compared to non-corticosteroid groups. HPA axis analysis where performed, was not predictive. That is, there was no discernible effect on the HPA axis by conventional measures, such as high dose, close entrop and stimulation testing, or more in cortisol, in spite of the measurable growth effect.

The findings of these proprietary and well

designed published growth studies raise a number of issues for which we do not yet have answers, in particular: the effect of intranasal and orally inhaled corticosteroids on final adult height; the relative impact of different corticosteroid products on growth. As has been repeatedly stated by the agency, there are no adequate and well controlled studies known to us comparing the relative growth effects of the different corticosteroids.

The impact of different dosing schedules, or continuous versus intermittent treatment are also unknown. The latter brings up the issue of possible catch-up growth. Information concerning the lowest effective dose for these products is, in general, lacking. The effect of downward titration on growth and efficacy is not fully known.

The growth effects of intranasal corticosteroid products have not yet been fully elucidated; few studies have been conducted, or at least published. All such products are systemically bioavailable, and the potential for decreased growth velocity should be assumed. Research is also needed to identify a test or some other measure which might correlate with, or be predictive of growth suppression and other undesirable systemic effects.

In summary, orally inhaled and intranasal corticosteroids can decrease growth velocity in children. Growth inhibition appears to be a class effect of

corticosteroids. The impact on final adult height is not known. Conventional measures of HPA axis effects are not predictive. The magnitude of the effect appears to be dose related. More data on the lowest effect doses are needed, and short-term measurements or tests predictive of the growth effect or other systemic effects remain to be identified.

Our recommendations are as followed. As stressed in the NAEPP Expert Panel II Guidelines, growth should continue to be monitored in all children receiving orally inhaled or intranasal corticosteroids. Adjustments should be made in a dose or in the overall management of children with apparent growth suppression should actually be considered. The latter should especially be considered in the case of the intranasal product, where the risk/benefit ratio is clearly different from the risk/benefit ratio for the inhaled corticosteroid products.

Studies are needed to identify the lowest effective dose of these products to allow downward titration, and research is needed to identify factors which might correlate with the adverse growth effect.

Thank you for your attention. I would now like to take questions.

[Applause.]

DR. BONE: Thank you, Dr. Purucker. I'm sure

there will be questions for a number of the people who made presentations. We'll just start with Dr. Hirsch, please.

DR. HIRSCH: I have just a technical question. I don't know who the best one is to answer this, but one of the things I notice repeatedly is that in the categorical analyses that you have done, in which you look at what percent of the children have achieved a certain percentile of growth, which is a very important and appropriate thing to do, that it seems to me that nearly always in the placebo or control data these children are much bigger. That is to say, 30 or 35 percent achieving the 50th percentile.

So it's correct I think, to ask the question of are your fundamental reference data the best thing you can do? Now to answer that question it seems to me what might be an interesting statistical manipulation is to take your placebo data and do a curval linear regression versus time, and then to do a traditional observed minus expected now with the treated, and see whether they are significantly different or not. That almost has to be done, doesn't it?

MS. ELASHOFF: Well, you have to remember that those were just the completers. A higher rate of drop out was seen in the placebo or the control group. So that might be why there are only 30 percent of the control patients growing under the 50th percentile.

DR. HIRSCH: Do you know that the completers are

different from the non-completers in respect to that? That's a fundamental thing you have to know if that is your answer?

MS. ELASHOFF: I reviewed one of the five studies in detail. In that study, the drop outs were fundamentally different than the completers.

DR. HIRSCH: They are more normal in growth, you mean?

MS. ELASHOFF: Well, that was hard to tell, because we had so few data points on those patients. Since the data was so variable, making a regression line on those patients showed growth velocities very strange -- negative or very, very high. But in general, among those patients the active treatment patients were growing faster than the control patients. So in that sense, they were very different from the completers patients.

DR. HIRSCH: That makes the final interpretation a little difficult, I think.

MS. ELASHOFF: Yes, it does.

DR. BARANIUK: Could somebody help me put the overhead projector up, please? I had a couple of overheads that I think will reflect the FDA's position a little better.

DR. MALOZOWSKI: We welcome anything that reflects our position a little better.

DR. BONE: Let's go ahead with Dr. Davidson's question while we are arranging the audio-visual aid for Dr. Baraniuk.

DR. DAVIDSON: There is no question, in every single study there is a decrease in growth velocity. There are two things. One, the younger the patient, the more the effect of the drugs in growth velocity. From all the data that you have, is the final growth, if you have any of that data, different, or will it have any data on children after they started growth and they finished their growth? No.

DR. MALOZOWSKI: We don't have any data. That's all the data we have.

DR. DAVIDSON: Thank you.

DR. BONE: Just to follow-on here. I think Dr. Malozowski showed the one study where you had pre-treatment growth velocity data. Do I recall correctly that that also showed an underrepresentation at the lower percentiles prior to treatment in both the placebo and the control group? Am I right about that?

MS. ELASHOFF: Yes, but again, those were just the completers patients. Even at baseline we didn't use the entire cohort of patients for that slide.

DR. BONE: So that's the pre-treatment data for the completers only? But you do have the pre-treatment data for all the subjects, and could look and see if there was a

difference between the completers and non-completers with respect to baseline growth rates? I mean, this is conceivably a significant confounding issue if we knew why the completers didn't complete, and if that was in some way related to growth for instance.

DR. MALOZOWSKI: I think that there are two issues, I think going back to previous question. One is that the size of the study is such that we are not expecting a normal distribution in 50 kids. Meaning that 3 percent will be below the 3rd percentile, and 10 percent of them will be below the 10th percentile. I think if we would have 500 kids, probably we would expect this to happen, but with 50 the distribution is a little bit difficult to predict. This is one point.

The other point is that we can compare the active drug to the placebo or the control, and the difference is still there. I think this is the correct comparison.

DR. BONE: I think Dr. Hirsch was getting at the point though that you had I think five out of five studies in which this pattern was apparent in the control group.

DR. HIRSCH: That's correct, that was my worry.

DR. MALOZOWSKI: Four or five.

DR. BONE: Dr. Baraniuk.

DR. BARANIUK: I went through all of the data that was available to us. I know you didn't want to show dose

responses, but I just wanted to plot out the changes in growth velocity from the controls for each of the steroid doses in each of the drugs.

The BDP is the open circles here. I'll get to that in a second actually.

What you see is that overall we've got a significant relationship here. The correlation co-efficient is  $-0.5$ . The R squared is  $0.25$ .

This is all studies, nasal plus bronchial. I separated out the BDP data, shown here with the solid squares. It then gives a correlation co-efficient of  $0.57$ . If you take all of the other drugs -- that will be the solid line -- you see that there is also a significant dose effect, but it is not as severe if you will, as the BDP. I think that the predominance of BDP studies is skewing our interpretation of these growth results.

MS. ELASHOFF: I'd like to respond to that. The budesonide study and the triamcinolone study, the patients were titrated down in dose.

DR. BARANIUK: I think there is a whole series of confounding things, but I think given the data that is available, I think this is suggestive that there is a dose response curve, and that there may be differences between drugs.

Finally, the five nasal studies are shown in the

dark squares of the BDP. The two triangles are the budesonide studies. The lower shows the bronchial studies only, and again, the solid line represents the BDP data. The correlation co-efficient there is 0.58. For all of the studies not involving BDP, but involving drugs for asthma, we see a correlation co-efficient of 0.59. Again, this would suggest there may be a class effect, but BDP may have a larger effect than the other drugs.

DR. BONE: Excuse me, what was there about that, that made you say BDP had a larger effect when the R values are the same?

DR. BARANIUK: No, the R values are parallel. I did a statistical comparison of the growth rates for BDP compared to the other drugs. The difference is significant. The P is 0.037. I apologize for the Ns that are on there. They are not supposed to be on that study.

DR. KREISBERG: That's a two point regression line, is that what you are telling us?

DR. BARANIUK: No. When I took all of the studies together and compared the growth velocities for BDP, as opposed to all of the results for the other drugs, BDP was significantly showing greater suppression of growth velocity.

DR. KREISBERG: But if you look at the 400 microgram dose, you have four squares at that one level,

right? The net effect if you look at those is that they will neutralize themselves and fall on that line.

DR. BARANIUK: It's actually this analysis that was the statistically significant one. So you've got four drug doses.

I guess what I concluded from that was that we can see a dose effect for the growth velocity reduction. Overall, I think there is a significant difference between BDP and the other drugs. The nasal data is clearly incomplete, with only BDP and budesonide being tested. I think the bronchial data shows the same sort of trends.

DR. BONE: So you thought there might be a difference, but you thought that all the drugs tended to have the same qualitative effect?

DR. BARANIUK: Yes.

DR. BONE: Thank you. Dr. Oppenheimer with a question.

DR. OPPENHEIMER Throughout this discussion I haven't heard any comments on the potential use of animal studies to supplement the information we have available. I wonder whether any of the panelists would comment on use of animals for this purpose.

DR. BONE: Any comment from anyone from the agency? Is anybody aware of a suitable experimental model that has been used for this?

DR. MALOZOWSKI: We use many different animal models to assess growth. The problem is that the ones that are more accessible, meaning drugs, are not very good models. You can look at many different markers. Either way, they have changes in bone length when you sacrifice the animals. But they are really very poor correlators to these kind of things.

Other animal models like monkeys, are extremely expensive, difficult to do. I think we have gone a long way already in human use, that probably all the available data will be very useful to look at maybe lower doses or dose range studies in looking at these endpoints.

DR. OSBORN: Two kinds of questions. One is it's hard for me to tell what the prevalence of the problem is. If we assume there is a reduction in growth velocity in some of the people with asthma, I can't tell whether this is 10 percent of them, 20 percent of them, or if the whole population shifted down by a certain number of percentage points. Maybe you could clarify that for me.

Then did any of your data help us in terms of a minimally effective dose?

DR. MALOZOWSKI: I will have to clarify that, but I cannot. I think the only data we can talk about is what the last overhead will show. I think what we see is that the patients as a group are moving to slow growth

velocities. I think our quest here is in trying to measure these kids, identifying early on who is suffering the most in order to decide why this is happening. This is the first point.

Your second question was?

DR. OSBORN: I think all the doses were in the 400 microgram per day range. I may be off by a little bit. But I just wondered if you had any evidence of a minimally effective dose?

DR. MALOZOWSKI: There were only a single study comparing two doses. You saw the data. It seems that there is a trend there. Because two of the studies adjusted the doses as needed, yesterday you showed a presentation in which one of the sponsors stated that there is a correlation between dose and growth.

DR. FINK: In the proprietary and the literature data typically in asthma studies the greatest enrollment tends to be white, somewhat middle-class families. Yet there is a disproportionate disease burden among black and Hispanics. Did you look at the data at all to see whether the typically underrepresented minorities, who definitely bear a greater disease burden with asthma, were adequately represented, and whether there may be any differential growth effects based on ethnicity or race?

DR. MALOZOWSKI: No, I have not looked at this. I

think in these studies probably these populations are underrepresented, and I don't think you can make this kind of assessment.

DR. WOROBEK: I just wanted to clarify. In the published literature, almost all the studies dealt with Caucasian patients. It's really impossible to make any kind of a subanalysis based on the data that was provided in those studies.

DR. BONE: Dr. Davidson, did you have a question?

DR. DAVIDSON: One comment. Actually, in the data that was shown yesterday -- and that was one of my comments for later this afternoon -- very clearly Dr. Shapiro told us yesterday that some of the affected people here are underserved populations and minorities. However, none of the studies had even 9 percent of minorities. When they show minorities, we don't know who they are. Therefore, when we look at studies from Scandinavia, they may show something that is of no particular benefit to us in the U.S., where the populations are totally different.

DR. BONE: Thank you. I guess that cuts two ways in a sense. If the studies are less representative of the population, but more comparable between studies for the purposes of looking at this particular effect. So this may be a mixed blessing or problem.

DR. CHINCHILLI: I had a general question first.

That is, what is the primary response variable? I agree that there is strong evidence of growth suppression if you are looking at growth velocities in these over a 12 or 18 month period. But is this just a surrogate variable? Is final adult height really the primary outcome variable we are interested in?

Or even beyond that, there is something that Dr. Peterson mentioned yesterday, and that is with doing bone scans, he didn't elaborate, but is it really the length of the skeletal structure that is more important, or is it the quality of the skeletal structure. I'm assuming we're concerned about health risk later in life as well. If a person is two or three inches shorter than they should be, what about the quality of their structure? Are they going to be at risk for osteoporosis and other fractures and problems later in life?

So I know bone scans are more expensive and more difficult to conduct, but really is that something that we want to look at, or is it final adult height? Or really is it true that we want to just focus on these height velocity measurements over a 12 or 18 month period?

DR. BONE: Are these responses to Dr. Chinchilli? Or does anyone from the agency wish to respond to Dr. Chinchilli?

DR. WOROBEK: I'd like to comment that first of

all, bone densitometries -- there are some inherent problems with using that really to look at bone density. That is that usually you have wait at least six months before you see an effect. So in terms of study designs, that becomes a problem.

But I think there is an issue we didn't really touch upon today, but in reviewing the Medwatch database we do also see certain types of adverse events which are also signals of something else going on. That is, in some of the children there are reports of things such as high glucose levels, high blood pressure, elevated cholesterol levels in association of use with oral inhaled corticosteroids. In many of these cases they have not received oral prednisone.

So in essence, what is this telling us about what these drugs may be doing apart from the growth velocity? And that maybe the growth velocity change that we are seeing is a surrogate for other types of effects we don't even know the implications of. I think that Dr. Hirsch touched upon this yesterday with his question, in that this is not simply an issue of vanity and height, but maybe these findings that we are seeing is telling us something more about what these drugs can potentially do in other organ systems.

I think we seek the opinion of the committee and others here in terms of really how to carry this forward in trying to better understand this.

DR. BONE: Actually, just to speak from the standpoint of the chair, the agency really did want to focus on the height issue, the growth issue here, rather than dealing with those other issues, and explicitly preferred not to address those other issues. That's why we have a narrowly focused meeting.

But I think that that's a different matter altogether than asking some of these more global and general questions. Obviously, there is only so much that one can accomplish in a particular meeting. But when we look at risk/benefit balance and other considerations of this kind, if we are analyzing each consideration separately, we might have a different conclusion or a different impression about the relationship to overall health and welfare of these patients than we might if we were looking in a broader view.

So this may beg this issue of other metabolic effects, and how those should be weighed. But I think that for the purposes of today's discussion, I think we are being asked to focus on this particular labeling issue at the moment. I gather that a number of people would be interested in how we might generate information that could be useful in looking at a more global impact of this very, very important type of therapy.

MS. CONNER: I just had a question. Was there any indication in the studies about the delivery mechanism of

the MDI? Was it an open mouth technique, closed mouth technique? Was there use of a spacer or anything that might have impacted the deposition orally pharyngeally or into the lungs, or may have enhanced absorption?

DR. WOROBEK: In the published literature, the later studies did use spacers. Obviously, the older studies did not. Also, in some of the studies they used drug powder inhalers. But that's really all we have available from that.

DR. MALOZOWSKI: I cannot comment on this, but I would like to elaborate on the following issue. I think that we shouldn't focus on the fact of whether these compounds are absorbed through the gastrointestinal tract, and I think we showed yesterday evidence as to the limitations. We have to measure some of these compounds from down to time in blood.

I think there is clear evidence that these are absorbed. Whether this is through the lung, I think so, or through the nasal mucosa, I think so. Whether is a component 8 percent, 20 percent through other mechanisms, I don't think it makes any difference, because I think the effects are clear.

DR. JENKINS: Let me just follow-up on that. From the proprietary studies it is very likely -- I don't know for certain -- but it's very likely that those studies, the

ones that were done with metered dose inhalers, were done without spacers. Because from a regulatory perspective, we always ask for the studies to be done without spacers, because that's how the products are approved.

Remember that the asthma court study would have been done with their "built-in" spacer device. Actually, the fluticisone study that you are seeing, was a dry powder inhaler formulation of fluticisone, not a metered dose inhaler formulation.

DR. AHRENS: I think the issue of dose relatedness that has surfaced recently is an extremely important one. In some of the presentation that we heard from Dr. Peterson yesterday, and in some of the writing for example that he has participated in recently, the concept of a dose that seems to be a maximally safe dose, so to speak, seems to surface. That is certainly related to the dose response issue.

In his presentation yesterday, he indicated that his data seemed to support that a dose of budesonide for example of 400 micrograms per day or less seemed to have minimal risk of the kind of growth signal we have been talking about here. In his writings, I believe the figure 200 for CFC, BDP arises.

This is an extremely attractive concept to me, particularly as a clinician I think having that kind of

information would really help to know how to respond to this growth signal issue. We all seem to believe that there is a dose response relationship. It's in the package, the recommended changes to the package insert, in the form of saying that you ought to use the lowest dose that is necessary to control the disease. In all the discussions, everybody seems to support that concept.

Clearly, the data that is now available, and that has been presented here today is not sufficient to clearly define what those levels are. My question is really first of all, is that a viable concept?

Second, would it be possible to design studies that could be done over say the next couple of years that would, for each of the preparations, recognizing that this probably is both drug and drug preparation-specific, would it be possible to design studies to gather that information for the preparations in question?

So that three years from now we would have more specific information that I, as a clinician, could truly use for a specific preparation, to know when I'm in a green zone so to speak, and I have less worry, and when I need to start to worry about this biologic signal, even recognizing we don't know what the long-term consequences are.

DR. BONE: Thank you. I'm assuming that that was a rhetorical question, not one where you are expecting an

explicit response, or did you ask a question?

DR. AHRENS: Well, I'm not sure that's true. I guess is it a viable concept? I guess I would be interested in perhaps the agency's response to that. Is it viable to consider if not right now, sometime in the future, being able to define criteria where that kind of information could be included?

DR. JENKINS: At some risks, I'll try to take some of those points on. I think the concept of a maximally safe dose is in some ways the inverse of the minimally effective dose. They have to be linked together. The way that these products are normally studied from a regulatory perspective is that they are studied in efficacy trials primarily, to support their approval. And the growth studies are usually not part of those trials, because the efficacy trials are shorter duration than would be necessary for the demonstration of the potential or lack of potential effect on growth.

So we usually have two separate databases. We have efficacy trials that give us some safety information. And we have the longer-term trials designed for growth that don't give us as much efficacy information, and they give us more safety information.

You could imagine that you could design longer-term studies to look at both efficacy and growth. You are

starting to talk about fairly complex studies, particularly if you are putting in several different arms, or different doses of the product in question, and maybe different doses of the comparative products.

We clearly, as a community, need more information about comparative effects of these effects on these endpoints than we have now, because while there are not enough data for us to make regulatory decisions about comparative statements about lack of effect or effect, clinicians everyday have to make those decisions. We desperately need more data.

So I would strongly support your call for more studies over the next couple of years to try to not only link the lowest effect dose and the safe does from a growth perspective, but also comparative data so that we can get a better handle on the idea that I think several people have that maybe there are differences in these products. We need to know that, and we need to know it sooner rather than later.

DR. CARA: Thank you. I think one of the difficulties that we're dealing with is the order of magnitude in the change of the growth velocity, and translating that into clinical practice. While on one hand the change in the growth velocity doesn't appear to be that significant, it does indeed have a significant impact over

time.

Part of the difficulty is also taking that into consider in view of the fact that we don't have any final high data to suggest whether or not, or to tell us whether or not there is in fact catch-up growth later on once these medications are discontinued or tapered off or whatever.

I was wondering from more of a practical standpoint if you could translate the observed differences in growth velocity into what they mean in terms of growth? That is something that can be relatively easily done by simply taking a growth chart and maybe showing what happens when a child grows at a growth rate that is at the 50th percentile versus 10th percentile versus 3rd percentile.

Could you put that together and show that?

DR. MALOZOWSKI: It would be more than a few minutes. It would be very speculative to do that. I can you this, when you look at the data within the first month, and then you continue to look at the data the second and so forth, clearly the curves of those exposed to the drug and the control are separating.

If we assume that the patient is losing one standard deviation, 1 centimeter per year, if somebody starts on these drugs, and this will continue to accrue, but this is something that we don't know. These patients will be at least 5 centimeters shorter, 7.5 centimeters, 10

centimeters shorter, depending on whether it's 1.1, 1.2, whether the patient is treated 1 year or 10. This is one point.

I can tell you this, we have approved drugs in the agency that do exactly the opposite. That you increase maybe the final height by 5 centimeters after 4 years of treatments for some indications.

I think we shouldn't focus on this difference of one standard deviation. We have to look at the individual patients that may be falling from the growth chart, and act on these patients. I think that the spirit of the labeling suggests that.

DR. BONE: Thank you, Dr. Malozowski.

DR. KELLY: In concern about the labeling or potential labeling, I wasn't all that impressed that you do continue to get growth suppression as you stay on the drug. I'm a little bit more impressed with some of the published literature, and that from Dr. Peterson that even with continued use of the drugs, you might get catch-up growth.

You might not continue to go on that decline. Have you looked at the proprietary information in terms of do you continue, or is this a 3-6 month phenomenon that occurs and sort of disappears whether you continue the drug or not continue the drug?

DR. MALOZOWSKI: We don't have data for more than

one year. What we know is what happened between the first month and the twelfth months, and the curves diverge. They expand and expand.

I really liked the data that was presented yesterday, but we didn't have a chance to look at these data, and these data are not controlled. These are not really what would have happened if these patients were controlled and compared with another group. These were very interesting, very reassuring somehow data on final height.

I don't see any reason to believe that when you continue on these drugs, the curve will not continue to separate.

DR. KELLY: In the Simon study, for instance, after the first three month period, there didn't seem to be any difference between placebo and the beclomethasone treatment group. They were basically parallel.

DR. MALOZOWSKI: That's true. That's correct, you saw this in the Simon study. But there are many confounders in that study. First, the patients at baseline were not similar. The groups are different. If the look at the paper, the first table, you will see that the groups were not similar.

The data were adjusted to address the difference, but we don't know really whether you would see a difference when patients are exposed to the drugs for a longer period

of time. We don't know how to adjust for puberty. This is another very strong confounding factor in that study, in which some of the patients were 14.

At age 14 you can have a girl growing at 2 centimeters per year, and she could be at the 95th percentile, because already stopped growing. We don't know what happened really there.

DR. SZEFLER: I think just to follow-up on Dr. Kelly's question, because I had the same question of Dr. Simon's data when I looked at it. The first three month period seemed to be a factor, and then as you were presenting this data, I was hoping you would extend it, because we get these kind of pendulum shifts.

I think we have been lead to believe there has been nothing there, and we look at your data, and you can't help but be impressed that there is something there. What I worry about is that the tendency is to make decisions on basically two points, 0 and 12 months.

As Dr. Kelly pointed out, is there something that is happening the first three months that doesn't happen in the sort of last three months of that year? I think we have the ability to look at that with Dr. Simon's data. We would be remiss not to see that, or not to hear about that.

The other thing I think we have to keep in mind is we are always looking at fixed doses, regardless of age. I

got the impression looking at your scattergrams, which I think is excellent, and a very nice contribution, and I wonder why that wasn't looked at before, a long time ago, but I got the impression that most of the effects were occurring in the younger age group.

Which if you just mathematically put it in your mind, they would be getting double the dose per weight. So if you did have a dose response relationship, that dose response relationship should naturally translate to the younger children, and have a greater effect.

Which then kind of gets us to Dr. Ahrens' point in terms of establishing doses. We may have formulations. We have been on the scale of having formulations that go up on the dose, and maybe we need to be thinking, this has implications for pediatric-specific formulations that have lower amounts per dose.

So I wonder if you could comment. You must have looked at it. You had all the data there. You showed individual patients with points. You must have looked at the first six months and the last six months.

MS. ELASHOFF: I looked at it in the one study I reviewed, budesonide. The difference did widen as the study progressed, however, as I said before, there was the problem of drop outs. Yesterday the company showed us that in the fluticasone study, the difference widened after the first

six months. But again, they had the problem with the drop outs.

DR. BONE: Thank you. Is there anyone who hasn't asked their question yet? Oh, yes, I'm sorry. This is Dr. Crim. My apologies.

DR. CRIM: This is more of a technical question you can just kind of clear up for me. Yesterday one of the pharmaceutical companies had presented data in terms of standard deviation. I think one of the speakers today alluded to that.

Just for my own edification, I gather it's not a great way of looking at the data in terms of basing the scattergram plot as well. But just what is the rationale for using that, and can you expand upon the limitations of presenting data that way?

DR. MALOZOWSKI: I think it's a great way to present data, but we have to choose what way to do it in order to show some of the outliers in the patients that are most affected. That's the reason we decided not to go that way.

But the important message in expressing the data in that manner that shows you how a particular patient or group of patients is going further down, or going further up from what is expected. Somebody that will continue at the line 0 is a patient that will continue growing at what was

expected. If the group is growing at -1 standard deviation, it indicates that the group as a whole is growing in this particular case, X number of centimeters less as a group.

The same when you go up. If you are looking at the growth promoting agent, if the group is going up, or if let's say we assume that asthma inherently has a problem with growth, and patients that have asthma do not grow, then you use another agent, you will see an increase in the standard deviation curve if this were true. You control the disease, therefore the patient should grow faster.

Is that clear or not?

DR. CRIM: That's fine.

DR. MALOZOWSKI: Thank you.

DR. LIU: For fear of sort of repeating a lot of what everybody else has said, I would really like to thank the FDA presentation, because I have sort of walked out of here believing that there certainly is an effect on growth velocity using the best available data. I sort of congratulate the companies that also provided proprietary information to help make these analyses possible and certainly more convincing.

I guess as a comment, I really believe that one of the big issues, which I think will be dealt with later on, has to do with this issue of safety. Certainly, from a theoretical standpoint, nobody doubts the effect of systemic

corticosteroid exposure on multiple aspects of metabolism and growth and that sort of thing, and the fact that all of these are systemically absorbed certainly indicates that there will be an effect at some dose.

Now it's a matter of what is the safest dose, and what is the dose that allows efficacy? And having said that, I think that's perhaps one of the goals of this meeting. Having said that, I think it's a very complicated issue, especially in light of some of Dr. Peterson's data that indicates that you can actually get away with a lower dose if you start early, and you may improve lung function to a greater extent starting earlier. Which also affects certain therapeutic decisions that we all sort of make on a day-to-day basis.

So I guess this is more of a weighing in, in terms of what I believe. So I think that part of it really has to do with deciding there is no difference in terms of a dose response in one study that Dr. Peterson showed in budesonide of 100 versus 250 or 400 micrograms in terms of efficacy in pulmonary function.

I really think that lower doses and studying lower doses in terms of efficacy, and then finding some surrogate marker for what would be significant side effects with lower doses of steroids would be useful in terms of making therapeutic decisions about these drugs.

DR. BONE: Thank you. I think we have questions and comments from Drs. Cross, Fink, Osborn, and then we'll get everybody else.

DR. CROSS: Since we'll be addressing the issue of intranasal versus oral inhalations, and since we all agree that the risk/benefit for the intranasals are not to the degree of the orals, I would like to ask the FDA who presented some studies, it looked like even using the same dose, for instance BDP, on comparing oral versus nasal, do they have any feeling as to whether the nasal is less potent at inducing growth inhibition effects compared to the oral?

DR. MALOZOWSKI: We didn't compare the two studies to reach that conclusion. We cannot reach that conclusion.

DR. CROSS: It looked at first glance where you had some BDP data at 168 BID for oral and intranasal, that the intranasal was about a third the growth suppression as the oral. I just wondered if that was fair to say or you didn't really compare those two studies?

DR. JENKINS: I think those types of comparisons are very hazardous. You are assuming that the systemic exposure from the same nominal dose given intranasally and by the inhaled route are going to be the same, and I don't think we have good data in the same population to define that.

You are also doing a lot of cross-study

comparisons. So we have been very reluctant to get into that hypothesis game of what do the data tell us when we do those types of comparisons. It would be wonderful to have some good, solid comparative trials to try to reach those type of conclusions, but I don't think we want to speculate on whether the effect is a third intranasal, and what it is when it is given by the orally inhaled route at the same nominal dose.

MS. ELASHOFF: One thing I would like to say about the data from the inhaled beclomethasone study, for some reason the data that we received was rounded off. The height at baseline and the height at the end of the study was rounded to the nearest integer. Age was also integer. And I don't know if they rounded up or down. For all the other studies I considered a 7.6 year old patient as 7 years old, and they may have considered a 7.6 year old patient as 8. So that may be one reason why it looks very different.

DR. FINK: This is more a comment I guess, than a question. It seems like we are aware of the fact that there is marked individual variation in steroid sensitivity. And that maybe some of the discussions yesterday and today have given us some of the answers, that using the technique of knemometry, it would appear to be feasible to do longitudinal crossover studies on a small cohort of patients. That's where dose sensitivity and drug-to-drug

variation really should be studied.

I can't see how you could design cross-sectional studies of an individual drug or doses that would yield valuable data if we don't have a handle on the issue of individual sensitivity to steroid side effects.

So it seems to me like what we really need are some well designed longitudinal studies, with appropriate wash out periods, and that knemometry would be the ideal technique then to use to look at dose ranging studies in a fairly small cohort.

DR. WOROBEK: I wanted to comment on the use of crossover studies, which actually is a very attractive model. The problem being that oftentimes one has to also take into account what length of a run in period, in order to get baseline velocity. Also, a lot of the studies that were presented that were crossover studies, one of the problems that became very apparent is that these are not actually true crossover studies, and that patients are randomized to one treatment sequence.

In addition, the wash out periods between the different treatments were either one to two weeks, or no wash out period whatsoever. The other problem becomes how do we know what is the adequate wash out period? Do you wait one week, one month in terms of assessing whether patients are returning to a baseline growth velocity?

So I think those are some issues that need to be also considered if one were to pursue that type of a study design.

DR. BONE: Thank you. Dr. Osborn, and then Dr. Crim, and then we'll take our break.

DR. OSBORN: A quick question. Dr. Purucker, I, of course was very impressed with the data you showed this morning. One thing that caught my eye, although I know it's not the major topic this morning, was the low frequency of children actually taking both intranasal corticosteroids and orally inhaled corticosteroids; on the order of 5-10 percent respectively perhaps, given some of the looseness of the numbers.

My concern is that while we focus appropriately on labeling and the risks of a consequence of steroids, including growth velocity and so forth, I think an important message that jumps out is how to let people know the importance of using corticosteroids?

Certainly, the NAEP/EPR2 guidelines point out the importance of using corticosteroids and intranasal corticosteroids as a first line way of managing asthma. My concern is that that message may be lost in focusing on the appropriate concerns about effects of steroids. How can we make sure that the message that comes out includes the importance of using inhaled corticosteroids with appropriate

caveats?

I just what I'm asking is does labeling ever include the importance of using something when NAEP/EPR2 is so clear about saying it is the most important therapy. It really catches your eye that these numbers are so low; or it catches my eye.

DR. BONE: One thing we could do is include that in the discussion after Dr. Jenkins presents the proposed labeling. I think there will be other comments and questions along the same line.

Then if we'll go ahead with Dr. Crim's question on this morning's presentation, we could get to the break then.

DR. CRIM: Dr. Malozowski, I think the last overhead you presented included the baseline run in that was growth velocity data for one of the corticosteroid studies. My question is, I don't know if you had the individual data for those patients. Is it possible to take that data and look at what the individual patients' baseline growth velocity was, and then compare that to what their growth velocity was over the course of the study?

Or in that particular study, were all corticosteroids allowed in the baseline period? That that would sort of like confound the use of that baseline run in growth velocity data?

MS. ELASHOFF: I'm sorry, I missed the very last

part of that question.

DR. CRIM: Was the run in period in which that baseline data was collected such that systemic corticosteroids were allowed, that that would confound the interpretation of that baseline growth velocity data?

MS. ELASHOFF: I didn't fully review study, so I don't know the answer to that part of the question. I did look at the difference from baseline growth velocity and model that. Baseline growth velocity was an important factor in the model, and the treatment effect was still there, and statistically significant.

DR. CRIM: So in other words, let's say if a person -- could you look at the data and say that if a person was let's say on the lower percentile to begin in, that they were more susceptible to the effects than let's say a person that may have started off -- whose baseline run in was let's say at the 50th or higher percentile?

MS. ELASHOFF: We did look at the data in terms of what percentile the patients were at, at baseline, and how they shifted to what percentile afterwards. I didn't specifically look at if there was a difference for the kids who started out at the lower percentiles at baseline, and the children who started out at the higher percentiles at baseline, so I guess I can't answer that question.

DR. BONE: I think what Dr. Crim is getting at is

it's often extremely useful when we are looking at something like this to have, for example, a graph that shows everyone ranked by their starting growth velocity, and then shows the individual deltas on treatment, to give an idea of what the pattern is. This is extremely helpful in this type of thing. Is that what you are asking for, Dr. Crim? I think that would be most useful in a discussion of this kind.

MS. ELASHOFF: We considered that. Dr. Malozowski wanted to do that graph.

DR. BONE: He's a very wise person.

MS. ELASHOFF: Before I started it, I thought about what it would look like. If you consider the fact somebody starting out at the 3rd percentile, who goes to the 3rd percentile, would be a straight line. Now if there were more than one person that went from the 3rd, it would still be just one line. You wouldn't be able to distinguish how many lines were there.

So if you consider that at least one patient out of the 200 or so patients that were in the study, went from the 3rd percentile to the 3rd percentile, at least one patient went from the 3rd to the 10th, et cetera, we would just have a very random looking graph. We wouldn't be able to tell how many patients went from the 3rd to the 3rd, from the 3rd to the 10th.

DR. CRIM: I ask that question, and I think Dr.

Hintz's presentation yesterday it's important to know what a person's run in, so to speak, before they even randomize into the study, what their growth velocity curve is. So that's why I was wondering.

By now having those individual data points, that each person will you know for that particular person, whether or not they changed their run in growth velocity once they were randomized to a particular treatment arm.

DR. MALOZOWSKI: We looked at the data and we did analysis, but we didn't have time to share this with the company, and therefore because we don't have an agreement as to what we can present, we'll represent or misrepresent the data, because we don't know exactly how the data was collected, et cetera, we decided not to show it.

DR. BONE: Thank you. Dr. Ahrens has a question. What I would like to do now is have maybe the last question, if it is pertinent to the presentations from this morning. Take the break. Go ahead with the presentation by Dr. Jenkins, and then have more opportunity for general discussion after that.

Dr. Ahrens, is your question on data presented, or more of the discussion?

DR. AHRENS: No, it's on the data presented.

DR. BONE: Go ahead then.

DR. AHRENS: Related to the nebulized budesonide

study, as we heard from the Astra presentation yesterday, that was actually one of three studies that they did, that were very similar in nature. This is the one study that showed a significant effect on growth. The other two did not.

In looking at the results of the graph that they presented yesterday, what happens on the budesonide group in terms of their growth seems to be pretty similar in the three studies, and the difference really is what happens to the control population. In the one that showed the significant difference, it was above; in the other two it was actually numerically, although not significantly below.

They indicated that they had done an overall analysis pooling those studies. And looking at the data, I strongly suspected that when they do that, and include a statistical interaction factor, it is immediately going to kick it back out and say you can't do that. There is something very different about those results in those studies.

I did ask one of the people from Astra, and the answer at least I believe I got was that was correct. That there is something very different about those. So it's not just that one by chance showed it, and the other two didn't.

To me, it's important what the difference between those two study populations are. The difference is

severity, at least as indicated by their baseline medication was. Am I correct in saying in the one where there was no effect was the -- I mean where there was an effect was the group that was on one prior medication? Whereas, the other two, at least the majority of the patients were on prior medication?

So this says to me that there is a difference in whether you see this growth suppression signal based on severity of disease. There is something related to severity of disease. I think we can't look at the one study in isolation. You have to say that it really reinforces the point that with greater severity, that you are less likely to see this growth problem, and the risk/benefit ratio shifts.

I was wondering if I got a correct impression of these data? Do you have comments related to the -- can you tell us more about those two studies that didn't show an effect?

MS. ELASHOFF: I didn't review those two studies. We just received them about three weeks ago or a month ago. I think you could make that conclusion from looking at that graph and the patient population from the three studies. However, all three studies were the extension studies that started right after the efficacy study ended. There was no wash out in between. They were not designed as growth

studies. Height was one of many safety endpoints.

The other problem that may be introducing more variability and noise into two studies that did not show an effect is the use of the rescue medication. Because since those two studies had a more severe population, perhaps -- I don't know, I haven't looked at the data -- but perhaps those patients used rescue systemic corticosteroids more than the patients in the study that showed a significant effect.

DR. BONE: Thank you.

DR. HIRSCH: Can I just make one comment? This is maybe a misunderstanding you can clarify immediately. The issue is very important as to whether some children are sensitive to the growth inhibiting effect and some or not. If that proposition is true and is provable, you would have seen a bimodality in the treatment group on some of your plots. You did not see bimodality.

Therefore, we must conclude that the phenomenon that some children are sensitive is no by means provable. There is not one cintilla(?) of evidence that some children respond to this and others will not. We are just seeing the usual kinds of distribution. Is that true or false?

MS. ELASHOFF: That's true. In those graphs they were just growth velocity during the treatment period. As Dr. Malozowski pointed out, we don't know, possibly the

patients that were growing below the 3rd percentile during the treatment period were also growing --

DR. HIRSCH: I said there is no evidence of bimodality.

MS. ELASHOFF: But then in the one study were we have the baseline growth velocity, and I figured out the number of percentiles the patients shifted -- but we cannot present these data today -- it did appear there was a bimodality.

DR. HIRSCH: It's sort of an important issue for us to know whether there is or not differential sensitivity to this effect in some children. So your conclusion is what, that there is or there is not?

DR. MALOZOWSKI: We don't know, and I think your point is well taken in the sense that the first thing we do is we assume that some patients are more sensitive than others, but we don't know.

DR. BONE: A final brief comment from Dr. Jenkins, and then we'll take our intermission.

DR. JENKINS: I think there is a very important point that we have to emphasize when we are talking about this differential sensitivity. Remember that these are inhaled or intranasally administered products where there are a lot of patient factors that determine the actual exposure to the drug.

So it's possible that those patients that are more affected, could be patients who are using the device more properly, and getting exposed to a higher dose of the drug. We don't know that, but remember that these are not tablets or capsules; that everyone is being exposed to the same dose.

These are inhaled products. These are children where inhalation technique can markedly alter the amount of drug that gets delivered to the airways or to the oral pharynx and can, depending upon the pharmacokinetics of the drug, have a big impact. So sensitivity may not just a patient response to a drug issue. It could be an issue of dose delivered as well.

DR. BONE: Thank you. On that note, I have 10:48 a.m., and we'll break until 11:00 a.m. sharp.

[Brief recess.]

DR. BONE: The meeting is back in session. I would like to introduce the director of the Division of Pulmonary Drug Products, Dr. John Jenkins, to make his presentation concerning the draft class labeling.

**Agenda Item: Presentation of the Draft Class Label Document - John Jenkins, M.D., Director, Division of Pulmonary Drug Products, CDER**

DR. JENKINS: Thank you, Dr. Bone.

I have a very difficult task of trying to set the

stage for your discussion this afternoon. It's difficult, because I have to follow so many outstanding presentations that we've heard over the last couple of days, but I'll give it my best shot.

Before I go much further, I think it's important that I reprise what I said yesterday about acknowledging the people who have made this meeting so successful. Yesterday I complimented them on helping to put the meeting together so that we could get to the point where we were yesterday morning.

Today, I really need to compliment all the invited speakers for giving truly outstanding presentations yesterday morning to give us background on these issues, but also participating in the discussion, to give us privy to their expertise in these areas. Thanks again to Dr. Hintz, Dr. Levine, Dr. Allen, and Dr. Shapiro.

Also, I can't emphasize enough our thanks to Astra, GlaxoWellcome, Rhone Poulenc Rorer, and Schering Plough for their willingness to allow us to not only discuss their data today, but allow us at the agency to have the individual patient data so that we could do many of the subgroup and post hoc analyses that you saw presented this morning, to try to help elucidate what the data can tell us, and what the data did not tell us about these products and growth in children. So again, thanks to those four

companies for your willingness to participate.

Finally, it goes without saying that this meeting could not have been as successful as it has been, and the presentations this morning would not have been as good as they were had this working group that we put together many months ago not put in many hours of very hard work to make that a reality.

You have met most of the people on the working group today through presentations, but I want to highlight that there are some other members of the group that you didn't get a chance to meet: Dr. Chin from the Biopharmaceutics Division; Evelyn Farinis(?), who works very closely with our division in reviewing the post-marketing adverse event reports that come into the Medwatch system; David Hilfiker, who did an outstanding job as the project manager for this very difficult project; and Ann Trontell, who is another medical officer in the division who contributed significantly.

I think I need to point out that these people did this work while doing all their other regular work as well. In many cases, it meant spending long hours here at night, and long hours on weekends, and they truly have been dedicated to this project. I think we owe them all a debt of gratitude. I know I'm certainly proud to have been associated with them on this project.

In trying to set the frame for this afternoon's discussion I thought it would be useful just to remind ourselves briefly of where we have been over the last day and a half. Yesterday morning we heard presentations from the expert invited speakers to try to set the foundation.

We learned about the normal growth and development in children. We learned about some of the technology and assessment tools that are available to measure adrenal function in children, and some of the limitations of those assays. We also learned about some of the impact of corticosteroids on growth, as well as one individual's perspective of the impact of these products on growth in children.

We then learned about how these products are actually being used, or possibly not used in the pediatric community, both at the subspecialty level, but more importantly at the primary care generalist level from Dr. Shapiro. Finally, we heard some information from Dr. Hintz that has been repeated I think several times during the meeting about important and very vexing issues that have to be addressed in trying to design and analyze these important studies.

Yesterday afternoon we were privileged to hear the presentations from the four companies who have actually conducted these studies. Again, I think the companies

should be congratulated for committing the resources to actually do these studies. Some companies have not done these types of studies with these products, and I think again, these four companies are to be congratulated. We enjoyed hearing their presentations and their interpretations of the data.

Yesterday afternoon during the open public hearing we heard some very divergent opinions on what the data show, what the data mean, and what people think about the agency's proposed class labeling. I was very fascinated to listen to that discussion, since often we were hearing very opposite viewpoints from very similar groups of professional individuals.

Finally, this morning we heard the FDA's perspective on the available data. I think we tried to approach this in a comprehensive manner. By that I mean we looked at not only the proprietary studies that the companies submitted, but we also went back and looked at the epidemiologic data that are available, as well as adverse event data that are available to us at the agency.

We very carefully reviewed the medical literature. I know that Alex did many, many hours of pouring over those studies to try to ferret out all the information that could possibly be gleaned from those studies. We also talked about the statistical issues in the design and analysis of

these studies.

And finally, we reviewed the proprietary studies from the agency's perspective. And again, we had access to the individual patient data, and were able to do a large number of very interesting post hoc subset analyses, to try to learn what these data could tell us, and also what these data really couldn't tell us.

Which brings us to this afternoon's session. I guess my slide was made in advance of the changes in the agenda, but really this afternoon's session will primarily be focused on your review of the proposed draft labeling that the agency had developed, as well as the questions or the points for discussion that we posed to the committee.

The draft labeling that the agency working group has written was made available to the audience. If you don't have a copy, I think they were out on the table this morning. And the committee members should have a copy of those draft labeling statements. I remind you that those are draft statements. We are interested in hearing your comments on how those can be improved, if you think in fact they are warranted.

Let me also remind you that while we are talking here about adding class labeling statements regarding growth to the labeling of these products as a class, there are data already, and there are statements already in many these

products' labeling with regard to growth. So this is not a completely new issue that we are dealing with. In a lot of ways, it is an issue related to the evolving database, but it is also an issue related to trying to maintain and insure some consistency of message that goes across these various products.

If you look at the intranasal corticosteroid labeling, as I mentioned yesterday, there are currently some products that have no reference to the potential impact on growth in their statements. Those products that do have statements on their labeling regarding growth have a wide variety, and a wide mixture of some of the statements that I listed here.

In many cases, these statements are as many as 15, 20, 25 years old. These labels have not been changed in this regard in many, many years, and I think it's appropriate that we try to make them as up-to-date as we can.

The same is true of the orally inhaled corticosteroids. These products already have statements in most of the labels with regard to growth, although many of these have been in there for many years without being updated based on newly emerging data. And there is one product that currently does not have any reference to growth in its product labeling.

Yesterday morning I went through our objectives that we hoped to achieve by holding this meeting. I'm not going to walk through those objectives again, but I do want to walk through the caveats that I went through yesterday, because I think those are very important, and I want to make sure that we don't lose that context to the meeting.

First of all, FDA is not suggesting that orally inhaled or intranasal corticosteroids are unsafe for use in children. FDA is not considering restricting the use of these drugs in children at this time. I certainly do not want the message to go out to the practicing community, or more importantly to the press that there is any concern about the overall risk/benefit ratio of these products.

These products are approved for use in children. They are very important to the treatment of these diseases in many children, and we are not trying to say that the sky is falling here, and that these products should not be used. On the converse, these products are definitely very important, and we don't want that to be a message coming out of this meeting, that people should avoid these products.

On the other hand, it is important to note that what FDA is seeking to do is to insure that this class of drugs is properly labeled with regard to the potential growth suppression, in order to inform health care providers, and to promote the safest use of these drugs in

children where therapy is indicated.

We all know that no drug is completely safe. If a drug is completely safe, it probably has no efficacy. These products have tremendous efficacy, but they also carry some risk. We feel that it's important from a regulatory perspective that their product labeling adequately and accurately reflect those risks so that the practicing community can make informed decisions about how to use those products in the safest manner possible.

So while we are not suggesting that the sky is falling here, we also do not want to take the head in the sand approach of ignoring the risk of these drugs simply because we want to try to insure that they are being used to help treat patients with these diseases. We fully support the National Heart, Lung, and Blood Institute's program to try to improve the diagnosis and treatment of asthma in the United States. I don't think our approach today is in any way contradictory to that.

We are simply trying to make sure that accurate information is in the label, so that people are aware of the risk, and they can weigh the risk versus the enormous benefit of these products, and use them in the safest fashion.

Again, we consider this to be a class issue, and that is how we would really like to try to focus the

discussion. We don't think that there are adequate data to make regulatory decisions that state that one is less likely to impact on growth than another. Those are clearly very important practicing physician decisions that have to be made every day, and I recognize that.

I think we need more data. One of the calls I think that should come out of this meeting is that we need more comparative data of these products. We need more information about the lowest effective dose. We need more information about whether one product or one dosage form is less likely to be associated with growth suppression than another. Even in the absence of knowing what the long-term consequences may be, we need that information.

Finally, from a promotional standpoint, I want to remind everyone that from a regulatory standpoint we consider the available data inadequate to support valid comparative claims or promotional claims regarding the potential growth effect of these various approved active products.

We would welcome companies developing studies of a comparative nature to try to identify some of these issues. We are not opposed to that in any way, but they need to be well designed studies so that you can reach a scientifically valid and rigorous conclusion. These are too important of issues to be promoted on the basis of inadequate studies.

With that as a back drop, let me move on to our discussion points that we put in the agenda for the committee to address, as well as the draft proposed class label.

The first question that we posed to the committee relates to whether or not you believe that the available, by that I mean all of the comprehensive data that we tried to present over the last day and a half, are sufficiently compelling to support class labeling for all corticosteroids regarding their potential negative impact on growth velocity in children?

We would particularly be interested in hearing your comments on the proposed class labeling document that was prepared by the agency. I'm going to walk through that now with you. I want to emphasize that it is considered to be a draft document, so we are certainly interested in your input, so we can try to reach a final document, if in fact that's the way we choose to go.

I would like to walk through the proposed class labeling document for the intranasal corticosteroids just so that we can all know what exactly it says, and you may want to follow along with me. Before I do that, let me clarify a couple of things that came up yesterday. Several people referred yesterday to adding warnings to the labeling. It is important for you to understand that from a regulatory

perspective there is a warning section of the labeling, and there is a precaution section of the labeling.

The warning section, clearly, as it implies, contains much more serious information about the potential adverse effects of the drugs, whereas the precaution section is used to convey information to practitioners about how to use the drug safely, but for information that may not warrant being in the warning section.

Our proposal for the class labeling for these products includes adding information to the precaution section, not to the warning section. So please keep that in mind. There were some misstatements yesterday from some individuals suggesting that we were adding warnings. We are suggesting precautionary statements.

Under the precaution section of approved labeling there are multiple subsections. There is usually a general subsection in the precaution statement. We have proposed that under there we would add a statement that would say "Corticosteroids, including intranasal corticosteroids have been shown to cause a reduction in growth velocity when administered to children and adolescents. As with any drug, the expected clinical benefits of using intranasal corticosteroids should be weighed against the potential risk, including the potential for inhibiting growth."

As we often do in the labeling, we refer for

further information to the precautions pediatric use section of the labeling. So this is intended to be an introductory statement in the precaution section, that then refers the reader to a more specific section.

Now under the pediatric use subsection we're proposing that the language be, "Corticosteroids, including intranasal corticosteroids, have been shown to cause a reduction in growth velocity in children and adolescents. This effect have been observed in the absence of laboratory evidence and hypothalamic-pituitary-adrenal axis suppression, as assessed by ACTH stimulation or basal plasma cortisol levels. This observation suggests that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in children and adolescents than some commonly used tests of HPA axis function."

Continuing that pediatric use subsection, "The long-term effects of the observed reduction of growth velocity in children and adolescents using intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for 'catch-up' growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied."

Continuing, "The growth of children and adolescents receiving intranasal corticosteroids, including (here you would insert the name of the product for which the

label relates) should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained, and the availability of treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including (again, insert the product name), all patients should be titrated to the lowest effective dose."

So that's the language that we would propose to add to the pediatric use subsection of the labeling.

We're also proposing that in the adverse reaction section of the labeling, which is separate from the precautions section of the labeling, there would be this statement: "Cases of growth suppression have been reported for intranasal corticosteroids (here we would include the name of the product for which the labeling is relevant if in fact cases have been reported for that product). In addition, controlled clinical trials of intranasal corticosteroids at recommended dosages in children have demonstrated significant reductions in growth velocity in treated patients. Monitoring the growth of children and adolescents receiving intranasal corticosteroids, including (the name of the product), is recommended."

Again, they are referred to the precautions, pediatric use section of the labeling for further information.

Let me make a couple of other points here. This would be the standard wording that would appear in all the labeling of this class. This does not mean that other information about growth and the individual product would not also appear.

So for example, in the beclomethasone products, where we have an intranasal growth study for beclomethasone, we would also present the data from that study. We would probably have to do some minor adjustments to the language of the class labeling to incorporate the actual data from the study available.

For products that do not have studies available, then the class labeling would apply. If there were products that had a well controlled, well designed growth study that did not show an effect, we would also show that data in the product labeling. You would probably need to modify then the introduction to the class labeling statements to say something on the order of while this study did not show an impact on growth, corticosteroids, including et cetera, and you would merge into the rest of the proposed class labeling. This is the template that would go on all labels, but it would have to be adjusted by data or by lack of data.

The second question that we have asked you to address is basically the mirror image of the first question. Here we are asking you to focus on orally inhaled

corticosteroids. We asked you take these up separately, because I think it's clear that the risk/benefit ratio for intranasal corticosteroids for treatment of allergic rhinitis may be very different from the use of orally inhaled corticosteroids for the treatment of asthma.

In addition, the dose range for intranasal corticosteroids is often lower than the dose range that is approved for the inhaled corticosteroids. So I think it's appropriate that they be separated out as two separate questions.

Again, we are asking for your comments on the language of our proposed labeling. I'm not going to walk through the labeling for the orally inhaled corticosteroids like I just did for the intranasal, because the wording is identical, with the exception that where "intranasal" appeared before, substitute "orally inhaled," in this label. So again, it would be in the precautions general statement that would be the pediatric use subsection, and the aversive reactions section of the labeling.

Turning to the third point for discussion, and we have talked about this a lot over the past couple of days, and I think Dr. Ahrens even introduced a new term that we had not thought about, which was the maximally safe dose. We asked you to comment on whether the sponsors of new inhaled or intranasal corticosteroid products should be

required by the agency to determine the lowest effective dose for the product prior to approval.

A couple of points I need to make clear here so that you will understand. This part of the question talks about new products. So that does not necessarily mean a new active moiety. We are asking this question in reference to new products. A product could be a new beclomethasone product that is being delivered using a different dosage form, for example, a dry powder or an HFA propelled metered dose inhaler. So we are focusing the question here on products, not on active moieties. We are also asking you to comment on whether we should require this prior to approval, as a requirement for approval.

The third point is to point out that we are talking about lowest effective dose. I think I mentioned yesterday a little bit that not all products that are approved by the FDA have necessarily been studied carefully to determine whether or not the lowest effective dose for that product has been determined. There is no absolute regulatory requirement that the lowest effect dose be established for approval, because if you can establish that the dose is safe and effective, then you have met the standards for approval.

Obviously, in drug products that have a higher toxicity profile, there is more of a need to try to learn

about the lowest effective dose, to try to minimize the toxicity, while maximizing the efficacy. That may be appropriate in this class of drugs, where we may want to give practitioners more information about what is the lowest effective dose that they may be able to use in their patients, and in that way may be able to avoid some of the toxicity.

The smaller question that we asked at the bottom here relates to currently approved products. So those products that are already on the market, where possibly the lowest effective dose has not already been previously established, should we request -- and again, the word here is different; it's not required, it's request -- should the agency request these companies develop these data?

Question four goes to the issue of whether given what we know now about the impact of these products on at least short-term growth in children, should the agency be requiring growth studies for these products either prior to approval, or should we be requiring a Phase 4 commitment for the company to conduct these studies after approval within a specified time frame? So we are interested in hearing your comment on that.

Again, the language is very similar. We are talking about all new products. So we are not talking about active moieties, we are talking about products. So this

could refer to a new beclomethasone product. We're asking should we require a growth study for a new beclomethasone product before it is approved? Should we require a Phase 4 commitment?

Again, at the bottom we ask you to address the same question for currently approved products with regard to if the companies have not performed an adequate assessment of the impact on growth, should we request that the companies conduct those studies?

Question five, here we ask you to give us some advice on how we should be advising companies on the design of these studies. If we are going to do these studies, we want them to be adequate and well controlled and well designed studies. So we are looking for your expert advice on what are the key features that you think we should be incorporating.

How long should the study be? How long should you follow the patients after the study to look for catch up growth? What age group should you study, and how should you assess their pubertal status? What is the appropriate control group? How long should we evaluate the patients at baseline, to get a good assessment of baseline growth velocity before they are randomized into treatment? What should be the measurement technique for assessing height? And other -- we didn't list all the other potential topics,

but we're interested in your comments.

The final question, Question six, gets to the question of what's the long range impact of these products. Given the data that we've seen on the short-term impact, how can we get a better handle on the long range impact?

Dr. Peterson presented some very interesting data yesterday that he has conducted in Denmark on I think it was inhaled budesonide. How can we get good data to try to address the long-term impact of these products? So here we are asking you to help us with that type of study design. We are particularly focusing here on final adult height, although earlier in our discussion this morning as we noted, we are limiting the discussion to growth today, and we are primarily focusing on the long-term impact on final adult height.

There are a myriad of other potential systemic effects that could be reasonably be brought in the question about metabolism, bone accretion, et cetera, that may also be important.

So that's an overview of the proposed class labeling that we have drafted for your comment. It is the questions that we are interested in hearing feedback from you regarding. I'll be happy to clarify any of those points if you would like.

DR. BONE: Thank you, Dr. Jenkins. I think that

we have about 27 or 28 minutes until we would like to break for lunch, with the idea of having the general discussion in the afternoon. Perhaps for the remaining time before 12:00 p.m. we could direct questions specifically to Dr. Jenkins about the specific labeling issues that people may want to address. If there is time, we can broaden that discussion.

Dr. Cross has a question.

DR. CROSS: I had one question, Dr. Jenkins. Does this mean that ever company that has a fluorocarbon-based delivery system, as they switch over to non-fluorocarbon-based systems would have to do growth studies, for instance? That would be a new formulation of an old drug that is meeting another goal of the FDA. But would they then have to have another dimension to their presentation?

DR. JENKINS: Just for everyone's clarification, the products that Dr. Cross is referring to are related to the Montreal Protocol that mandates the phase out of the use of chlorofluorocarbons in all uses, and that includes most of the metered dose inhalers that are on the market currently. Many of the sponsors of those products are redeveloping those either in metered dose inhalers using a different propellant or a dry powder inhaler, or as under unique dosage forms.

To try to get to your question, we do consider those new products. They do require new drug applications.

So you should take those into consideration when you are thinking about your response to our Question 4 I believe it was, about whether you think we should a growth study for those products, or should we require a Phase 4 commitment for those products? So they would be included in those groupings.

DR. BONE: Dr. Jenkins, just to pursue that question briefly, how are those drugs going to be approved? Will that be on the basis of clinical efficacy studies for the alternative delivery systems? Or will that be on the basis of some kind of dose equivalency study?

DR. JENKINS: That's an important point that I need to bring with the members of the metabolic committee. Our committee is more familiar with this issue. Where the replacement propellant dosage forms or the dry powder dosage forms or whatever new dosage forms of these inhalational products required clinical safety and efficacy studies for approval, we're generally trying to limit the scope of those programs by including active comparators with the current CFC-based products so that we can make a comparability assessment, and rely to some degree on safety and efficacy data available for the CFC product.

But these are clinical safety and efficacy studies, generally 12 week studies, as well as long-term open label safety data, but it is not as extensive as you

would see for a product that has not been previously approved.

DR. BONE: We have a number of questions. Dr. Kreisberg.

DR. KREISBERG: Just a short question. It seems to me that the recommended labeling is pretty soft on monitoring growth. The wording is "is recommended," which almost sounds like it's optional. The sense of the discussion that has gone on here for the past several days is that the whole issue is to be a trade off of the benefits of the use of steroids with regard to disease suppression versus the potential risks. I wonder if you wouldn't want to use stronger language for that, such as "is required."

DR. JENKINS: Well, obviously we can't require that a practitioner who is prescribing a drug, actually do the growth monitoring. We would certainly be interested in hearing your thoughts about how you might want to modify the language if you think that section is not adequate the way that it is stated.

DR. BONE: Dr. Davidson.

DR. DAVIDSON: You know being an endocrinologist and not an allergist and a pulmonologist, from the data that was presented yesterday it is quite clear that those children need this medication. That is not a question in anybody's mind. The thing is, we will need to do two

studies that you are asking us. One will be to look first at the lowest effective dose. And then with that dose, do the growth studies.

My second comment is you know in general, most practitioners will not read the whole recommendations from your label. I am concerned that they may only look at the general, and in that general we may need to be a little more specific with a few things. That's my recommendation, and maybe we can leave that for the later discussion. But that general needs to be as implicit as we can, because maybe that's the only thing people are going to read.

DR. BONE: Just a point of clarification. Dr. Jenkins, do I understand correctly that you are looking at this label from the standpoint of how it will inform prescribers, taken as an individual document? And also how it will influence product promotion by the company?

DR. JENKINS: Yes, clearly both of those have an impact. As I said, the companies have individual data for their products. We clearly will be reviewing that data, and if it's adequate data, we will include that in the labeling. Then they would be able to promote those data to physicians and prescribers.

The thing that we are trying to avoid is cross-study comparisons or cross-label comparisons that are not valid, to try to say that one is better than another.

Although as I pointed out, we desperately need those studies, because we all as clinicians have to make those decisions when we see patients.

DR. JENKINS: Thank you. Dr. Gross I think had a comment or question.

DR. GROSS: Yes, I'm particularly mindful of what was said yesterday about the possible adverse effect on the use of these drugs, and how important they are, and the tremendous beneficial effect that they had already on the severity of disease, morbidity, mortality, and things like that. I think one has to be particularly careful that anything that we do or recommend does not adversely affect the use of these very, very important drugs. I want to say more about that this afternoon.

Could I ask you right now to explain -- because I'm new to this committee -- what's the philosophy of the FDA in terms of how important do you think it is to mention every side effect that comes up with a drug? I don't mean this facetiously. Please don't imagine that I'm being critical of the agency. But to what extent do you feel it's necessary to include as a precaution, everything that turns up about a drug during the course of clinical investigation?

DR. JENKINS: I think that's a very good question. I think we as an agency, have a regulatory responsibility to try to make sure that the product labeling provides the

practitioners with as much information as we can to help them use the products safely and effectively. We often have to include information in labeling about adverse events or about precautions based on fairly limited amounts of information, simply because that's the best information we have.

You often see statements in labeling about adverse events have been reported, and sometimes we have to caveat that by saying the clinical significance of that with regard to this product are unknown, or the association is not known. But we do feel an obligation to let practitioners know about the possibility of adverse effects.

So I think it's a very important balancing act that people are suggesting here. I think it's important that people understand that these products do have a risk, without undermining the use of the product, because they also have tremendous benefits.

But personally, I think there are hazards of underplaying the risk of these products, because you may see not just underuse of the product, but you actually see patients being treated with doses much higher than they really need to be treated with simply because the physician is not aware that higher doses may cause systemic problems.

I know anecdotally I have talked to several members of the committee over the past couple of days about

pediatric patients that they have seen on very high doses of these products, where it was probably not appropriate to be on those high doses.

So we are really trying to inform the prescriber about the risk, so that they will be aware of those risks, and therefore will take the advice that they titrate to the lowest effective dose, and they monitor for systemic effects without trying to frighten the people away from using these drugs where they are appropriately indicated, because they are so efficacious, and they are so important to the management of asthma, and to the management of rhinitis.

DR. GROSS: Can I just follow that up very briefly by saying that I entirely see that point of view, but then we have to be concerned with the overall use of these drugs. If including a statement like this were to decrease the use of a drug by say -- just to name an arbitrary figure -- 5 percent, the impact on the overall management of asthma and the care of it, and the results of that care would be very substantial in this country.

Whereas, the advantage to the physician and to the patient of knowing that there is a risk, which clearly they should accept in terms of the benefit, the advantage is pretty well zero. So I can see that the agency's expression of its responsibility in terms of putting this information out for the general use of the profession, but on the other

hand in terms of the effect of that, I'm afraid it might be negative.

DR. JENKINS: Well, I certainly respect that viewpoint. I don't think I agree that the potential risks are minimal or negligible. I think when used inappropriately, when used at higher than required doses, I think the risks do become a concern that people need to be aware of.

Someone earlier today talked about the pendulum swinging. It wasn't that long ago that they had oral corticosteroids and that was the primary way of treating patients with these diseases. The inhaled and intranasal corticosteroids were evolved as a way to try to minimize the systemic effects, but to maximize the benefit.

I think they have accomplished that goal, but sometimes the pendulum may swing too far into people thinking there is no risk; it is all benefit and no risk. What we are trying to do is simply to inform people of what the data say. I think we have very convincing and very compelling data that at least in short-term studies, these products can suppress growth, and therefore we feel an obligation to make people aware of this risk.

DR. JENKINS: Thank you. Let's see, I have questions from Drs. Fink, Ahrens, Szeffler, Cara, and Liu, in that order, and we'll get anybody else afterwards that we

need to.

DR. FINK: I guess I would have to say that although I would have to say that although I conceptually like the idea of lowest effective dose, unless the FDA can come up with a standardized way of measuring that, I think it is an impractical concept to require of the manufacturers.

Are you talking about the lowest effective dose for mild, moderate, severe asthma with concomitant use of other controller medications, by itself, with good inhaler technique, with poor inhaler technique? I think it could lead to just drug companies trying to stack the deck in their favor, and not any clinically useful information unless you had some standardized assay, that I don't know of at the present time.

So I really have problems with how that could possibly be implemented, even though the statement the patients should be titrated to their effective lowest dose I would agree with entirely.

DR. JENKINS: I agree with what you are saying, and it's a very difficult, trying to establish the lowest effective dose for all drugs, in all patient populations, disease severity, et cetera. It would have an added benefit though in helping practitioners decided about how low to titrate the dose.

Some people may be reluctant to go below the stated dose range in the labeling, because that's what the label says to use. So you can lower the dose that's approved in the labeling as being effective, it might help physicians feel more comfortable that they can go down to the lower dose.

For example, the fluticasone product is currently labeled at 50 micrograms twice a day as the lowest dose in children. Is it possible that a lower dose in that would be efficacious? We don't have the data on that, but if we had data saying you could go down to 25 twice a day, or 50 once a day, that would give many physicians, I think comfort to continually going down in the dose, because you have expanded the lower end of the range.

DR. BONE: Aren't we talking about two different questions here, just to further try to clarify this issue? The labeling is designed to be advice about the actual prescribing of the drug. I wonder, from the standpoint of this being advice to physicians about how to use the drug, if you would accept the recommendation that this be the lowest effective dose here, be clarified to be the lowest effective dose, effective in that patient, or their lowest effective dose.

And regard the question of dose finding for the product as something that the agency is in a position to

regulate in its interactions with the company about what studies will be performed in Phase 2 and Phase 3 trials, to look at what range, and with what adjustment for body mass, which doesn't seem to have been done in these studies at all. The point was made earlier that this whole business of giving a fixed dose to people of variable sizes may be a major issue here.

So it seems to me like we could possibly clarify by separating those two questions. How would you feel about that, Dr. Jenkins?

DR. JENKINS: I don't have any objection to that. I think that's a reasonable interpretation of what we're asking.

DR. FINK: Just a comment. I think the other risk of lowest effective dose, particularly in labeling, is that if you titrate down to a dose that is effective in a newly diagnosed mild asthmatic, many physicians would then find the drug non-effective when used in moderate to severe asthma, and would throw it out as a therapeutic agent.

DR. JENKINS: So you would prefer to talk here about the individual patients?

DR. FINK: I think it really should be individualized.

DR. BONE: Well, that's consistent with what the agency is saying, I think, in this particular point. Thank

you.

Next is Dr. Ahrens.

DR. AHRENS: My initial question was I think covered well by the two of you, really dealing with the definition of lowest effective dose. I do also think that there is a real danger of confusing the lowest dose that you might be able to give of that product, and have some statistically significant effect in a clinical trial, versus the lowest dose that you can still control symptoms in, in an individual patient.

I would suggest that you find two different terminologies for those two concepts, in particular to avoid eventually confusing the clinician when that information gets out there. You would really hate to have, as you were alluding to, have someone assume that the lowest effect dose is the dose that virtually all patients should be on, because that should have a sufficient effect in that patient.

The other issue I wanted to comment on, or ask a question about was the off label use. A few minutes ago you talked about, Dr. Jenkins, the fact that you had heard anecdotally -- and I was one of the people who provided one of those anecdotes -- about a number of patients who come in on much higher doses than are recommended, that are in this age range we are concerned about.

We're much more able to do that in the recent years with the availability of the preparations that it is easier to give high doses like the fluticisone 220 preparation and budesonide preparation that is now available.

Do you have any indication, just for example, of what the use figures are for prescriptions of fluticisone 220 in this age group? Which would be totally off label; would have to be.

DR. JENKINS: I do not have any data to address directly that question. It may be possible that someone from GlaxoWellcome may have data to that effect. I have data on the overall sales of the fluticisone products. There are three dosages strips. I have seen data that suggested that the highest dosage strip was the biggest selling member of those three, which leads to some question about the use of the product, or whether it's being used at a higher dose than needed.

It's hard to say that in the abstract, because we don't know how that breaks out into children versus adults. We also don't know about the severity of the patients who are being treated with the drug. So it's hard to make generalizations about whether those people are being overtreated. But it is important to remember that the highest approved dose of fluticisone in children is 100

micrograms twice a day. So the 220 microgram dosage form that is administered twice a day would be double the highest recommended dosage in children.

DR. AHRENS: At least in my region of practice, prescriptions of that particular preparation are not at all uncommon. I suspect that that's true many places as well.

I just wanted to reinforce the point that we are not only talking about providing information about the recommended doses, but alerting physicians to the fact that there is in all probability, dose related effect, and in the process to provide additional warning that those higher doses in many patients, should be very seriously reconsidered I think.

DR. SZEFLER: There were a couple of things that I was thinking about. One of the areas that I'm concerned about is the area of counter detailing. A package insert often gets highlighted in sections. I think as we think about the wording of this statement, we have to think about it in that context, because that is a very common habit.

The inhaled steroids are receiving a lot of competition from other classes of medications. Is there a reluctance or is there some way that this general statement can be worded to reflect the common knowledge that inhaled steroids, speaking particularly of the oral inhaled steroids more than the nasal, are the preferred medication? Because

in the NIH guidelines they have been labeled as the preferred medication, particularly for older children.

The other thing, and I'll come back to that, it seems as if there was a lot of time spent on criticism of the data in terms of the weaknesses of the studies. Then that same data was used to put a strong position about the effects. Do you have to be limited in terms of your statement to say that it has been recognized to cause a reduction in growth velocity in the first year of treatment?

Because the connotation, if you extend this, is the vision that growth velocity is continuing to decrease with time. So how limited of a scope do you have to have in terms of warnings based on data?

DR. JENKINS: I'll take your last question first, since that's one I can remember the best right now.

DR. SZEFLER: The first question is in terms of indicating in a general statement, the word "preferred" treatment.

DR. JENKINS: As a general rule, the agency does not take positions in labeling about what treatments are preferential over other treatments, although occasionally there are statements about a treatment being second line therapy, and usually that is related to toxicity.

We did touch on the issue of counter detailing earlier. I don't want to address that topic, but let me

point out that we were concerned about that as an issue with the advent of the glucocorticoid receptor(?) modifier class of drugs. So the only one of those products that is approved for use in children below the age of 12, we actually have an agreement and a commitment from the company that sponsors that product to do a Phase 4 study of growth effect in children.

Because while it is not a corticosteroid, I don't think any of us were really clear what impact a glucocorticoid receptor antagonist might have on growth in children. Since a lot of those comparisons might be made either by the company or by practicing physicians just thinking about those issues, we asked for that data. So I would like to thank the company for very willingly agreeing to that commitment.

But again, we don't normally take advocacy positions in labeling about preferred therapy. There are a few rare occasions of that, but it's primarily situations where we recommend second line therapy related to toxicity.

The second question about the wording in the labeling, should it reflect that it is a one year effect, or more generally the way it is worded now? I think we are certainly interested in hearing your input. One point that Ms. Elashoff was trying to make in her critiquing one of the studies and the statistical procedures and the analyses were

that a lot of those factors introduce a lot of variability, and might actually make it more difficult to detect a treatment effect.

I think an important point to remember is that despite all of those problems, the treatment effects were still seen. I think that is part of her point, was to emphasize that as well. So we weren't trying to say, oh, these are bad data, but they tell us something. We're trying to point out that there are a lot of variables that are introduced into those studies that introduce variability, but despite all of that, there is a consistent trend in all of the studies showing an effect.

DR. BONE: Next would be Dr. Cara.

DR. CARA: The overall impression that I get from reading your precautions is that you have obviously chosen your words very carefully, and it appears to be a very politically correct sort of recommendation. While on the one hand I can understand that that needs to be the case, on the other, I keep waiting for the punch line. Which is in some ways related to my question.

Is it within the scope of your organization to actually provide some recommendations in terms of what to do if the growth rate should be abnormal or should deteriorate with use of these medications?

DR. JENKINS: Well, we are certainly interested in

hearing your comments on that. Some of that will have to be speculation, and some of that gets into practice management. Once you have seen someone who seems to be falling off the growth chart, what should you do? There are so many variables that go into that, that it gets very difficult.

DR. CARA: Yes, my question is directed at my feeling that to a large extent this class of drugs is one that has shown a tremendous amount of benefit for children with asthma. On the other hand, that's often used as a crutch for people that are unwilling to really look at some of the other side effect issues.

As a result, I would like to see perhaps a stronger statement in there about the use of the drug being questioned perhaps more intensely when issues related to growth deterioration arise.

DR. BONE: Next comment would be from Dr. Liu.

DR. LIU: This is just a practical question as to why it is necessary to put it in both areas, under both adverse reactions, and in precautions? Because I would think that just putting it in the precautions section, since there is scientific data to support it, would cover the issue.

DR. JENKINS: One reason you might put it in the adverse reaction section is the first statement that we have in the adverse reaction proposed labeling is it would make

people aware of whether or not there have actually been reports of growth suppression with that individual product. If we have reports of growth suppression for a product, they would naturally go into the adverse reaction section, because that's where we put the post-marketing reports of adverse reaction. That's why we incorporate it there.

In the class, as Dr. Graham presented this morning, we have reports of growth suppression. We suggested that the labeling say cases have been reported, and if we have specific reports when the product is labeled is in question, saying including for name the product. But we are open to hearing your comments on that idea.

DR. BONE: I take it that normally the controlled clinical trials data -- were these reported as AEs in the clinical trials? You also in the AE section have discussed the clinical trial data again. Were these reported as AEs in the clinical trials?

DR. JENKINS: Well, they were usually endpoints of the data assays. I'm not sure if there were adverse events reported in the clinical trial of growth suppression. I will ask the reviewers if they actually remember anyone actually reporting an adverse event as growth suppression in their trials. I don't recall that. I don't think there were any.

MS. ELASHOFF: I don't recall any.

DR. BONE: So these were statistical changes, rather than individual cases that were identified.

DR. SHAPIRO: I have some issues with the semantics of the message. I think the total disclosure of adverse possibilities are very important for the practitioner and for the patients. When these drugs are prescribed, it's the patients who get the package insert, it's not just the prescribing physician. I'm concerned that the way it's worded now really closes the door, and has a major negative impact, but could be modified and still convey the same information.

It first of all combines corticosteroids, and then includes the orally inhaled, and then says that have been shown to cause a reduction. By not saying in some patients, or may cause a reduction, it seems to be universal. The way it struck me when I first read it was that notice these drugs cause a reduction in growth, rather than notice these drugs may cause a reduction.

While that isn't very different, to me, as a practitioner and as a parent, there is a difference in the way it is said. So I would hope that it might be looked at again with some softening that might be a way to get people in to ask questions. But I'm concerned about this growth suppression, rather than I'm not touching this because this is growth suppression. There is a difference there.

DR. BONE: Dr. Shapiro, would you want to a sharper distinction drawn between oral and other routes of administration in this language?

DR. SHAPIRO: Personally, I would like it to just address orally inhaled or intranasal, rather than lumping them together, because I think that would allow you to modify that this may be growth suppressive to some patients, or may be, rather than universal. I can accept the universal for the oral preparation, but I think there is more room for qualification with the other preparations, and that it would be totally honest of course, to do that.

DR. BONE: I guess what I was wondering about is the way it's worded now, it does say corticosteroids, included orally inhaled, or including nasal.

DR. SHAPIRO: Right. It doesn't give any advantage to the newer preparations, and being a little bit more favorable possible.

DR. BONE: Compared to say oral prednisone or something like that. How would the agency respond to making that kind of distinction?

DR. JENKINS: I think I heard two different messages. If you clarify what you are asking me to address.

DR. SHAPIRO: Well, I think that my major point is to convey the same information, and more to suggest that the growth issue affects some patients, or may be an issue,

rather than having it sound so universal. The fact that it groups all corticosteroids together encourages the more universal negative message.

DR. JENKINS: I think we are certainly receptive to suggested rewrites in the text that may address some of your concerns. We're certainly willing to consider them. I think I also heard from Dr. Bone an issue of whether there should be something in there to distinguish oral prednisone versus the impact of these products. I think we have to hear what you are thinking about putting in there.

DR. BONE: I was just trying to clarify Dr. Shapiro's question in my own mind, because this sort of has the character not only of class labeling for inhaled steroids, but class labeling for corticosteroids in general. It says corticosteroids, including orally inhaled steroids, or including nasally administered steroids. It is inclusive, rather than making a distinction between the very well known effects of tablets, as opposed to the -- I think that was confusing.

We're talking about orally administered and orally inhaled, but it doesn't distinguish between pills and sprays. I wondered if that was part of what Dr. Shapiro was getting at as well.

DR. HIRSCH: Can I just comment on this very point. What you're saying though is just not true. What

has been found is that there is a small effect, so you can say something smaller or significant, whatever you want to say. But there is no evidence that there are responders and not responders in terms of this effect on growth.

The statistical data do not support the notion that some people have it. The statistical data are more constant, with the idea that everybody has this, but to various degrees. It may all be insignificant or whatever you want to say, but I don't think we have the data to break up all of these patients into two groups.

DR. SHAPIRO: It may relate to the dosage that is prescribed. So they or may not be affected depending upon variables, including the dosage that is prescribed. The "may" can live. It is truth.

DR. HIRSCH: But we don't know that, so right now it's on random grounds. Some people have more response or less, but you can't separate patients at this moment into those, and say you may be in the good group who won't respond.

DR. SHAPIRO: But you can't say that you're going to be affected by growth suppression either.

DR. HIRSCH: Or anything else. I mean, you can't be sure about anything when it's a population effect. But I don't think it's to say that some people may respond this way, as though this is an aberrant or unusual or

unanticipated thing. Statistically, is that correct? I think you're the only one who can help us with that.

MS. ELASHOFF: You have two statisticians on your committees I think, right?

DR. HIRSCH: But only that's seen the data here, and that's you.

MS. ELASHOFF: There were some patients in the active treatment groups that were growing very fast, between 10-12 centimeters, and even greater than that.

DR. JENKINS: Dr. Shapiro, is part of what you are talking about maybe related to making some sort of a quantitative statement or a qualitative statement about the magnitude of the effect? A small, but statistically significant effect; is that kind of where you are going?

DR. SHAPIRO: It has more to do with the way in which the drug is prescribed for the individual. In most cases, a modest dose is prescribed, and is quite effective. For that patient receiving a modest dose, the risk is small. So when the opening statement is scary or dramatic, it is out of proportion to that patient who is going to receive the small dose.

I wanted some modifying of the terminology so that it didn't seem that there was a universal risk of great magnitude for all patients receiving any dosage of this medication.

DR. BARANIUK: I quickly echo that, especially from the perspective that only two drugs have been tested, and by the intranasal route. Are we going to generalize that for the first sentence in the precautions as a result?

DR. BONE: Thank you. The next question was from Dr. Li, and then Dr. Cross, Dr. Osborn as well.

DR. LI: I had two specific questions; one having to do with the wording on our recommended monitoring. I was wondering if we could perhaps include some more specific information about what kind of monitoring we might be recommending in the labeling? For example, it might be measuring height every 3-6 months. Otherwise, with the monitoring from the discussion we had even yesterday, it wasn't clear exactly what the nature of that monitoring might be.

When we make recommendations for monitoring liver function, for example, usually it is fairly specific in terms of measuring ASD in six weeks, and every three months for six months and so on. That is one specific question.

The second has to do with again, the lowest effective dose, and what the meaning of that is. I would just want to entertain a point of caution that even when we talk about the lowest effective dose of an inhaled corticosteroid for an individual patient, it is not clear that all physicians will take that to mean the same thing.

I think one concern that I have is that some clinicians will take that to mean for example, either the absence or symptoms, or even the presence of tolerable symptoms, both of which from a specialist point of view, would be markers of poor control, especially if objective measures such as peak flow, or more specifically, spirometry were far less than optimal.

So the second point is just a point of caution. If we do talk about lower effective dose, is there opportunity to be more specific about what that might mean? \*

DR. JENKINS: I'm going to take this as a rhetorical question, not to me, but to the committee.

DR. BONE: Thank you. Dr. Cross.

DR. CROSS: Could I ask you if anywhere in the package statement, does it mention anything about pulmonary function studies? We have just a partial glimpse here, but we're going to have these 90 percent of family practitioners with their measuring sticks measuring the height.

And hitting behind your point, is there anything in the package insert that to measure effectiveness, you can't do it by history and physical exam from 65 percent to 100 percent of the predicted APV-1. Is there anything that tells them maybe pulmonary functions might be worthwhile to do, rather than measure height?

DR. JENKINS: The only reference to pulmonary

function that might be in the labeling, might be references to the study data. So in the clinical trials section of the clinical pharmacology part of the labeling, if APV-1 or peak flow were an endpoint, those data may be presented. But I don't recall any of the labeling recommending monitoring pulmonary function as part of the care of the patient.

DR. LI: Carroll, if I may. The point is the same as the one I made. Maybe you made it more clearly. I think I would be concerned that if we recommend titrating to the lowest effective dose, and we don't word it properly, that we will actually be promoting and recommending poor control of asthma.

DR. CROSS: Right. I was hitting behind supporting your point. I wanted to pick up Dr. Shapiro's. I too, would like to have that general statement weakened. I feel pretty strongly that since patients will be getting this, the patients that need the big doses are the ones that are saving oral prednisone intakes. And they may be on very big doses, and they would have their wits scared out of them by looking at the dose recommended, and then seeing they are on a big dose, and then reading the package insert.

I think as a minimum we need to say that oral steroids are known to have a major effect on growth, and that the inhaled forms -- put some sort of perspective for the patient to see that the inhaled forms are much less of

an effect on growth. I think that there is concern about this minimum effective dose, because those that need it the most, are going to be those that are on oral prednisones, that are looking at the savings effect of the inhaled, and are going to be on pretty big doses of it.

Maybe even fluticasone 220, because we want them on 10 oral prednisone instead of 25 of oral prednisone to control their asthma. So I think there is concern to try and get the general statement to really say something about the orals, and then compare the inhaleds to the oral effect, and say there may be a small effect on the inhaleds.

DR. JENKINS: Dr. Li, if I could address your point. Is what your trying to get at maybe expanding the comment about titrated to the lowest effective dose, to say something along the lines of titrated to the lowest effective dose that can adequately control symptoms, and maintains near normal pulmonary function? Is that what you are getting at?

DR. LI: That is what I'm getting at, yes, Dr. Jenkins.

DR. BONE: I think we have Dr. Davidson and Dr. Crim.

DR. DAVIDSON: Obviously, I think that again the two groups of us are concerned about different things, and the well being of the patient is the most important thing.

Maybe a question to the agency, could we include in the label something to the effect that there is no conclusive data that the final height is affected? Or do you have conclusive data on that?

DR. JENKINS: We obviously do not have any conclusive data. There is a brief in there that says the affect on final adult height is unknown, but we are open to hearing your ideas about how to make that clearer, if you think it needs to be clearer.

DR. DAVIDSON: The concern is that obviously we are concerned about the endocrinological part, and obviously I want the kids to achieve the best possible height. But on the other hand, I don't want them to suffer. I want them to get treated in the appropriate way for their asthma. The question is, if something can be added to that effect, so that maybe the other group -- I think we need to think about it, but there may be something that we can add there to strength the positions.

DR. BONE: Thank you. Dr. Crim and then Dr. Osborn.

DR. CRIM: The question I have is just something I want Dr. Jenkins to clarify, because I have been hearing comments from my fellow committee members that seem to sound more educational in nature, that we would we give a practicing physician if we were giving a lecture to.

My question in essence deals with since I guess we are supposed to address this question in terms of giving the FDA advice from a regulatory standpoint, as opposed to how do you follow height or the best way to manage asthma, I guess my question is, from a regulatory standpoint, what type of things can go into this document in terms of measuring height, how you measure height, pulmonary function studies, the treatment for asthma?

My sense is that from a regulatory standpoint, you can't put those things in there. If that's the case, I think we need clarification for me personally, and for the committee as a whole.

DR. JENKINS: I think we're careful to be cognizant of not putting statements in the labeling that start getting into the practice of medicine, and the individual discretion of the practitioner unless they are really important. For example, if a product has significant impact on the white count or the liver function testing, that it's important to monitor those at certain minimal intervals for safety reasons. Then we might be more inclined to map out exactly a regimen of testing to insure the safe use of that product.

When you are starting to get into the range of maybe it's friendly advice to the practitioner, we try to stay away from some of those, because you are starting to

limit the practice of medicine by recommending that growth be assessed every three months. What if the practitioner chooses to do it every six months? Are they now not doing good medicine? Or are they simply using their own discretion and their own knowledge about the patient?

So we try not to put in statements that aren't warranted by the data to insure the safe use of the drug, or the effective use of the drug, and stay away from those friendly advice statements that can actually do more harm than good in today's litigious society.

DR. BONE: Dr. Osborn and then Dr. Baraniuk.

DR. OSBORN: To follow-up on a point from Dr. Szeffler, and still get at whether there should be something in the labeling about the importance of using inhaled corticosteroids, particularly for persistent asthma, you had pointed out of course that it would be very usual to do so. This is usually done in a very different way, to talk about second line drugs and toxicity.

My question is, when would it become something important enough to take an unusual course like this? I'm thinking of two obvious reasons. One is of course both the patient and the physician concerns about steroids, which are high in this country, and which we have talked about for the last few days.

The other is that I had the good fortune to sit

here when we discussed glucocorticoid modifiers and their approval. I was certainly aware that in my opinion it was very important to get all classes of the drugs that could help asthma on the market, and have their use played out in the marketplace.

However, I think when there is so clearly good efficacy data with inhaled corticosteroids and asthma, somehow that needs to be balanced with some of the data we have talked about in the last two days.

DR. JENKINS: I think you have asked a gray hair question. I think I'm going to defer to my boss, who has more gray hair than I do, and see if Dr. Bilstad would like to address that question. He has much more experience across the whole range of products and putting statements into the labeling.

DR. BILSTAD: Certainly, among approved products within a given class there may be differences in degrees of effectiveness. We don't have anything within the Food, Drug, and Cosmetic Act that indicates that we can't approve a drug if it is perhaps not as effective as another drug that is already on the market.

It does become a benefit/risk judgment on whether for that particular drug, the benefits outweigh the risks. So there may be within for a given indication, a spectrum of different degrees of effectiveness. We don't normally, as

Dr. Jenkins indicated, discuss relative effectiveness, unless it has been specifically studied by for example a company, where there are very well controlled studies, head-to-head comparisons that do in fact show a difference. Then we may very well allow statements to go into the labeling.

Generally, again, we don't indicate differences in labeling between different classes for the same indication. Also, as Dr. Jenkins mentioned, sometimes we will say that a particular drug is indicated only for a second line therapy, but there has to be very strong evidence and agreement in the community that that is the case. Usually it's on a safety matter.

DR. BARANIUK: Can you include guidelines within the precautions here? For instance, the last line for the inhaled steroids, where the sentence begins, "The growth of children and adolescents." Could you say as recommended in the NAP-ERP-2 guidelines, the growth of children should be monitored. Is that an acceptable inclusion in a package insert?

DR. BILSTAD: That certainly is a possibility. We have, for example, in the lipid lowering labeling, referred to certain guidelines. So that's something we could take under consideration.

DR. BONE: Other questions? Dr. Oppenheimer, and then Dr. Ahrens.

DR. OPPENHEIMER It seems to me that the question is not so much a comparison, but the complete absence of any positive statement about the use of corticosteroids, and especially intranasal or orally inhaled steroids. I don't think that this necessarily implies any preferential desires, but why couldn't a positive statement such as although corticosteroids have been shown to be effective in the treatment of asthma, such and such and such precautions need to be taken. But some sort of positive statement, which is absent in this version.

DR. BONE: Dr. Liu?

DR. LIU: I think this echoes this comment. I do think this first sentence, for example, really lumps systemic corticosteroids, and doesn't make this distinction. I think that is very important in terms of what is a known side effect of systemic administration. A statement regarding the topical high therapeutic index of topical steroids versus systemic steroids.

Then perhaps a sentence that really says something, a small, but statistically significant effect of inhaled intranasal corticosteroids in growth velocity has been demonstrated, which accurately reflects the data, but also prefaces it with what is a system steroid effect, with what is a high therapeutic index for the topical steroids in general, and then what the recent analyses have shown.

The way it stands now, it really lumps them altogether. This is really following up on Dr. Shapiro's and Dr. Cross' points.

DR. AHRENS: I would like to bring up another aspect of the same issue, and that is the impact of this first sentence that is has been discussed. That is a difference from what is in at least a couple of the package inserts for the most recently approved for pulmicort and flow vent. I believe it's the same in both of them. I'm reading from pulmicort here.

"A reduction in growth velocity in children or teenagers may occur as a result of inadequate control of diseases such as asthma, or from the use of corticosteroids for treatment."

Now that has a different impact I think, than the current statement. Now I heard Dr. Allen say yesterday that there is no compelling evidence that asthma does slow growth. On the other hand, we would have said the same thing perhaps about inhaled steroids not that many years ago. It is very clear to me that the effect of asthma on growth has not been studied with the same degree of rigor that we have now begun to study inhaled corticosteroids.

So I doubt very much at the time that this statement as it is in the pulmicort and flow vent package insert, I doubt that the data was more compelling then than

it is now. So first of all, I would like to know what hurdle that statement had to clear to make it into that package insert. And why are we changing that hurdle now to exclude it from the current statement?

While I understand that it is not as clear cut as we now have data for inhaled corticosteroids, I'm torn between the impact on the clinician, and having perfect science behind the statements.

DR. JENKINS: I don't recall the exact entry exactly, but I suspect that the statement that you just read probably originated in the flow vent metered dose inhaler labeling, which was approved as I recall in 1996. So some of the studies that we talked about this morning have come to our attention since that labeling was approved and written.

The other thing to be aware of is that the labeling process is kind of an interesting process. It kind of reminds me of this committee process of trying to write a statement by a group of people. Usually what happens is the company submits their draft labeling, and then we tinker with it. So the evolution of the wording is always a complex phenomenon.

I think there are more data, and I think we are more fully aware of the at least short-term studies that clearly show an impact on growth in our mind, than we

probably were when we approved that flow vent labeling in 1996, although you can argue that we also approved the same wording in the flow that wrote a disk labeling(?) just six or eight months ago.

So again, labeling is a very complex area. Once things get in a label, they sometimes snowball and get perpetuated, because one company wants the same wording that another company had. Or one company wants to try to one up the wording that another company has.

DR. BONE: Thank you, I think we're close to getting where we -- did you need to pursue that, Dr. Ahrens?

DR. AHRENS: Yes, I just wanted to say that the part I was specifically referring to the fact that inadequate control of asthma may impair growth. It really has to do with the risk/benefit relationship. And I take it back to the three budesonide studies; that the only difference between those is the one that showed an effect on growth, and two that clearly did not, really has to have to do with something about severity of asthma.

DR. JENKINS: I think, Dr. Ahrens, that statement about uncontrolled asthma having an effect on growth, I'm sure it was not one that we reviewed data, and we agreed to put that in the labeling in the first place. I think it was more kind of the standard knowledge that people would generally agree to in the literature. Or if you had gotten

together a panel of experts two years ago, they may well have agreed then, and they may well agree now that uncontrolled asthma impacts on growth.

DR. BONE: Thank you. Dr. Allen had a comment, and Dr. Levine, before we break for lunch.

DR. ALLEN: Just a point of clarification about the statement of asthma and growth. That is that what I said yesterday was not that moderate or severe asthma doesn't have an affect on growth, but from what the current trials that are recruiting mild patients into the trials, mild enough in some cases to be randomized to a placebo group, what they suggest is asthma of that severity isn't having a significant effect on growth.

I wanted to add my support to Dr. Shapiro's suggestion about clearly separating any appearance of linkage between the systemic corticosteroids and the inhaled or intranasal. I think the statements as they are written, they imply a degree of clinical relevance to the growth suppressive effect that I don't think we have proven, certainly not beyond one year. So I think that is important.

I did want to call the committee's attention to in the second paragraph under the pediatric use, the two sentences that talk about the relative sensitivity of a growth suppressive effect versus an HPA axis. I think that

is a very debatable point that probably reflects more the inadequacy of the adrenal axis assessment. I think that's just a couple of confusing sentences in there that don't add valuable information.

My third comment is if my memory serves me correctly, that in the intranasal well designed studies that we were shown the data from this morning, there was one out of the two that showed a relevant clinically significant effect. The paragraph, the third line under adverse reactions implies that there is more than one trial. It says "controlled clinical trials of intranasal corticosteroids." So that might be a small correction.

Just I don't lose my train of thought. Then my last point that I image maybe would be appropriate to take up this afternoon is I'm struck by the difference in the weight of evidence as it relates to orally inhaled steroids versus the intranasal. I guess I'm a bit surprised that we are not hearing more comments. We are talking about using essentially identical language in these two labels, but we are basing a lot of our conclusions about intranasal on one study.

DR. JENKINS: Let me try to address a couple of those points. One of the reasons for suggesting the language about the inherent insensitivity of the adrenal function testing as a predictor of the growth effect is

because almost all of these labels have information in them about adrenal function testing. A large majority of those study results are negative, i.e., they tend to show no impact on adrenal function testing.

Which might lead some people to the mistaken impression that there therefore would be no effect on growth. I think the intranasal beclomethasone study that was presented yesterday by Schering, and this morning clearly shows that despite absence of findings in those types of tests, you can see growth effects.

So that is in there to try to link other parts of the label to this part of the label, so that people don't get the false impression that oh, there is an AM cortisol statement here that says no effect was seen on AM cortisol, therefore, I don't need to worry about growth with this product.

The other point is for the intranasal products, there is more than one study. Dr. Worobec mentioned that there were two studies in the published literature, one of which was positive. The other study was a beclomethasone study that Schering conducted and presented yesterday. I should say that we also reviewed other growth data for other intranasal corticosteroids that we haven't presented, because it is weaker study designs, but there are some suggestive trends in other studies. So it's not just a

single study.

DR. ALLEN: If I could just follow-up on that. Your point is very well taken about the HPA axis, where what appears elsewhere. Perhaps language that could compress that and convey the same message would be that effects on growth can be seen in the absence of abnormalities in commonly used tests of HPA axis.

DR. BONE: Dr. Levine, it sounds like your cue.

DR. LEVINE: Yes, well Dr. Allen has said some of the things I was going to say. You could reverse it and say that there could be changes in the HPA axis which have yet not been demonstrated, because we haven't done the right test, that may be seen in the absence of growth effects. So it may be ultimately there may be a reverse of this. We really don't know.

But what I was going to say is that my reading of the literature and of the briefing document is certainly that changes in the HPA axis have been demonstrated, and I don't know whether you want to include it. I'm sensitive to the concern of the clinicians about steroid phobia, but certainly changes in the HPA axis have been demonstrated with both intranasal and the inhaled steroids. Again, we don't know the long-term significance of these.

DR. BONE: Thank you.

MS. ELASHOFF: Can I just try to answer the

question that I wasn't able to answer before from Dr. Hirsch?

DR. BONE: Sure.

MS. ELASHOFF: It was about whether some patients may not exhibit an impairment in growth. Dr. Shapiro wanted the wording may reduce. In all clinical trials, you never see in the treatment group, all the patients going in one direction. You expect to see some patients going out, and some patients going down.

In the efficacy part of the label, we never put such and such may decrease asthma symptoms. So we may want to -- I think it's more of a clinical question that safety is different from efficacy, and possibly we look at individual patients closer than the mean.

DR. BONE: This I think goes back to Dr. Hirsch's question about whether this was something where there was a shift in the curve with the same shape, or there was a skew or bimodal. I think you had two different answers, depending on whether you were going to disclose some of your data or not. Is that correct?

MS. ELASHOFF: I guess that's correct.

DR. BONE: Okay, thank you. On that note, I think it's time to adjourn for lunch. We are going to reconvene at 1:15 p.m.

[Whereupon, the meeting was recessed for lunch at

12:38 p.m., to reconvene at 1:15 p.m.]

A F T E R N O O N S E S S I O N (1:18 p.m.)**Agenda Item: Discussion and Committee****Consideration of Issues**

DR. BONE: I think the way we will proceed for the rest of the afternoon's session will be something like the following. We'll have an opportunity for each member guest at the table to make a general comment or two, and we'll just go around in order to do that. Then we'll address the specific questions about which we were asked to comment.

In some advisory committees there is an actual yes/no up and down vote on topics. Today this is more of an essay question than a yes/no. We will ask each member to comment on the questions and their implications, but this is not considered a vote, and there will not be a vote count, as there sometimes is as advisory committee hearings are conducted. So that may be an important point here as far as understanding what the committee is doing, and also interpretation of what we come up with.

I think I'll ask Dr. Kreisberg to begin the remarks, and then we'll just go around.

DR. KREISBERG: Thank you, Henry. I guess the reason that Henry is letting me go first is because I'm going to be leaving and trying to get home.

I'm so sure that I have anything original to say that hasn't been said. I think this has been a very wide

ranging type of discussion, and consequently this is just an opportunity I guess to express my opinion on some of the issues that have been discussed so that Henry can have a better idea of what the consensus.

As I view this, I view part of the problem here as a labeling issue, and I think without getting into the wording of the label, my impression is that the agency should have uniform standards and criteria, and that all companies should meet those standards and criteria. I think the variability in the labeling across the various products needs to be corrected in whatever manner that the agency chooses to do that.

I think the wording of the label should be done in such a way as to properly convey the concern about growth retardation, but without scaring physicians away from the use of the drugs, which I think are the cornerstone of therapy for patients with asthma, and I know much less about allergic rhinitis.

I'm a little bit concerned that the label has nothing whatsoever to do with what physicians do. And that for the most part, the use of these drugs is based upon prior experience with other drugs of the same class, or something that they may have heard incompletely at some type of conference. And that the real issue here is how to properly educate physicians, and the label doesn't do that.

If we want to translate better care for these patients, at the same time minimizing the adverse side effects, it seems to me that physicians have to be more aware of the possibility of growth retardation, and need some guidelines as to how to use growth measurements to re-evaluate their patients to make certain that they are using the smallest, but most effective dose for those patients.

It may be that the severity of the illness in the patient will require use of high doses, even though they are faced with growth retardation. But it is in this area of education that I see making a big impact on this.

Which gets me to who should properly instruct the physicians, and it's obviously not the FDA. But I think the message might be to appropriate agencies -- NIH to prepare guidelines, or societies who prepare guidelines -- to work more carefully with physicians, so that they better understand the implications of the rewording.

It is my opinion based upon the data that has been "presented by the FDA," is that corticoids have an adverse effect on the growth of all children, and that there is a shift in the distribution to a lower level. The vast majority of children remain with a plus or minus two standard deviations, but a small number actually fall beneath the normal distribution. And there has to be ways of identifying these kids.

I think it is a responsibility of the various societies, and perhaps of the pharmaceutical companies to better educate, because they wield a lot more power than they should over what physicians actually do. I think to the extent that they are willing to be on the table with this type of issue, and to better inform the physicians, it will result in better care for these kids.

And I think there are lots of things that pharmaceutical companies do for physicians, and there are things that could be done here that would address this, like giving an accurate way to measure the height of these children.

The last thing I would like to talk about is what future studies need to be done. It is obvious that growth studies need to be done that will address short-term and long-term effects of glucocorticoids on growth, although I am not personally sure how to do all of that. Some of the best minds in the country are at this table, and it would seem to me that with appropriate consultation, proper types of studies could be designed to minimize the noise within the study, but not to make perfect studies.

I endorse Dr. Hirsch's comment that the impact of glucocorticoids on the skeleton that is more readily detectable than some other subtle abnormalities may be just the tip of the iceberg. I think since so little is known

about the effects of inhaled steroids on metabolism in general, that any studies that are designed to look at growth, ought to also be designed to look at other types of more subtle abnormalities that might occur in these children as a consequence of long-term exposure to inhaled glucocorticoids.

Things that come to mind, but are not exclusive would be changes in body composition, which can be readily assessed non-invasively; impact on glucose homeostasis; lipoprotein metabolism. As examples, impact on adrenal androgen production.

I think the idea that this is a temporary therapy, which has pervaded the discussion because catch up growth keeps coming into the discussion, probably doesn't exist for many of these children. They are going to be on lifetime suppressive therapy, and we do not know what the long-term consequences of that may be, even though we can get by with relatively few significant adverse effects at this particular point in time.

So I think it's a great opportunity for multidisciplinary investigation of the impact of inhaled glucocorticoids not only on growth, but on a variety of other things. As I said, and I didn't want to take the credit from anybody else, none of these are original thoughts with me. I have heard everybody around this table

mention these types of issues in the discussion that has gone on in the past two days.

So I would like to just thank everybody for sharing their wisdom with me. I would particularly like to compliment the agency on what I think is one of the best presentations I've ever heard them do.

Thanks.

DR. BONE: Thank you very much, Dr. Kreisberg.

We'll just go around, and back around this way to each person, to ask for general comments and remarks before we get to the questions. We'll next hear from Ms. Conner.

MS. CONNER: Thank you. As I have said, I'm the consumer representative here, and in my current professional position I'm primarily responsible for implementing asthma disease management programs to various managed care companies, which gives me the opportunity to come in contact with a myriad of family practice, general practitioners, pediatricians, who are either staff of these managed care companies, contract physicians, or gatekeepers.

It has given me an appreciation for a lack of knowledge, or a lack of exposure to things that we often take for granted here in this room. I think using this class labeling, I had a different opinion when I came in here, and I must give the agency credit for good information that has given me pause. I think the class labeling should

serve as a warning, without being frightening to these physicians, because I think any change in labeling is going to reflect a change in prescribing patterns initially for these physicians.

I agree completely with Dr. Shapiro about delineating all corticosteroids from inhaled and from intranasal, simply because of the well known and well feared side effects of oral corticosteroids.

The lower dose issue, I think it's important too that when we designate determining lowest possible dose, as Dr. Li mentioned, and I believe Dr. Cross, that this be not just lowest dose for symptom control. A lot of these primary care physicians, and as you well know, a lot of patients are not aware of changes in lung function, even though they feel fine. Lowest effective dose should be tied to pulmonary function testing, if it is available, as well as near normal pulmonary function testing, ability to sleep through the night, and normal activity levels for these patients, rather than just doing fine.

I also think that the onus of a lot of this is going to fall on the pharmaceutical companies, because you probably have the most direct access to this population of physicians that I'm talking about. If there is a way that you could provide growth charts, growth velocity charges, encourage their use, and maybe even provide measurement

devices, or encourage proper technique for measuring for monitoring these things, I think that would be a tremendous value that could be added to this, and maybe enhance the use of the products, as well as enhance the knowledge that we gain from long-term use.

DR. BONE: Thank you. Dr. Chinchilli.

DR. CHINCHILLI: I have a few points I want to make. The first one is I agree with what Dr. Allen said this morning about intranasal steroids. One of the two studies were positive, and I still fail to see why a class label is being pursued with that. Most of the intranasal steroids haven't been studied. So my suggestion is that the companies should be required to such growth studies, similar to what was done for most of the inhaled steroids.

In conjunction with that, flunisolide was the one inhaled steroid that was missing a growth study, and I feel that the manufacturer for flunisolide should be required to provide a growth study. It's just a suggestion.

In terms of some of the studies -- I don't want get into label issues. I think most of my colleagues here are going to talk about the label aspects, and they have more experience with that than I do. I do want to talk briefly about the studies that may be proposed or required of manufacturers in the future.

The first one is the suggestion of having minimal

effective dose studies. This is more of an estimation problem than would be a hypothesis testing problem from a statistical perspective. A lot of care is going to have to go into their design. It is not going to be easy. I think it is going to be easier to do the -- although Barb Elashoff talked about some of the flaws and some of the problems with designing growth studies, I think there are going to be more difficulties with the minimal effective dose studies. I'm not saying they can't be done, but I think a lot of care is going to be required to do them properly.

With respect to the growth studies, I've been thinking about that, and tried to jot down a lot of design issues, and what I would suggest seeing in such studies, and how they should be analyzed. If we don't get to it this afternoon, I've jotted it down, and I can hand it to somebody in the agency, and they can wait until after I leave to throw it away. But I will turn it over to somebody in the agency.

Finally, I think the committee and the FDA needs to think about what is the effect size we want to see in these growth studies? I didn't get any sense of that today. At what point do people get concerned about what's a clinically important growth velocity to be concerned about? Is it 1 centimeter per year? Is it half a centimeter per year? I didn't get a sense of that today, and I think that

needs to be addressed.

DR. BONE: Thank you. The next comment from Dr. Hirsch, please.

DR. HIRSCH: I'll try to be brief, because I think we have gone through so many of these. Fundamentally, I believe that physicians should know what we know. That we have the responsibility to tell them that wherever the chips may fall, but it has to be presented very fairly. I now have no doubt that some of these steroids, are tremendously important when given by the nasal or the oral route, can have an effect, and do have an effect on growth suppression.

I think whereas I have some interest in that, that is not the major point. I would almost think that we could delete some of the stuff about measuring kids' heights and all this sort of thing, because the important issue to me is that this may be a surrogate for other things.

What it indicates to me is that no matter how you give the steroids, it appears that some of these can be producing systemic effects. The growth, which is most obvious to us, may be the least of the story. There could be small amounts of immunosuppression, compositional changes, I don't know what over the years.

What happens when kids get little bits of steroids over long periods of time is simply not known, and therefore behooves the physician in each patient to determine what for

that individual is the minimally effective dose. I think this is more of a physician thing than a company thing right now, although more studies should be done, of course. So it is prudent to do that.

I think in the text itself, I would urge, as Dr. Shapiro suggested, that we separate corticosteroids from intranasal. That first sentence should say corticosteroids have been shown to cause a reduction in growth velocity. And as another sentence, intranasal corticosteroids recently have also been shown to have an effect. And then indicate to some degree what the level of the effect is. That in general the studies or something, whatever we can quote, are less than one centimeter per year, and so on.

I think also on the second page that we should again -- at the top of the second page -- indicate that these findings on growth velocity indicate or suggest that there can be systemic effects from use of intranasal steroids or orally inhaled steroids.

Finally, in that last paragraph where it says that a significant reduction in growth. I think we should say a statistically significant reduction, because I don't know whether it is significant otherwise or not. I just know it is statistically significant, and we ought to tell the physician that.

Finally, in terms of the research implications, I

think these are enormous and are extremely interesting. I think some of the research implications to learn exactly what the mechanism of growth suppression is. I still presume it works through the HPA axis, but that is yet to be shown, and we would like to know that for sure.

I think also the search for other effects. I don't think this can be a standardized thing, except that there ought to be a careful evaluation and studies going on in which the other effects of the long-term steroids are looked for.

Hopefully, this would lead to the development of even better drugs for the treatment of asthma over time, whether in this class or other classes. However good these things are, they are certainly not the last word on the treatment of asthma, and physicians ought to know this, and know that they ought to be careful. And the manufacturers ought to know this as well, to keep the pursuit going for better agents.

DR. BONE: Thank you very much. Dr. Osborn.

DR. OSBORN: I'll be very brief. I have nothing new to say, so I'll say it quickly. I think the major issue is undertreatment of children with persistent asthma, as I have already said. I realize that is not the focus of the immediate comments.

I certainly agree with class labeling. I think it

needs to be balanced and precautionous, as has already been mentioned. I think the amount of the effect and exactly what has been shown currently should be in there.

When I addressed lowest effective dose, I realize this is problematic in terms of experimental design, but it might be appropriate to have doses such as 50 microgram, 100, 200, 500, some specific requirements in the initial Phase 2 and 3 testing, and particularly Phase 2 testing be done.

In terms of the important outcome, it is not clear to me that we have identified what the appropriate outcome is to measure in terms of following steroids. But certainly if we are going to look at growth, we need to have at least a few long-term studies that look at baseline at least of six month, a follow-up of several years, and also some assessment of catch up.

I recognize that these are not small studies. We have at least a couple of hundred people in each arm to get a sample size with adequate power to look at outcome. But I'm not sure that need to be done for every drug. I'm concerned that that would be perhaps too much of a burden on industry.

Finally, I would encourage the reporting of side effects. This seems a situation where we have so little information. It would be great to have some kind of

registry for every kind of side effects that might be related to HPA axis or growth.

Thanks.

DR. BONE: Thank you. Dr. Liu.

DR. LIU: I think I have made most of my comments as the meeting has gone on. This is maybe out of line, but I think that some of the information that has been gathered and analyzed so carefully should be published, just to promulgate and disseminate the actual data on which the conclusions and everything are based. I guess that's really all I had to say.

DR. BONE: Thank you. Dr. Oppenheimer.

DR. OPPENHEIMER My first reaction is that this is a very negative message to the general physician, and would tend to scare off a lot of physicians from prescribing a very important drug. I think there has to be some acknowledgement in this publication and this class labeling that it is after all, still the best and most effective drug to be used under the circumstances, albeit with the potential of major adverse effects.

I was somewhat disappointed in the lack of breadth of the research going on in this particular area. For instance, I would like to know what the absorption of steroids is from the lungs. This is a central question. It could be analyzed with isotopic techniques. This, as well

as developing animal models, which could provide more information about the growth process and the potential effects of steroids.

Certainly by analogy to the thyroid area, we have learned a great deal about human growth and development by the similarities and differences that we find in the study of rats, and certainly we are able to develop concepts that are totally unreachable if we limit ourselves entirely to clinical investigation.

Lastly, the question of steroids as a surrogate, the growth as a surrogate is a very interesting issue, but one which should be capable of being resolved rather quickly by looking at the experience in treatment of craniopharyngiomas in children who have been conventionally overtreated with steroids for a substantial length of time, and see whether there are any adverse effects.

It's my own impression in seeing some of these children as adults is that there is significant osteopenia, and retardation in height, but otherwise they seem to be quite normal. Nevertheless, an analysis of overreplacement in children for other diseases could be quite helpful in this instance.

DR. BONE: Thank you, Dr. Oppenheimer. Dr. Gross.

DR. GROSS: Thank you. I want to begin by congratulating the FDA on a very careful and highly

temporary effect. It is probably one that only occurs for maybe the first few months, maybe six months, maybe even a year. There is very likely to be a catch up at the end of it. So I'm not sure that we're looking at really any long-term effect, even if it is a significant thing to be 1.5 centimeters shorter at the end of one's growth than otherwise. I'm not even sure that that is the fact. If it is, to me it's a much less important thing than to have the asthma well controlled.

So what I'm basically saying is just a question of balance. I think when the label is rewritten, rather than making specific statements put this in, take that out, I would just say for goodness sake, don't put anything in the statement that is going to frighten a lot of patients and a lot of their parents, that is going to overwhelm the practitioner with questions that now all he knows is there is a lot more to worry about, and he still doesn't know the answers to those questions.

And don't do anything that is going to decrease the use of inhaled steroids, because I'm sure that in the end that will result in inferior care.

Thank you.

DR. BONE: Thank you very much. Dr. Ahrens.

DR. AHRENS: Well, clearly none of us want to inappropriately scare physicians away from using these drugs

when they are appropriate, and in doses that are appropriate to control the asthma. I would certainly agree with what was just said.

On the other hand, in some of the comments that I've heard over the last two days, it seems like there has been an impression that we are proposing something here that is a drastic, major change from information that was out there previously, and that we're really afraid that when this new information gets out, it's going to scare a lot of people away.

I think it's important to consider who we are casting, what we are really doing here. As I view it, this really isn't a dramatic change. From the literature review that was discussed today, and the literature we have all read, this isn't a particularly surprising issue to have on the table. It goes back some years, that there is at least some indication that this may well be true, and in fact current package inserts, at least the more recently approved products, clearly reflect the information we are talking about.

It is not going to be new to those package inserts, it is just going to be new wording that perhaps brings things up to what the current state of the knowledge was, as opposed to the time that they were written. And perhaps in a few years, they will need to be rewritten again

when the state of knowledge advances further.

But it seems to me we need to cast this as making the package inserts for all the products consistent and current with today's state of knowledge. And realize that people know about this out there already. It is evident in the package inserts in one form or another in most of them currently. The issue is already on the table. So I think we need to cast this as making things consistent and accurate, rather than raising a new alarm bell that is dramatically different, a red flag that none of us had ever suspected before.

I certainly agree that the semantics we choose in how we accomplish that are very important. That it is possible to put in semantics, and to choose specific facts to put forward that do have the net effect of scaring people away. I simply think we need to look at it in that light. To me, it's obvious that the clinicians and patients deserve to know what we know, and by this venue, as well as many others, to be informed of what the current state of the knowledge is. We just need to again, choose carefully our words in accomplishing that.

DR. BONE: Thank you, Dr. Ahrens. Dr. Davidson.

DR. DAVIDSON: Well, I want to echo some of the previous speakers in congratulating the agency for an excellent presentation, as well as the industry, because we

learned a lot from both of you. They are very important issues. We don't know everything, it's obvious, and therefore, more research is necessary in the area so that in the future we can advise our patients in a better way.

I agree with Dr. Kreisberg, we need to also look at other metabolic parameters that are affected by steroids in girls, as well as in boys, because it may be two different issues altogether.

Finally, I would like to say that it would be look at some socio-economic data from these studies. Who are these that are affected? If there are a lot of minorities, if they have shorter heights, are we going to put them in a significant risk in the future competing with other people in this country? Do they eat well? What are the other confounding parameters that we need to look at that? Then I think some socio-economic data may be nice for all of us to look at.

I think that if we are going to do more studies, and we are going to recommend some more studies, I think a balance of the affected community is important. If 95 percent of the people affected are Anglo people, it's okay. But if we see African Americans and Latinos and Asians, we want to see minorities in these trials to see if they fare the same way.

Finally, I agree that the change in the label

needs to be there. It's there, but people need to look at it. I feel that not only for the physicians and the families to learn and make a wise decision depending on the wording, but also it may save some legal problems in the future. Then I believe that the changes are necessary.

DR. BONE: Thank you, Dr. Davidson. Dr. Fink, please.

DR. FINK: I think there is a lot of new data that has been presented over the last two days that does need to be disseminated to the physician community. I would definitely be in favor of class labeling, although I think it should be cautious and not scare people. But we don't want to reward drugs where there have been no studies performed, and give them a clean bill of health. That seems to be untenable.

I think it is really important that in future studies -- and we have outlined many of the areas where future studies are needed -- that minority populations be adequately represented, because they may have unique risk factors for growth impairment.

DR. BONE: Thank you. Dr. Baraniuk.

DR. BARANIUK: A couple of things came to mind. One is, should we take a new approach to growth here? Is it possible that the swallowed dose of these drugs is causing some change in the intestine, or a pre-hepatic effect that

is subsequently leading to a change in growth potential? That could be actually evaluated by having a treatment arm where a known oral administration of the drug is given, to see if that has any effect. That would help to sort out whether there is absorption with the systemic effect, or a liver effect.

From the nasal studies I think pharmacokinetic data is lacking. I think if you can't measure a drug after intranasal administration, it is unlikely that it is going to have an effect.

I would like to see more information about lower doses of these drugs. That they don't have to reformulate the canisters. For instance, you could try one puff a day, two puffs a day, four puffs a day of the existing drugs.

We were talking earlier about month-by-month changes in height. Is it possible that a one month period is sufficient to show a significant change in knemometry that could demonstrate a dose response effect, or allow comparisons between drugs?

With study design, I think clearly we have to have a pre-drug period where growth is assessed. Then the drug treatment period. Then clearly a post-drug or catch up period. That is critical, since our big question is does a decrease in growth velocity actually translate into a permanent decrease in attained height.

As far as the precautions go, starting out like this to say corticosteroids have a reduction in growth velocity. I would want to broaden that and actually say, oral, oral inhaled, intranasal, and topical cutaneous glucocorticoids, if you want to set the whole story straight, since each of those can have an effect. That tells the practitioner and anyone else reading it that steroids in general have this effect, and you have specifically shown that all products could.

Inhibiting growth, I think that suggests that you are permanently stopping growth, and all we have data for is a reduction in linear -- a decrease in growth velocity. With the pediatric use I think we should clearly state that it is six month to one year studies that have been done, and the range of effects.

With the inhaled steroids I think a new precaution should be added. Not using inhaled corticosteroids may constitute undertreatment of asthma and result in increased morbidity, hospitalizations, and worsening pulmonary status. These clear benefits must be balanced against the apparent dose dependent effect of inhaled corticosteroids on growth velocity in children and adults. These effects are less than those caused by oral glucocorticoids.

We have talked about the benefits of steroids, and I think it would be useful to have a table that would

demonstrate for mild, moderate, severe asthma for the recommended doses of the individual drugs, what is the percentage improvement in FEV1 in symptom scores, so that you can balance those benefits against the risks that are listed here.

With some of the newer steroids, there has been the introduction of the usual starting dose, which I would suspect is the maintenance dose when you are switching a patient from one drug to another. I think it is clear that there should be a distinction between that and the dose that you would use for treatment of an exacerbation. I would echo everyone else's comments about actively reducing the administered dose over time.

Finally, from the press' perspective, I think we have to talk about the bad news about asthma. The bad news that comes out of this meeting, is your child undertreated? Is your doctor not prescribing effective inhaled therapies that are proven to improve asthma symptoms and lung function? I think that's the big issue, not whether or not there is a minor reduction in height.

Thank you.

DR. BONE: Thank you, Dr. Baraniuk. We'll come to this side and start with Dr. Allen.

DR. ALLEN: Thank you. A few brief comments. First, I would also like to congratulate the agency on I

thought, a very sort of enlightened approach to looking at the data, which I think will have some effects on the way this topic is studied in the future. But I do have a few comments.

We have heard some remarks about what the function of the label should be. From what I gather, it is not only to provide information, but also to provide some education. I think with that in mind, it should reflect what we really know about this issue, and maybe what might be. While I'm certainly very interested in other possible systemic effects of inhaled glucocorticoids, and interested in studying them myself, I think that we should refrain from talking about those issues in the label at this point.

The label also might address, since it is interested in educating about the safe use of corticosteroids, one way to think about that is also the safe approach to the treatment of asthma. I think as I pointed out in one of my slides yesterday, when anti-inflammatory treatment is needed, the message has to be out there that should prompt more use of inhaled corticosteroids, and less use of oral glucocorticoids.

I think that somehow that message needs to be clearly communicated in the package insert, because we have already heard some comments about how we might actually see a paradoxical increase in amount of oral glucocorticoid

regarding the issue of monitoring. It has been stated quite clearly by the agency that they are not in a position to guide clinical practice, but I would urge the various academies that were here, or that are here and were speaking yesterday to consider taking a stronger stand about making recommendations for practice.

When I see children that come to me with asthma, it's clear to me that they are being treated for a chronic disease. It's not a whole lot different from the children with diabetes that I take care of. I don't see a reason why there cannot be standards of care that are widely publicized about the frequency of follow-up that is considered reasonable for those children, and that the periodic checks would include stadiometry and plotting of the growth data.

Thank you.

DR. BONE: Thank you very much, Dr. Allen. The next comment from Dr. Levine.

DR. LEVINE: Once again, Dr. Allen said a number of the things I was going to say. I think that if we agree that we should inform doctors of what we know, I do believe that in a cautious and measured way, we should include that there are changes in the HPA axis which have been demonstrated, however, the significance of these effects is really not clear.

Again, I agree with Dr. Allen that the

organizations who spoke yesterday, the representatives of those organizations, should be in a position to disseminate the appropriate message, and that included the Academy of Pediatrics and all of the thoracic organizations.

Lastly, that I would think that the data in regard to final height of asthmatics should be available in some way. That we should be able to document what is the final height of asthmatics, either those who have developed it only as adults, and those who were treated since childhood, to just get some idea as far as whether this seems to be an appropriate distribution of final height.

DR. BONE: Thank you very much, Dr. Levine. The next comment is from Dr. Hintz.

DR. HINTZ: I'd just like to highlight two issues. One is further research. There is obviously a lot of information that we don't know. First of all, I think we need to look at the length of time of the suppression effects. Is it six months? Is it a year? Is it as long as you are on steroids? Now parenthetically, the growth suppression effects of oral steroids essentially lasts as long as you are on oral steroids, but that may not be true for this situation.

I think the other critical issue I would like to highlight for future studies is the issue of catch up growth in this circumstance. The dichotomy between the data that

seems to indicate that childhood asthmatics reach a normal adult stature, and this data saying that they slow down their growth rate may well be answered by catch up growth.

So those are all I have.

DR. BONE: Thank you. Dr. Shapiro.

DR. SHAPIRO: I just want to thank the agency for giving me the privilege to be here as a guest. I would like to say that I can certainly understand the importance of a level playing field. If the class labeling is the way to make sure that all products in this area give the same information to doctors and patients, then so be it. I think that some labels now seem to provide reasonable information, and some don't, and that's not appropriate.

I do think that proper wordsmithing can get the message across without endangering the proper use of these medications. From a clinician's point of view, parents say, when you are engaging in a new patient intervention, that's not a steroid is it? Or that's a steroid, isn't it? That's a take off point for discussion. They may say, well what can I do to have my kid outgrow their asthma? That's the other big thing.

The use of the steroid and issues like the lung remodeling again, and early intervention and things we talked about yesterday are tied together. So we have lots of education to do in a short period of time. If the label

can be worded so that it helps us, rather than hinders us, it will be better.

DR. BONE: Thank you very much. Dr. Kelly.

DR. KELLY: I pretty much agree with almost everything that has been said, and I'm trying to figure out a way to make this interesting now. I particularly agree with Dr. Gross in terms of the issue of trying to find the minimal effective dose in a clinical trial, and I think that's almost an impossible task. Because when you start getting down to very low dosages, you get a wash out in terms of the severity of the asthma. I think demanding that of the companies for prior approval would be very difficult.

In terms of the statements in the class labeling, I agree with the class labeling. The agency has convinced me that there is an effect, and I really congratulate them, like everybody else did in terms of the quality of their presentation. However, I'm still not convinced that they have shown me that there is a long-term effect.

And in terms of presenting this in the precautionary and the pediatric usage, I think use of terms like "short-term," or how long the studies have been done is very appropriate at this time, because we really do not know the long-term consequences of these effects.

I also agree with the statements in which they talked about significant reductions in growth being

converted to statistically significant reductions in growth, and I'll stop right there.

DR. BONE: Thank you very much. Dr. Cross.

DR. CROSS: Like everybody else, I would like to compliment the FDA on the superb job they did with this topic. They are presenting the committees with increasingly tough issues that have more than just black and white. They are gray, and I think that has been presented superbly well, and I'm sure they will do just as well at meeting the challenge to wordsmith the package insert document to reflect the comments of yesterday and today. I hope we all get a chance to see how well they do the wordsmithing.

A couple of other things. I think the most interesting slide that I saw was one I believe Dr. Shapiro showed yesterday of the 5-10 percent use of inhaled steroids in the pediatric population, and a tremendous underuse that exists out there. This scares me. We all sitting around the table know that this underuse is in our inner cities' poorer population.

These inhaled steroids are already at the \$30-40 per unit amount. To put a tremendous amount of research on the companies, to raise the cost, to get more use into the inner cities is going to be very difficult. I don't favor getting companies to do more research, to raise the cost that is available to this community.

I do suggest that these research implications that should be done, that we agree on, should probably develop into research initiatives that are not met solely by private industry. And that the FDA could perhaps, with industry, with Congress, et cetera, develop strategies for getting better research done, but not at the sole cost of the company, and allow the peer review to get into manipulating the quality of the studies that are done.

I am reminded of the orphan drug program, which has tremendous support from Congress, which has tremendous support from industry, which as near as I can tell has good support from the FDA, which academics participate in enthusiastically, and which volunteer health organization participate actively. I take the cystic fibrosis community as an example.

I think that there ought to be a way to bring NIH, the FDA, industry, private philanthropy, volunteer health organization, and academics together to define more clinical studies of great need to the nation, which would be supported by the Congress, and which would be supported by industry, and certainly supported by academics.

And bring some of these problems to a focus where there could be peer review brought into the process, and where it could be collaborative efforts, and we're not going after an NIH budget item that then subtracts from some

molecular biology that needs to be done, et cetera, but is a collective research initiative that would be somewhat like the orphan drug program, and which involved the important issues that we all think should be done, but not under the purview of a given industry or a given government organization like the FDA, which has had enough problems defending their own merger research component.

So that I hope that this issue does at least give food for thought for who pays for this research, and how we could get it done at the most effective way for the nation, and get better quality research, and involve all of the interested parties.

Thank you.

DR. BONE: Thank you, Dr. Cross. Dr. Cara.

DR. CARA: I would also like to echo some of the comments previously made, especially by pediatric endocrine colleagues. I would like to compliment the agency for letting the cat out of the bag so to speak, and really addressing head on this issue of corticosteroids, which I think is very, very critical, and would look forward to having them continue with this process.

I have heard a lot about the fear of patients' physicians in terms of specific warnings regarding corticosteroids and inhaled either orally or intranasal administered corticosteroids of course, and the fear that is

instilled in the parents or physicians about their use if warning labels such as the ones that are being described are in fact put into place, especially in light of yesterday's comments by clinicians that have to work with patients.

But I too am a clinician, and I too work with patients. I have seen patients that have been referred to me because of problems with their growth; to some extent angry because of the added injury if you will, to their already underlying chronic illness.

I think one of the things that has been more challenging for me as a practitioner is to deal with some of the anger that parents have, not only because of the insult added to the injury, but because of the fact that they were not told that this could be something that could happen. Because they were not warned beforehand. Because this sort of information, either because of their own physician's ignorance, or because of an outright suppression of the information, they were not notified that this sort of thing could happen.

It has been a very difficult issue for me to deal with personally, and I hope I have given you the flavor of just what that is like.

I do have some more specific comments. That is that I don't think that there is in fact a need for trying to determine a minimally effective dose. I think that

clinicians need to determine for themselves what a minimum clinical effective dose is. However, that said, I think that if we can do one single one, and that is to get clinicians who care for children with asthma to measure them, and measure them accurately, we would be achieving a substantial improvement in their clinical care.

There has been also a lot said about other effects of corticosteroids. I think that they undoubtedly do occur. I do think that growth is a very sensitive indicator of a child's overall well being, but for the meantime, until we have a better idea of what some of those other effects are, what we are left with is a child's growth, and that is something that we need to address.

I think that the agency's providing some guidance to practitioners in their labeling document is going to be important. Again, if all we can do is just get clinicians to measure their patients, that would be a major achievement. However, I also think that providing them with some additional guidelines, i.e., need for referrals or reconsiderations of therapeutic alternatives or whatever is also important.

Thank you.

DR. BONE: Thanks, Dr. Cara. This will be Dr. Szeffler.

DR. SZEFLER: Thank you. At this point I should

probably agree with everything that has been said, but I won't. I should probably be brief, but I won't.

I think there has been a lot said in terms of the issues, and the best I could say is we asked for this. Five years ago when John took his office, we whined about how much we don't know about the comparative aspects of inhaled steroids. He took on this challenge.

The Academy of Pediatrics complained about not knowing enough information about drugs and children, and he took on this to give us some information. He gave some information, and we may not like it, but it's real, and it is actually an assimilation of data that has been there. It is compelling.

We have been through some eras which have been marked by change, which have been really moved ahead of practice. There has been kind of unbridled enthusiasm in terms of going to higher potency steroids, higher doses of steroids, higher lung delivery, earlier use, and more extended use. It's a whole different era than what has been explored in the past.

I would compliment the companies and the FDA for taking on the challenge, because there have been companies who have been very responsible, and have been conducting studies to get the information we need, we've been asking for. To those companies, they now have the data to answer

the questions, and their product inserts should reflect that.

Some of the other companies have benefitted by not doing the studies, and have had some of the weaker statements in the package insert. So I would say they should be all on the same table. Some of the newer drugs that have done the studies have had stricter labeling. That labeling has been out there. Physicians have read it.

The small percentage of treatment of steroids that have been used in the United States is not a reflection of ignorance, it is a reflection of concern. Some of the data that has been presented actually reinforces the concern. We would be negligent if we didn't inform the public about the information that is there.

The case reports are compelling. Many of us in our own practice have gotten calls from physicians -- I think like Dr. Cara mentioned -- from physicians and from patients who have had abnormalities. I think with the unbridled enthusiasm, the changes in managed care, if there aren't good monitoring systems for adverse effects, some of these cases will go unrecognized, and we'll pay in the future.

I think there has been clear identification of potential risk factors and underrecognized areas. I think the point about looking at race effects is very important,

because that has an underemphasized area.

I think the dose effect -- we have kind of gone with this is a dose you use, and use it for all ages. I think some of the compelling features, at least to me, were maybe that the younger children receiving a higher dose are the ones that are at risk, and they should be looked at.

I think there is a great need for -- we've been talking about asthma as a long-term disease, and we really need better information on the long-term effects of the treatment. So I would really promote longer-term studies, particularly in children.

I think that the points that you raised about the developmental aspects and the duration of treatment, and the pinpoint of treatment and adverse effects are very important areas. If we didn't get that message, we have not been listening, because there are important developmental aspects, and as a pharmacologist, I would support looking at those aspects.

So I think we have been issued a lot of challenges. Many of us should take on those challenges to try to develop new drugs; try to understand the disease better; to teach our colleagues about the safe use of the drugs. I'm glad this information kind of came to the surface, because many of us in the audience have been asking for these kind of studies, have been participating in these

kind of studies.

And this brings it to a higher level, to really take good information and get it back to our colleagues in pediatrics, so that they can feel comfortable. There is nothing like sitting in an audience and talking to a group of pediatricians who look at you cold, and then say to you, doctor, can you guarantee me after your talk that 20 years from now I'm not going to be dealing with a growth defect or a cataract defect?

These questions are being asked, and I think the drive has now been issued for us to get the information, and invest the appropriate funds to get that information.

So, thank you very much.

DR. BONE: Thank you very much. We'll have Dr. Crim and then Dr. Li and myself.

DR. CRIM: A lot has been said over the past couple of days about this issue of steroid phobia. I would say that personally, I don't have a problem with it. I don't look upon this concept of steroid phobia as something negative. I look upon it as an opportunity.

It has been mentioned at to how the NIH asthma expert panel emphasizes the use of inhaled steroids in the treatment of asthma. But I would also remind my fellow colleagues that they also mentioned that the optimal management of asthma entails a partnership. That is a

partnership between the patient, the physician, the family, the pharmacist, et cetera, et cetera.

So that is in terms of a partnership, I believe everyone needs to be informed in terms of the optimal management of this particular patient. Therefore, to me, this issue of steroid creates an opportunity where the physician is now compelled to discuss with the patient and the family, the optimal strategy, why he or she feels that steroids are indicated, and at the same time, mentioning these potential side effects of steroids.

When we treat a patient with oral steroids for whatever type of systemic problem, we sit down, as a physician, with the patient and explain to them why we think steroids may be indicated. We also mention potential side effects of steroids. So therefore, for me, I think it's something that the patient and the family, particularly the parents, should be aware of as far as potential side effects. And therefore, this should create a dialogue, if nothing else.

Along those same lines, I also agree that I don't think that whatever labeling is chosen, that it should be suggesting to the physician how to practice medicine. I think most practicing physicians really get ticked off about someone telling them how to practice medicine, even if it is other physicians so to speak. Definitely they have problems

with either the pharmaceutical industry telling them how to practice medicine, and particularly the government trying to tell them how to practice medicine in the form of the FDA.

So I think if we chose language in the labeling that suggests to a physician how to practice medicine, they will not look at it as coming from an austere group of physicians sitting around this table. They will look upon it either as the government or the pharmaceutical industry telling them how to practice medicine, and that might in fact be a turn off, if nothing else.

The issue of this lowest effective dose, I would also agree that that would be difficult to study. I think we all recognize that treating asthmatics, that we can, in some patients, after we get them stabilized with higher doses, we can cut them back to doses of inhaled steroids even lower than what is recommended in the package insert.

I think the emphasis there for if we touch upon that in the labeling, we should just emphasize that there are some patients who can be maintained once they are under control, with a lower dose than what is indicated in the package insert.

In terms of the label, I think it probably would be helpful to educate the physician that in terms of the reductions in the growth velocities, we can include the data where we do have data in terms of what the range of the

reduction is, be it from 0.5 centimeters to 2 centimeters per year in the studies that were conducted for a year.

At least when they discuss with the family or the patient and/or their parents, they can say, yes, these studies have observed this, but this is the range in reduction that we have seen. Exactly what it means, we don't know, but at least it will give the physician some numbers in which he can educate and intellectually discuss with the parent and/or the child in terms of the magnitude of the problem that we have recognized.

Finally, as far as potential studies, and this has been touched upon to some degree. I think that they need to be large, and probably it would be best to do these types of studies in mild persistent asthma, so that you can one, in addition to accounting for their approximately 25 percent drop out rate, you can hopefully have a large enough sample size that a significant number will be able to go through the study without having to require steroids bursts.

I would be nice to see if there is any type of correlation between measurements made by knemometry, as well as stadiometry. Likewise, whether or not it would be helpful to see what happens to knemometry in patients who receive steroid bursts, to see exactly what the effect of steroid bursts are in these types of growth studies.

I'll leave it at that.

DR. BONE: Thank you very much. Dr. Li.

DR. LI: First, I would like to also congratulate not only the FDA for their excellent presentations, and for putting the meeting together, but I would like to thank the sponsors for sharing their proprietary information, and for conducting the studies, at least those companies that did conduct the studies, because I think that really in the long run will add to our information and benefit our patients.

I think particularly, Dr. Purucker deserves credit for her team doing a really terrific job of synthesizing the information for us.

The management of the diseases that we're discussing, asthma and allergic rhinitis, are both complex. In fact, they are highly complex. The stakes are higher in asthma probably, but both conditions are complicated in terms of assessing the problem, evaluating many factors, including environmental factors, as well as weighing the risks and the benefits of the variety of the different types of therapies.

So our discussion about the effects of intranasal and inhaled corticosteroids on growth really adds another level of complexity to taking care of these patients. And that's a fact that really doesn't have anything directly to do with the labeling. We really have to face that right up front.

So when we address the issue of stay steroid phobia, or the issue of sort of the general practice, or the primary care management of asthma, which in many studies is less than optimal, we really shouldn't look to the labeling as either a solution, or really as part of the problem. I mean we have to put the responsibility in part where it lies, and that to me, would be the medical community.

I mean, we in the medical community need to do the education job that I have heard around the table needs to be done. That would addressing the issues of steroid phobia in the public, and to other physicians. And also addressing the education of the medical community and providers of all types who take care of patients with asthma and allergic rhinitis. So let's just put that responsibility where it belongs, which is with us -- with us not as a committee, but with us as physicians and specialists.

As I looked through the draft labeling document, I kind of pulled out three of the action verbs that came through, which I think kind of highlight what the labeling ought to convey. The three that I pulled out were: to monitor for growth; to weigh risk and benefits; and third, to titrate to the lowest effective dose. I think those concepts ought to be retained.

I'll also answer my own question which Dr. Jenkins threw back to be as a rhetorical question. In terms of the

idea of monitoring, I have perhaps back tracked a little in view of what I've heard, and I think the wording is actually in my view, acceptable as is. Rather than putting more specific recommendations in the labeling document, I think it is up to again, the medical community to come up with a consensus and recommendations, and for us to share that with others.

So whether that is height every three to six months, or using growth velocity charts, or height charts, or bone age, whatever that happens to be, again, that is the job of the medical community. Hopefully, our endocrine and metabolic colleagues will be able to contribute and help us with that.

The other verb I will comment on is the titration to the lowest effective dose. I have to admit I was convinced by Dr. Gross' comments that perhaps that phrasing could be changed. I think we have an idea of what that concept means, but perhaps using the word, the dose of the treatment can be individualized or something of that nature.

So in order to support those recommendations of monitoring, weighing, and titrating, the precautions need to be consistent, and need to be in the product label. So I certainly support wholeheartedly the concept of class labeling, both for consistency, and also for information and partly education.

Based on the data that we have heard, it really would be almost irresponsible for an inhaled or intranasal corticosteroid product to be made available without a precautionary note. I think that the draft that we have here really will serve us well.

As far as specific studies go, I'd like to get back to the idea of the lowest effective dose, because someone brought up the fact that we are really talking about two different aspects of this, and I think that is absolutely true.

On one hand, we were talking about the most appropriate dose for an individual patient, and the importance of adjusting the dose upward, or in this case, the relevance is downward. Again, I would use the word "adjustment" or "individualization" for that, and I think that concept is sound.

The other concept of lowest effective dose really has to do with the product insert and the clinical studies that are used to support the effectiveness of the drug. I know that when you look at a lot of the studies that are done to support the efficacy of inhaled corticosteroids, it is very clear -- well, two things are very clear. I think one is that in many cases, not all, but many cases the dose response curve is very flat.

So that in any one study, there can be a two-fold,

four-fold, ten-fold difference in dose of inhaled corticosteroid, and the clinical effect is indistinguishable. So that issue needs to be addressed, and I haven't heard that mentioned before, at least not today.

The second point with these dose response studies is often when you look at these studies, the lowest dose that is studied is as effective as the highest dose, as I said. Usually, the usual starting dose, or the doses that are marketed then end up being much higher than perhaps what is necessary.

So the type of study that I think would be helpful as a clinician would be a dose ranging study, a clinical study. I would ask the studies to include lower doses so we have some idea of when the effect starts to fall off.

The concept of underuse of inhaled corticosteroids or overuse is kind of a complex one. I think for any individual patient an individual might be overtreated with inhaled corticosteroids, because they are on the usual dose, the two puffs four times a day, the two puffs twice a day of whatever product that happens to be, and the dose is not reduced further, or the formulation is of such high potency, that even one or two puffs a day is much more than is necessary.

The idea of underuse may be that there are patients with asthma -- let's just keep it to asthma for

right now -- who would benefit from fairly low dose inhaled corticosteroids, and who are not using that product at all. So that would represent the idea of underuse.

I guess the last thought I would share is regarding this relatively flat dose response curve, I think we need to rethink our clinical guidelines and recommendations for inhaled corticosteroids inasmuch as a strict adherence to a step care, meaning a higher dose of inhaled corticosteroids is better and more effective than a lower dose may not always be true.

I think one of the concepts that I think is worthy of emphasis is for an individual patient, it is important that the patient's on appropriate medication; that the physician weigh the risks and the benefits, not only of inhaled corticosteroids, but of all alternatives. And that the dose of inhaled corticosteroids be adjusted and individualized, which in many cases will mean a lower dose than what they are already getting.

So I'll stop there.

DR. BONE: Thank you very much, Dr. Li.

I'll just add one or two comments of my own, and then I think we can go around and have the individual committee members' responses to the questions, which we can make quite concise, everyone having had this chance to make their remarks.

I think the impetus to the development of these drugs was the substantial side effect profile of the usual oral systemically used steroids. We have been benefitted greatly by having a group of drugs that minimizes those side effects. I think this has led to much more aggressive and expanding use of these drugs, with good effect in many cases, but it's not surprising that we're starting to see that we see some similar effects, but of lesser magnitude than were seen with the previous oral doses.

We've identified this somewhat quantitatively in the case of growth, but it will not be startling if, with more careful attention and longer studies, we find some other more subtle, long-term effects. None of this means that this we shouldn't use these drugs, but it will help us to understand how best to calculate the benefits from these drugs in relation to the potential costs.

This is just going to be an ongoing process. It is going to drive drug development toward compounds that may have advantages as we go along, or to treatment schemes that may have advantages, and it's just how we make progress.

I think my only other comment would have to do with just endorsing the suggestions others have made about the drawing of distinctions between these drugs and oral systemic steroids, and making the other adjustments that have been recommended in the labeling to let's say make

clear the context when these adverse effects on growth are being described.

I think now we can go around. I believe there is a gentleman standing at the microphone, but we are voting now. There won't be an opportunity, I'm afraid to --

PARTICIPANT: [Remarks off mike.]

DR. BONE: Thank you very much. I appreciate your contribution, but we're going to have the committee and the guests go forward.

If we'll just I think go around. I think the most efficient thing to do is to combine the first two questions. One is are the available data sufficiently compelling to support class labeling for all intranasal corticosteroids, and the other is for all orally inhaled corticosteroids regarding their potential negative impact on growth velocity in children.

Then please comment on the proposed labeling document. Most of us have already commented on the labeling document in our general discussion. So what I would appreciate each member of the group doing is to answer the question about the available data being sufficiently compelling to support class labeling separately for nasal and oral steroids. Then if they have something that they haven't already said about the class labeling, please concisely mention that, otherwise it is perfectly fine to

refer to one's prior remarks or those of others.

Perhaps in this instance we would follow the same pattern and start with Ms. Conner.

MS. CONNER: Yes, yes, just to keep this brief. I do believe there is sufficient data available for both intranasal and oral inhaled. And the comments as far as the labeling document I think were addressed earlier and sufficiently by colleagues. The lowest effective dose issue would be nice information to have if it were easily --

DR. BONE: That's come back to that first question. We'll take the first two. As far as keeping track, it's much more practical if we don't do too many at once. We'll go around quickly, and then come back to that.

DR. CHINCHILLI: No for the intranasal steroids, yes for the inhaled steroids. No comments on the label; they have been made.

DR. HIRSCH: Yes and yes.

DR. OSBORN: Yes and yes.

DR. LIU: No and yes.

DR. OPPENHEIMER: Yes, yes.

DR. GROSS: No, yes.

DR. AHRENS: Yes, yes.

DR. DAVIDSON: Yes, yes.

DR. FINK: Yes and yes.

DR. BARANIUK: Yes, yes, but I'd like to add a

caveat actually that wasn't brought up. If future studies with an individual drug demonstrate that there is no effect at a specific dose, then I think that the label should be modified. This would provide an incentive for companies to study this effect, and may provide a marketing advantage over other drugs. It may also inspire companies that wouldn't be doing these studies, to perhaps consider them.

DR. ALLEN: I would vote yes, yes --

DR. BONE: Excuse me, we're not voting. We are just commenting. This is a distinction we have to make here.

DR. ALLEN: I'm just commenting yes, yes. I want to comment on number one though that I base my feeling on this more -- I just want to make it clear that this is on theoretical grounds rather than on the data presented.

DR. BONE: Well, the question was about the data.

DR. ALLEN: Well, it's a tough question. I guess I would abstain from number one then, and say yes to number two. With regards to the labeling, the only point I wanted to make was, I thought one of the excellent points that was made that I would like to endorse was the inclusion of specific ranges in the class labeling with regard to say growth effect and dosage, because I think that means much more to the practitioner than seeing significant or little bit.

Also, if the companies are allowed to include data about their own growth studies in the label, it will allow the practitioner then to see where that growth effect of the preparation that they are prescribing falls in that range.

DR. BONE: Dr. Levine, do you wish to comment?

DR. LEVINE: Yes, yes.

DR. HINTZ: Yes, yes.

DR. SHAPIRO: Yes, yes.

DR. KELLY: Yes, yes, but I have a comment about giving the range in the studies. I think if you are going to do that, you need to give the actual range, which is zero effect to whatever the effect is, not the means of the different studies. Because that is not the true range of effect.

DR. CROSS: Yes, yes.

DR. SZEFLER: Yes, yes, with agreement with Dr. Baraniuk and Dr. Allen's comments.

DR. CRIM: Yes, yes, and again with the ranges, both for the intranasal and the oral inhaled.

DR. LI: I comment yes, yes. A brief comment is I think I would look at the level of evidence that is compelling for a precaution to be one that involves significant trends in the evidence. I just remind myself and perhaps others that as we label precautions for other drugs, often it is based on essentially anecdotal type

reports, and we have certainly much more than that here.

DR. BONE: All right, with regard to the orally inhaled corticosteroids, I would say that the data are sufficiently compelling to warrant the class labeling. I think the comments have already been made about the kinds of distinctions that people have made as to modify the tone somewhat of the draft, which I'm sure is the reason why the draft was circulated, is to get those suggestions.

With regard to the nasal corticosteroids, I think this is a little more problematic, because at least based on the data we were shown, they were rather skimpy about this. The pattern of use is quite different there I think, in terms of being more seasonal and occasional, whereas we were looking at a long-term study.

So on the other hand, Dr. Jenkins mentioned some additional studies that we weren't shown, so I would I think have to defer on this. I wouldn't be convinced that the language selected would be appropriate here, but perhaps something about long-term use has been associated with.

We have comments from the members who have had to leave, and I think we'll ask the executive secretary, Ms. Reedy, to read those.

MS. REEDY: Dr. Burman would not care to see the labeling in the intranasal, but would in the orally inhaled. Dr. New believes that class labeling is necessary in both.

DR. BONE: Thank you. Next I would like to go around and discuss this lowest effective dose question. This is again a concise comment, because we have all had a lot of discussion about this. This is truly a comment. I think we'll just follow the same circuit.

MS. CONNER: I think having lowest effective dose information, both on new products, as well as existing would be wonderful to have, but we need to determine just exactly what the definition of that is, taking into consideration concomitant medications, disease states, and other situations without maybe conflicting and allowing physicians to step up and step down therapy.

DR. BONE: Would you recommend requiring that to be information prior to introduction of the replacement products that are to replace the fluorohydrocarbon products?

MS. CONNER: I have a problem with that, because what you are replacing is a delivery component. There is no change in necessarily the active moiety. I understand it is a new product, and if that's the wishes of the agency, then that would be, but it's really difficult for me to see putting the pharmaceutical companies through the expense of doing that just from switching from maybe a CFC to an HFA or a dry powder inhaler.

DR. CHINCHILLI: I think for new products, some of the Phase 2 studies that companies do, do some dose ranging

studies. They could probably modify them somewhat to try to address this issue of minimally effective dose. In fact, some of the companies may already do that.

For the already existing products that need to be replaced, I really don't know. I think that's such a problem, that I don't want to get into that now. So I have no real comment on that right now.

DR. HIRSCH: Very similarly, I think for the new products it should be required, but perhaps not lowest effective dose, but range of effective doses. For the products that are currently approved, it seems that they are unlikely to be able to do this at the present, so I'm not for that.

DR. OSBORN: I also agree that for the new products it's appropriate to look at lowest effective dose, probably by giving specific doses that should be looked at in the 50-100-200 range. I am against requesting it from the sponsors for all currently approved products.

DR. BONE: Now by new products, we have to go back to what Dr. Jenkins was talking about and I mentioned a few minutes ago. By new products, do you mean new chemicals, or do you mean the reformulations as well?

DR. OSBORN: I think both are considered new products by the FDA.

DR. BONE: Yes, but you can make a comment if you

want to.

DR. OSBORN: I would agree with that.

DR. LIU: I also agree that because of differences in availability and particle deposition of even new formulations of old drugs, that the potential for efficacy and side effect profile can be changed dramatically from these. So I would really like to see lowest effective doses incorporated into the trials for approval. So I give a yes to that. Then a no for the existing products.

DR. OPPENHEIMER: Yes, no.

DR. GROSS: Yes, no.

DR. AHRENS: I think it would be appropriate for all the aforementioned reasons required for new products, but not recommended perhaps for existing products in the sense, and only in the sense that under the definition of requiring a better exploration of the lower end of the dose response curve to really enhance the range of dose options that the clinician has available.

I really would link that also to the concept that Dr. Baraniuk mentioned earlier, and really is the same concept that I brought up this morning in terms of the maximal safe dose concept. That's an unfortunate term. I think Dr. Baraniuk described really the concept much more appropriately. I would never include that wording in a package insert.

But I really do think that companies should be encouraged to come forward with data that might support statements like these effects on growth were not observed in doses that were less than X. Or perhaps that they were observed only when doses of greater than dose Y were observed. Or even better yet, that these effects on growth were only observed in doses above the ranges recommended.

So I think that concept is one that I didn't invent, nor did Dr. Baraniuk. It's one that is well out there in the literature, in the review articles in particular, and it's there for a reason. I think that is an extremely valuable concept for the clinician to know where the yellow light, as opposed to the green light comes on, and even better if we had information where the light truly becomes red.

DR. DAVIDSON: Yes, yes.

DR. FINK: Yes and no.

DR. BARANIUK: I think with new moieties and delivery systems they should be included in dose ranging studies. There should be a growth component there. For currently approved drugs, I don't think that they necessarily need to be tested. However, as I mentioned earlier, if it can be shown that they have no effect on growth, then the label should be changed to reflect that.

DR. ALLEN: I think the concept maybe should be

changed to a lowest effective dose, rather than the lowest effective dose. I favor yes, no.

DR. LEVINE: Are we talking about just number three?

DR. BONE: Yes.

DR. LEVINE: So I would say yes for new drugs, and no for reformulations of previously approved drugs.

DR. BONE: Thank you. What about the same formulations of drugs that are already on the market?

DR. LEVINE: I thought that's what I was saying no to.

DR. BONE: There are two kinds of new drugs. There are two kinds of new products. One is a new chemical, one is a new formulation or delivery system of the same chemical. That's sort of 1a and 1b.

DR. LEVINE: So yes, yes, and no.

DR. BONE: Okay, thanks. Dr. Hintz.

DR. HINTZ: Other people have voted yes, yes and gotten away with it.

DR. BONE: They were including both, and Dr. Levine was making a distinction.

DR. HINTZ: Yes to 1, and yes to 2a and 2b.

DR. BONE: Dr. Shapiro, what do you think?

DR. SHAPIRO: I would say yes to dose ranging studies, and no to previously approved products.

DR. KELLY: I agree with Dr. Shapiro. I believe in the concept of doing dose ranging studies. I still do not believe that you can do a minimal effective dose study and require that. So that's sort of a yes. Somehow that's a yes. And no.

DR. CROSS: I'm going to do the third in a row that's a yes to dose ranging studies. I have no idea what lowest effective dose means. Do you mean the dose that would require the taking of prednisone to be halved, or do you something that is going to reverse a methacholine challenge? Or do you mean something that is going to take somebody that is 90 percent of predicted to 100 percent of predicted, et cetera? I don't know how you define the term, but dose ranging study, yes. No on the other.

DR. SZEFLER: I would say no, because the concept is too poorly defined. I would replace the word "required" by "encouraged" so that industry could work with the FDA in defining that term. Then as far as the label goes, previous comments I would agree with to individualize that concept for the individual patient.

DR. CRIM: Since the operative term is required, and to extend what Dr. Cross said, lowest effective dose, I don't know if we are talking about FED1, peak flow, symptoms. So in that context, as well as since the operative term is "required" as opposed to requested, I

would say no and yes, that is, it should be requested, not required.

DR. LI: My comment is yes and yes. My other comment is I understand this question really to relate to a dose ranging study, with particular attention to the lower end of the dose ranging curve. In that context, yes and yes.

DR. BONE: In my view, the dose response curve for any drug that I can think of should be elucidated. I think that the point about which endpoint is the principal endpoint is a well taken one. Undoubtedly, what should be examined are several endpoints, to see if they are in concurrence.

It is essential to find at least the steep part of the curve, and to have an idea of how to advise people about practicing. I think it is useful in early clinical trials to see what the no effect dose would be, given that we have to make some judgments about what endpoints to look at.

I think this has emerged in our discussions that this is a particularly important problem in children, because children are different sizes. And we don't seem to reflect that very well right now in the dosing, and there are good reasons from the discussion to be concerned about this. So I think this has to take into account age or body mass or some other measure of the size of the child, because

there is obviously a huge difference between 6 year olds and 12 year olds in terms of what the drug effects might be of various kinds.

I think this information should be required certainly for new chemical entities. I think that even the new products being developed to switch over from CFCs, since the studies are only 12 weeks, is that there is adequate time to accomplish this.

I think this is a little more problematic for formulations that are already on the market. I'm not sure how much longer most of them are going to be on the market after the CFC issue. I'm not sure how many of those will be affected. But it seems to me that if a company does not have that information, the labeling should have something to the effect that the minimum effective dose, or the dose response curve for this drug has not been worked out. Although I would really favor having a deadline for getting that done for all the drugs that are on the market.

We have comments on a couple of these points by our other colleagues I believe. Ms. Reedy.

MS. REEDY: On number three, Dr. New recommends that the lowest effective dose be sought. On number four that we require measurement of height four times a year during treatment.

Dr. Burman disagrees that the lowest effective

dose should be a requirement. Let me add that Dr. Cara did speak to the first two in the positive before he left.

DR. BONE: Thank you. Now let's go around and in the same way, cover the question about the growth studies. This is a fairly complicated question just in its structure, because we are asked whether a growth study should be required for registration, so that's one question. Should it be required for registration?

The second question is, should it just be a Phase 4 commitment after registration for new drugs or new products, and also for existing products if the company hasn't already performed such a study for that product? This is starting to remind me of one of those complicated multiple choice tests that we all used to love so much.

As usual, we'll start with Ms. Conner.

MS. CONNER: I think growth studies should be required, and probably as a Phase 4 commitment to allow for the length of the study. And I think maybe not requested, but definitely encouraged, maybe with encouraged being a stronger word than requested.

DR. CHINCHILLI: Yes.

DR. BONE: That applies to all?

DR. CHINCHILLI: Yes.

DR. HIRSCH: Yes, not Phase 4 for new things that are approved. And for all currently approved ones that have

not had adequate growth studies, yes, they should be.

DR. OSBORN: I actually think it's very difficult, and I think further discussion with FDA and industry and appropriate statistical colleagues would really be indicated. Having said that, I'll give an example of what I can come up with off the top of my head, recognizing that three hours in consult might change my opinion completely.

I think a Phase 3 and Phase 4 should be considered. The Phase 3 would be for new products only, obviously. And the concept here would be the kinds of studies we have already seen, and look at type of drug dose, height with stadiometry, and look at age and pubertal stage. That sort of thing, and maybe the duration would be a six month lead in, with a 6-12 months follow-up. These would be required just for approval of the drug, and these kinds of studies are truly ongoing in any event.

The Phase 4 component would be that one would have a series of patients, well characterized, that could continue to be followed at a minimum with height measurements over some years of time. I'm not sure what is feasible to request the industry to do, but something along those lines, with the idea that following a drop out, compliance, medication use, as well as the pubertal development of the children would be crucial.

A database could be set up at the FDA to get input

from the various industries according to drugs, so that they could analyze it as a class effect, as well as a new drug.

DR. BONE: Thank you. Actually, Dr. Osborn rather cleverly combined questions four and five, and I think that's a good idea. Would any of the first three speakers wish to add an additional comment about the design features of the growth studies?

DR. HIRSCH: I agree with everything that has been said. I would add one feature, and that is to the extent that one can examine mechanisms whereby the reduction in growth velocity occurs, that would be very helpful, with better indices of hypothalamic-pituitary-adrenal axis function.

DR. BONE: Thank you. Dr. Chinchilli.

DR. CHINCHILLI: Yes, I mentioned earlier I have written two and a half pages of things I would suggest, so I'll turn them over to the FDA, unless you want to hear them.

DR. BONE: Ms. Reedy will be happy to communicate those. Obviously, those of us who have made comments earlier on this point, we can just refer to those.

MS. CONNER: I just think it's very important that we allow for a long enough run in period, to determine a baseline growth velocity before starting a study.

DR. BONE: Now Dr. Liu for questions four and

five.

DR. LIU: I agree with the comments that have been made. I do think there should be some uniformity in what is required with these Phase 4 studies, so that there can be at least some attempt at a comparison of these. That should be part of the agreement, if you will. Because I think what has come out of this is that part of the difficulty in comparisons is the different study designs, different patient selection, different methods used, all these things. If that could be made uniform from here on, I think that would really help in terms of comparative effects.

DR. OPPENHEIMER: Ditto.

DR. GROSS: Yes, I think studies should be done. And I leave it to my pediatric colleagues to suggest exactly what are the most important things. But I certainly agree with the standardization. I think that would be very helpful.

I would like to suggest two other things. One is that crossover studies should be done, because of the enormously greater statistical power of comparisons. There was some comment from the FDA staff earlier today about that and the problems with that. I really don't see that that is such a big problem. I think it would be possible to do crossover studies quite easily, provided one was able to extend these studies for at least a year.

I don't think you need more than at most, a month wash out between after the steroid administration phase, before you can assume that there is no longer any steroid effect on growth. I may be wrong about that, but that would seem to me to be reasonable. We already do 12 months studies on asthmatics and CFBD patients. So I don't really see that that would be a big problem, if you can make consistent measurements within a six month period. That kind of a study can probably be done.

Then one other thing occurs to me might be able to provide a lot of supporting evidence is to do a retrospective epidemiologic study in former adolescents, children, asthmatic patients who have been treated, case controlled, just to see whether there is a measurable difference in height between those subjects who have taken steroids in the past during their growing period, and case controlled subjects who haven't.

DR. BONE: Dr. Gross, did you think that the growth studies should be carried out prior to registration?

DR. GROSS: Yes, that was the first part of my response.

DR. BONE: Okay, thank you.

DR. AHRENS: Yes, I do think that studies should be carried out during the approval process, as well as during the Phase 4, as noted earlier I think. The kind of

intermediate term one year type studies we have discussed so extensively here, preapproval, and Phase 4 for longer-term follow-up.

The existing products, I think it is really important that studies also be required there, especially for chemical entities that are on the market for which we have really no usable data to date. I think that probably flunisolide is the greatest example of that. Odds are it probably doesn't have a significantly greater effect, larger in magnitude than the ones we have discussed here, but in fact we don't know that. We don't know that it might not in fact have a considerably larger magnitude effect. And I think it's essential that that kind of information become available on products like that as well.

DR. DAVIDSON: Yes and yes for both. It should be in Phase 3 for all new products.

DR. FINK: Yes and yes, although with the provisos that one, minority populations must be included in these growth studies, as they are reflected in the asthma population. And I guess secondarily with the proviso that the requirement for growth studies not impede the approval for use of drugs in pediatrics, or lead manufacturers to not apply for pediatric indications for their drugs.

DR. BARANIUK: I guess I'm a yes and yes.

DR. ALLEN: Yes and yes. I think the combined

Phase 3/4 approach is a very good way to encourage high quality study designs that are going to be longer-term, while also giving us direct comparisons with the data that we have for the studies that have been done already.

DR. LEVINE: Yes and yes.

DR. HINTZ: Yes and yes. I want to emphasize though the importance of a long-term Phase 4 commitment, because some of the questions that we have been talking about the last two days can only be answered by long-term observations. I think I would emphasize that as part of question five there of crucial issues. Only with essentially a follow-up as long as we can do it, are we going to answer some of the questions about catch up growth and length of time of the growth suppression effect.

DR. SHAPIRO: Yes and yes.

DR. BONE: Any comments on the question five section, in addition to those that have been made?

DR. SHAPIRO: No, just the importance of some uniformity.

DR. KELLY: Yes and yes. I would extend that to I think growth studies should be done in all products going to be used as long-term controller medication in children. I don't care whether they are steroids or non-steroids.

Then in terms of the study design, I pretty much agree with Dr. Allen and Dr. Osborn.

DR. CROSS: Yes, yes, and I certainly agree that study design should be uniform.

DR. SZEFLER: I would say due to the nature of the study, that it would not be a requirement for approval, but for Phase 4 commitment it would be important, because in order to get adequate information I think the data is compelling that we need even longer than a year. So I think in terms of design, you are talking about a two year study, but I would add also that an interim analysis be considered in terms of shortening the length of the study, so that if there is no effect after a year, you would have the option of stopping a study.

And looking at potential populations at risk, and the focus in terms of a design, I think the compelling information seemed to be that the 4-11 year old group would be important. Then there should be standardization of study procedures, a recognized stadiometer, with methods of procedure defined in terms of standardizing the equipment.

As far as drugs available on the market, I think they should be requested. I don't know if there is any power at the point to say they be required at this point. They should be requested for the good information and practice.

DR. BONE: Dr. Cross has an additional comment.

DR. CROSS: Yes, I just want to make the comment

that the CFCs are a concern, because if we are throwing two or three years more studies that they didn't know about until six months from now, we'll never get them converted. I think that waivers for those, or making them Phase 4 certainly would be in order, and we ought not to hold up approvals for the CFC conversions until a three year growth study analysis is done.

DR. CRIM: Yes, yes, and as far as the studies, again, just to kind of emphasize what I mentioned before, that is, the patient population will probably need to be, at least for the growth studies in my viewpoint, the mild to persistent, so that you can minimize the effects of steroid burst.

In terms of the study, it can be a way of determining whether or not something like knemometry would be a tool to assess the effects of the systemic steroids in case they are used for rescue.

DR. LI: As I looked through the wording of this question, I'm going to qualify my answer. I think over the last two days the deliberations clearly have led up to the point where we recognize that we need this kind of information. But the first part of the question regarding new products, we have an or here. Should the sponsor be required to conduct a growth study prior to approval, or to commit to a Phase 4 study. I believe a Phase 4 study would

be adequate in that setting. So I would not require a growth study to be completed prior to approval.

I also comment yes for studies for existing products.

DR. BONE: Thank you. With regard to the completion of a study prior to registration, I think this is probably much more reasonable and important for a new chemical entity. I think that there is a great advantage of having a one year study with an extension phase, which would be carried out during Phase 4, and that is that you know that the Phase 4 study is going to be carried out, because it is fully enrolled before the drug is registered, and the arrangements about that study can be evaluated.

I don't think it is going to be possible to have a controlled study for Phase 4 if we are going out five years or ten years, which is the sort of duration that we may be talking about. Remember, we are doing ten year follow-ups now with extension studies in osteoporosis for example. I think though that the control can be maintained for a year if the mild persistent patients for example, are selected for that.

I think with regard to the study features, I mentioned about the follow-up and duration. I think the ideal study group is probably going to have a pre-pubertal cohort that is then followed through puberty. And one may

also want to have a stratum of children who are pubertal at the time of the initial study.

I think stadiometry is clearly going to be the appropriate way to measure height for this kind of long-term study, although knemometry may be of interest in short-term studies.

I think that requiring this for the conversion products, while it would be ideal, it probably is realistic to say that we would look for that in Phase 4 from the converted products. And from existing products which will remain on the market for a long period of time, I think Phase 4 studies will be highly desirable. It's rather difficult to force this, but I think the agency is in a position to create an advantage in labeling for companies that have done this work. And if someone hasn't carried out the growth study, that should eventually work to their detriment.

Dr. Li has an additional comment.

DR. LI: I believe I heard from one of the comments preceding mine, close to an implication that if a preapproval study did show an effect, that that product might not be approved on that basis. I guess I would say that would not, in my view, necessarily be the case. If a preapproval study showed an effect, depending upon the specifics of the study, that it still may be a product that

ultimately would be approved.

DR. SZEFLER: One proviso, and I think to add on to the statement that was made before is that if a reliable bioassay or an assay like knemometry was found to be useful in terms of defining -- I'm not sure if the term is right -- as negative predictive value, that it could be used in place of a long-term study.

In other words, if it was defined in knemometry, and a short-term study was useful in terms of predicting the absence of affect on growth, then that could be a replacement for long-term studies.

DR. BONE: It sounds like that would have to be a component of the first wave of this studies, if we wanted to see any kind of long-term validation. So it wouldn't be a substitute in the immediate future.

DR. FINK: My comment is, as a pediatrician I guess I would be remiss if I didn't remind people that the most important time of growth is potentially fetal. Although a controlled study is not possible, there really is a dearth of data on what is the outcome of pregnancies where is using inhaled steroids. With the obvious bioavailability and systemic effects, some kind of observation data collection on pregnancy outcome seems to be appropriate in this regards.

DR. BONE: I would just add on my own to the

comments about study design, that I think this is the opportunity for the sort of thing that Dr. Hirsch referred to earlier with respect to body composition studies, looking at measures of glucose metabolism and so on. If we have this kind of opportunity to acquire high quality metabolic data systematically, it would be a terrible waste not to do that.

I guess we may want to make some very brief remarks about question -- I'm sorry. Pardon me. We had some comments from the others.

MS. REEDY: Dr. New would like to see required measurements of height four times a year during treatment -- this is number four -- for all forms of corticosteroid treatment, and for the approved products also. And for number four, Dr. Burman would like to see them as a Phase 4 study.

For number five, Dr. New recommends that height be measured for three years after corticosteroid treatment is discontinued, and evaluation of catch up growth and final height done. Dr. Burman feels that the growth studies should include bone mineral density, serum levels, adrenal function, growth hormone, and IGF1 measurements.

DR. BONE: Thank you.

The sixth item asks us to comment on approaches to better assessment of the potential long-term impact of

inhaled and intranasal corticosteroid products on growth in children, particularly the potential impact on final adult height. I think a lot of this was covered in the preceding questions, but there may be additional comments as we go around. I'm going to invite members to do this. Just for the sake of variety, perhaps well start with Dr. Baraniuk.

DR. BARANIUK: There have been lots of studies. There must be lots of patients out there. But I think if you retrospectively went back, there will be a lot of confounding factors that may not make a retrospective analysis viable. You just have to pay to have them come back I think.

DR. FINK: No specific comments.

DR. DAVIDSON: Yes, not to forget that the affected population needs to be represented in every study. I agree 100 percent with doing some metabolic studies maybe in a smaller sample size. But all of us will benefit from knowing what happens to bone densities in the short-term and long-term, and obviously glucose metabolism and lipid metabolism.

DR. AHRENS: I would like to see the prescription databases be queried if this is possible, and I believe it is, to find out just how many children are really receiving considerably higher than recommended doses of inhaled corticosteroids, especially of the again, newer

preparations, where this is much more possible than it was in the past.

If, as I believe is likely to be the case, that that number is substantial, then I would really favor either trying to access that group of patients. There is a natural experiment essentially going on which may really contribute to our understanding here in a very important part of the dose response relationship, at least as far as toxicity is concerned.

Now to access that group either with some sort of a retrospective approach, or perhaps an epidemiologic approach. I don't have a more specific design in mind, although I would imagine that with people who do this sort of thing, that there may well be ways to access that population. I think they are important.

DR. BONE: Thank you. Dr. Gross.

DR. GROSS: I don't have any further comments.

DR. OPPENHEIMER: Pass.

DR. LIU: I guess as a final shot here, I like the idea of an active comparator, both because of concerns about managing people clinically without inhaled corticosteroids. Certainly the groups have to be selected, but it would at least potentially eliminate a bias related to the fact that people were not well managed or symptomatic on just a control group receiving no therapy.

That active comparator certainly could be multiple ones, ranging from the historical theophylline, or long acting bronchodilator or newer agents, chromaline(?) or the glucocorticoid active drugs. But I like that as a potential way of at least providing a control group for a group that is actively treated with corticosteroids.

DR. HIRSCH: I just want to agree with that very strongly. I think there should be some sort of registry or whatever. I realize the statistical weakness of doing this, but there are some things that the numbers may be very high, and looking at individuals now who have been treated in different ways in childhood, their growth or health outcome, and how well this took care of their asthma.

It might in fact end up being a wonderful way of trying to persuade other people to take more steroids, because of the data. Included in that might be those who were already Phase 3 studied. So if it is possible to see them at a later age, this would be very helpful as well.

DR. CHINCHILLI: The only way to get an answer relatively quickly for adult height is to do some retrospective studies, and they will be fraught with biases. So I don't see other than just biting the bullet and doing some long-term prospective studies, I don't see any other option.

MS. CONNER: I have nothing to add.

DR. CRIM: Ditto.

DR. LI: I'm in the position of being one of the few people in the room who have actually attempted to conduct a final height study, which was retrospective, and was thereby necessarily limited. So I really think it's a win-win situation to suggest a long-term prospective type trial or study with concurrent controls, because that would afford the opportunity to collect the type of information that we were just not able to get with our retrospective study.

It is a win-win situation, because no matter what the results would be, if the study was well conducted, it would be useful for our patients. If there was a negligible or no effect on adult height, that would be reassuring and useful for patients and clinicians. If there was an effect, then we would know what the magnitude was, and that would kind of affect the weighing of risks and benefits of treatment.

DR. KELLY: Other than a long-term controlled trial, which also is an artificial situation, because patients don't take the drug in that way. When they get better, they will reduce the dose on their own. So I don't have any suggestions of any magical way to do this.

DR. CROSS: Ditto.

DR. SZEFLER: I think in the long-term trials that

are being set up as the Phase 4 requirement, those studies should have adequate numbers to be able to incorporate a plan to do a follow-up study at a future time.

DR. BONE: It seems to me that the ideal study was the long-term prospective trial, however, I'm concerned about the ability to maintain the control over a period of time, because I suspect there will be eventually a tendency for the people in the non-steroid group to want to take steroids.

So I think that it may be that the extension of the one year controlled trial looking at growth markers, the growth curves may be one way of looking at that over a period of several years. And just recording what was done in effect, and looking at the steroid burden over time.

It is a little discouraging to hear that the retrospective study wasn't entirely successful. Was that a Hennepin County study?

DR. LI: This was a Mayo Clinic retrospective study.

DR. BONE: It may be that in a large HMO that has been relatively stable over a period of time, or something like that, it would be possible where there is a consolidated medical record, to get some information about this. I don't know if the Mayo Clinic has patients coming in and out all the time?

DR. LI: No. One of the reasons that we embarked on the study is because we have a fairly stable population, and we have an integrated medical record. I think there are several pitfalls here, but one of the weaknesses is what's in the medical record. Not that we don't have it, or that it's not integrated, but in terms of what the notes are, and what the patients were actually taking over time.

DR. BONE: So that would be an argument for using clinical trials alumni, for example?

DR. LI: The idea with a retrospective study is you need some estimate and some measure of what is the type and the quantity and the dose and the frequency of inhaled corticosteroid use over a prolonged period of time. To get that information retrospectively is very difficult.

DR. BONE: Thank you. Dr. Fink.

DR. FINK: Just to comment that we already are six years into what could become the ideal prospective controlled trial, which is the childhood asthma management program that NIH, NHLBI is studying. That it may need to be communicated to them that rather than terminating that study in the year 1999, as currently planned, that it should be carried on for another five years to record the post-pubertal height of this big cohort of children, which was already in three arms, one of which is an inhaled steroid arm, two of which are non-inhaled steroids.

DR. KELLY: If you can communicate that to the NHLBI, it would be much appreciated.

DR. BONE: Thank you. Any additional comments on any of the discussion issues that we have just discussed? If not, I will issue of the summary and closing remarks, and then we can leave.

**Agenda Item: Summary and Closing Remarks**

DR. BONE: Well, we've had a very interesting two days here. I would like to endorse the comments of other members about how much we have appreciated all the hard work that has gone into preparation of these presentations and so on.

I would also like in addition, to take note of the advisors and consultants staff, that would be Mr. Madoo and Ms. Reedy, who have made the arrangements. I'm sure all of us who have been involved in the meeting are aware of their important contribution as well, but I'm not sure the public always is quite as aware of how crucial the executive secretaries are to getting the agenda together, getting the speakers and guests and members and so on all together, and getting things framed in the right way. I think we owe them a lot of appreciation as well.

We have had, as I mentioned earlier, an interesting transition. We had a highly effective, relatively toxic group of compounds, and we have managed to

contrive a second generation, if we can call it that, or later generation of chemical entities combined with an alternative form of administration that has minimized the toxicity, and allowed us to use these compounds much more freely.

We are now realizing that we have perhaps not totally eliminated some of the adverse effects, although we have certainly minimized them to the extent that they probably don't constitute a major impediment to treatment.

I think that we are going to be spending the next several years looking at issues like subtle effects on growth like possible subtle effects on skeletal mass and other subtle effects which are, as I said, probably not reasons to avoid using these drugs, but they may be elements that will drive us to more skillful use of these products and products to come, and will help us how to understand how to optimize their use for the care of our patients, particularly the pediatric for whom the management of asthma is going to be a lifelong problem.

The consensus of the discussants seems to be very much in favor of making sure that the product labeling discloses what has been found, but in a very measured way. I think we have had a very good discussion with the FDA about some of the sensitivities about the way that that is discussed.

There is a general position amongst the members of the group here in favor of having more thorough investigation of the effects on growth, and I think other metabolic effects as we go forward. I think then that this will allow us to have a basis as we go along for a better understanding of what we're doing, an enhanced level of skill in managing our patients for the very long-term, and a drive to innovation and improvement, taking note of the enormous therapeutic advance that this group of compounds represents.

With that in mind, I think we can close this joint meeting of the pulmonary and endocrine and metabolic drugs committees. I think that I can speak for my colleagues in the endocrinology and metabolism committee in saying how much we have enjoyed the interaction and discussion with our colleagues on the pulmonary committee. And we perhaps will have another opportunity to do that on another occasion.

Thank you.

[Whereupon, the meeting was adjourned at 3:35 p.m.]