following approval of pediatric exclusivity, AERS contains 157 cases including 38 pediatric cases. The pediatric cases did result in some serious outcomes including one death.

For the pediatric cases reported to us in the year after approval of exclusivity, we received more reports for boys than for girls, and most reports were received for children 2 to 5 years of age, and most reports were received for the inhalation product.

This slide shows the most commonly reported events in the pediatric cases in the year after the granting of exclusivity. Convulsions were reported most. Additionally, a number of events were reported that are indicative of systemic absorption of budesonide. Seizures are not an expected reaction with the use of budesonide. And when we looked at the cases we did not see a clear relationship between budesonide use and the subsequent development of seizures. One case was confounded by concomitant use of theophylline, and that case did not include a

theophylline level.

Two cases were not confirmed by health care professionals and the seizures were not well described. One patient was receiving CNS radiotherapy, and that same patient was receiving another drug concomitantly that is labeled for inducing seizures.

We have 17 cases showing possible systemic steroid effects including growth retardation, decreased blood cortisol, adrenal suppression and Cushing's syndrome.

As I said, we did receive a report of a death in the year following approval of exclusivity, and this case was reported from within the United States. It was a 3-year-old girl who had received Pulmicort Respules for 3 months. She stopped breathing, was transported to an emergency room, and she died in the emergency room. An autopsy was performed but not establish a cause of death.

We conclude from our review of the events reported to AERS for budesonide in the year

following approval of pediatric exclusivity that first, most events, including systemic steroid effects, are included in product labeling; and second, the convulsions are not labeled, but we didn't see a clear relationship to budesonide.

Now I'll go on to fluticasone. First, this is use data for fluticasone cream and ointment. Children account for about one third of the prescriptions for these products.

This is for fluticasone nasal spray. Prescriptions for nasal spray have remained fairly consistent over the past two years, with about 15 million prescriptions in 2003, and pediatric patients account for less than 10 percent of all prescriptions for fluticasone nasal spray.

This slide shows information for inhaled fluticasone. For inhaled fluticasone there are about 7 million prescriptions in 2003, and there;s been a downward trend over the past couple years. pediatric patients account for about one quarter of the prescriptions for the fluticasone oral inhalation products.

Now, to Advair. We're looking at this one separately. Advair's a combination of fluticasone and a long-acting beta-2 agonist, salmeterol. use of Advair has increased considerably over the past few years. Advair accounted for 17 percent of orally-inhaled steroid prescriptions in 2001. This increased to 54 percent in 2003, with pediatric patients accounting for 13 percent of total prescriptions.

Looking at the adverse events reported for all fluticasone containing products, AERS contains about 4,600 adverse event reports for all ages covering the lifetime of the fluticasone products. For the one-year period following approval of pediatric exclusivity, AERS contains about 2,100 cases, including 128 pediatric cases. The pediatric cases did result in some serious outcomes, including 5 deaths.

For the pediatric cases in AERS in the year after approval of pediatric exclusivity, we received most reports for children 6 to 11 years of age, and most reports were received for the

combination fluticasone and salmeterol product, Advair. You can see in the right-hand column, 82 of the cases that we received, 82 of the 128, were for reported events for that combination product.

This slide shows the most commonly reported events in the pediatric cases in the year after the granting of pediatric exclusivity. We looked at these cases and we found two issues. emerging from this.

The first issue we found was systemic steroid effects. There were 12 cases showing systemic steroid effects, and I'll address this issue in a couple minutes. The second issue in the cases was worsening asthma symptoms with the use of Advair. We had 22 such cases reported in the year following the granting of exclusivity, including four cases in which the patient died.

So first we will address the cases reporting worsening asthma symptoms with the use of Advair. And as I said, we received 22 of these cases in that one-year period. In 10 cases serious outcomes were reported, including four deaths. The

patients were 5 to 14 years of age. Race was not reported in most cases. The time to onset of symptoms ranged widely from the very first day the Advair was used to after two years of use. And the AERS cases do not show what the relative contributions of underlying disease and the use of Advair may be in the adverse event.

I'll present the four cases on which the patients died. The first case is a case originating from the United States. A 14-year-old black male was prescribed Advair after an episode of respiratory arrest. He had received Advair Diskus for 2 years when he experienced an acute asthma attack. He was transported to an emergency room. When he arrived he was in full cardiac arrest and he died. No autopsy was performed.

The second case also originated from the United States. This is a 13-year-old white male who had received Advair for about 6 months. He experienced an asthma attack and he died. An autopsy showed chronic bronchitis, hypertrophy of bronchial muscle, infiltrate of eosinophils, mucus

plugging of smaller airways, areas of pneumonia and air trapping.

The next case originated from outside the United States. A 14-year-old asthmatic girl was treated with salmeterol for an acute asthma attack. When she did not respond quickly to the treatment with salmeterol, treatment with a combined salmeterol fluticasone product was started. About 2 hours after her first dose of the combination product, the patient's condition worsened and she died.

The final case is a case, once again from the United States. A 13-year-old boy experienced cardiac arrest and died after receiving Advair for an unknown period of time. The report stated that while talking to a friend on the phone, the boy just stopped talking. An autopsy showed only lung changes consistent with asthma.

You saw this slide before. I'm showing you this slide again to remind you that most of the cases we received in the year after the granting of exclusivity were received for the combination of

fluticasone and salmeterol product, Advair. And once again, it was 82 of 128 cases. And while the use of Advair has been increasing in children, we don't think that the increased use explains the increased reporting in pediatric patients for the product.

This slide shows the pattern of reporting of pediatric adverse events with Advair, and the timing of important regulatory action and an important labeling change for Advair. Going across the bottom of the slide, each column is a quarter. So we start with a quarter in 2000 and go up to the first quarter of 2004. In January 2003 the FDA released a talk paper discussing the cessation of a salmeterol safety study, and the interim analysis of that study suggested that salmeterol may result in worse asthma outcomes. And in August 2003, Advair received a boxed warning about the possibility of worse asthma outcomes with salmeterol. And as you can see, the spike in reporting for Advair occurred around the time that Advair received that boxed warning.

This slide just shows the boxed warning in the Advair labeling, and again, the boxed warning was incorporated into the labeling because of the interim results of the safety study, not because of the AERS cases. So that's the first issue with the fluticasone containing products.

Now I'll address the other issue that we found in the pediatric cases, and that second issue is the systemic steroid effects with the use of fluticasone containing products. We had 12 such cases, including a case in which the patient died.

Now, to look at these cases a little more closely, most of the cases occurred with inhaled products. In one-half of the cases the patient was receiving more than one source of steroids concomitantly, and we had only one case that reported a systemic effect with the use of a product within labeled dose and without an additional source of steroids on board.

As I said before, we did have a case with an outcome of death. This case originated from outside the United States and we don't have

clinical details about the case. An 8-year-old girl, who used an unknown amount of a fluticasone containing product for an unknown dose, unknown period of time, developed adrenal crisis and died.

So what can we conclude from the cases that we've received for fluticasone containing products in the year after the granting of exclusivity? Most of the events reported are included in the labeling, including systemic steroid effects and including worsening asthma with the use of salmeterol containing products. In the AERS cases of asthma exacerbation with Advair, the relative contribution of underlying disease and Advair to the events is not known.

That concludes my presentation.

You've already met Dr. Chowdhury, but I'll introduce him again. Dr. Badrul Chowdhury is the Director of the Division of Pulmonary and Allergy Drug Products. He's been with the Agency since 1997. He's an internist, an allergist and an immunologist, and he'll be summarizing the pediatric programs for fluticasone and budesonide

that were presented previously.

x DR. CHOWDHURY: Thank you for the introduction, and I will very briefly summarize the programs that were done for fluticasone and budesonide containing drug products for allergic rhinitis and asthma indications, which are the nasal products and oral inhaled products. I'll go through them so that you can really put the presentations that you heard before, three of them, into context of the whole drug development programs and where we stand currently with the labeling status of these drugs, particularly for children.

Asthma and allergic rhinitis, as you have heard before, are common diseases, and in fact they're pretty common in children and impose significant burden on the health care system and also on individuals who have these diseases. And the prevalence of atopic diseases in general and asthma has been studied in depth. The prevalence of this disease is increasing, but recently, as yo have heard before, the trends in death and hospitalization are declining. And the various

factors which are contributing to this good outcome of a serious disease, including availability and use of various controller medications.

As you've heard before, corticosteroids currently are the primary controller therapy for all grades of persistent asthma, and they're being used, and their use is also being covered under various guidelines. For allergic rhinitis, again, corticosteroid is considered to be the most effective therapy.

These drugs, of course as we know now, are not completely free of adverse events. The topical drugs are applied on the surface or the body, and historically at one time they were considered to be really surface acting and not systemically active, but now we know that they are systemically active, and has adverse events, which came back to the systemic exposures, particularly those allergic to suppression of the HPA axis and also other metabolic effects. But the benefits of these are appropriately labeled and overall the risk/benefit supports the use of these drugs.

Now, I think we may have skipped a slide. Yes. I will, on the slide, very briefly go through the pediatric development of these drugs so that you can put the studies that you have heard in the context. Usually for asthma and allergic rhinitis these drugs are developed for adults first, and then the efficacy and safety goes down to the pediatric patients usually be generating data and by extrapolation, because we think the diseases are same in adults and children and the effect of the drug on the diseases are also the same.

Now, in going down in the age, one important consideration is to identify appropriate dose. Because this is surface active, therefore PK is not a good marker for dose selection. They are usually done through clinical studies, and for these diseases, asthma and allergic rhinitis, it is often quite difficult to design appropriate studies with efficacy endpoint, but again, they are being done to pick the right dose, and the aim here being, both for adults and also for children, to have a reasonably low effective and safe dose, and

then particularly for the children, show established safety of that dose.

So safety is a key in going down in the ages for these drugs, and safety assessment is done in a variety of ways and you have heard some of them. To summarize them here in the slide, we look at clinical trials and monitor them for adverse event, laboratory parameters, ECG findings, et cetera, and then look at HPA axis in varieties of ways, such as ACTH simulation test or look at plasma cortisol and urinary cortisols.

And these, which means the clinical studies and safety assessment of HPA axis are done pre-approval. Then the growth study comes in, process of linear growth, which really is a surrogate of systemic effect, and they're usually long studies, quite difficult to perform and interpret, and they're usually done post-marketing as a Phase IV. And then of course, after marketing, we look at post-marketing adverse events.

So the next three slides I'll quickly go

through these three aspects which is HPA axis safety, linear growth and post-marketing adverse events, and put some comments of mine on these three areas.

You've heard the pediatric studies which was done for specificity presented, and typically for asthma for both of these drugs, they were efficacy studies. And the ages that we ask for for efficacy study at the time we solicited request was based on what we already knew and what we wanted to know. For example, for budesonide, it was one year and below because the drug was already at that time approved a study for one year and above. For fluticasone it was 4 years and below for the same reason again, the drug was studied and indicated for 4 years and above.

For allergic rhinitis the study was a 6-week study primarily designed to look for safety, which means all kind of safety, adverse events reporting, clinical monitoring for adverse events, and also HPA axis safety. I will not go through the results of these. You've already heard Dr.

Buckman present results. Some of them are reflected in the label and some of them are not, and we made the decisions on a case-by-case basis, looking at the study, what we could come out from the study in terms of what could go on the label, and appropriate labels have been updated.

For assessment of systemic effects, as I said before, it is done really by two ways. One is assessment of HPA axis directly by either a stimulation test or by measuring cortisols in the plasma or urine, and these are done pre-approval, and for these drugs, generally they're negative, but again, not all. If you look across the drug classes, the product labels are quite different and they reflect the studies in the product labels.

And the growth study which, as you've heard before, you're studying the systemic effect and systemic toxicity perhaps, was also done for these drugs, and their effects are quite numerically small, and they're again reflected in the product label.

On the post-marketing side for adverse

events for these drugs, the large number of adverse events which is not unexpected, is systemic corticosteroid effects or effects related to suppression of HPA axis. These are expected and these are labeled, and these were seen in the HPA axis studies and also in the post-marketing studies, and the current label reflects these potential systemic adverse events.

The worst thing for asthma with Advair is something which is noted in the product label quite prominently, and whether it is coming from salmeterol contributing or whether it is coming from the fact that Advair is typically used for patients who have more severe asthma is currently unknown. One can speculate it can be either/or. Perhaps the patients with asthma who are more severe are put on Advair; therefore, having worsening of asthma is not necessarily very unexpected. And we also know recently that continued use of beta agonist, specifically salmeterol, can worsen asthma. Again, these are known adverse events that we know of now and is

adequately reflected in the product label.

To summarize this whole pediatric studies that we have, the safety concerns would be use of oral inhaled and intranasal corticosteroids, specifically budesonide and fluticasone which we are discussing today, are well characterized, so we know what the adverse events of these drugs are, and they're adequately described in the product label. The new data that we have obtained under pediatric initiatives in post-marketing adverse events are reassuring because we are not really seeing anything new which is totally unexpected. What we are seeing is what we expected to see, and they're not extremely, extremely common, and these are again adequately reflected on the product label.

So this risk/benefit assessment, these drugs of course have some adverse events, have some risk, and we think it is adequately reflected on the product label, and overall benefit of the drug is justified and well balanced with a safety and risk assessment of these drugs.

Thank you very much, and with this, I'll stop.

DR. CHESNEY: Thank you very much to all the speakers. A very, very comprehensive review of these two products. Questions from the panel? Yes, Deborah first, and then Dr. Fant.

MS. DOKKEN: I want to ask this question just because I have to leave in a few minutes, but as a lay person I have been scrambling to keep up during this discussion. And one of the things that struck me despite the overall conclusion that the results were reassuring, was of course both the rise in the use of Advair and the worsening of asthma, those adverse events reports. But then the fact that the labeling was changed, and somewhat for clarification for myself as a newcomer to this Committee, but also as I guess a consumer concern, when the labeling was changed due to the adverse events, would that be a trigger for the MedGuides that we talked about yesterday? I guess I think in particular because of the prevalence of asthma and the growing numbers, but also I think those of us

who either have children who have asthma or know families, there are a number of families who are very active if their children have asthma, and are good advocates. So they would be cognizant and would take note of information if it was made available to them in a way. So that's my question about the MedGuides. Would those go hand in hand or subsequently with a change in labeling?

DR. MURPHY: A Medguide is not tied any particular change. It is something that is, the decision that is arrived at depending on the circumstance, so it is an independent decision.

Badrul, do you want to talk about any products that have MedGuides?

DR. CHOWDHURY: I don't want to comment to the MedGuide here. The issue is that you are right, that when a box warning or some significant labeling or a doctor letter goes out, which had happened for salmeterol-containing products. It is quite likely that will increase the adverse event reporting by physicians or by patients.

And about the use of Advair and use of

Advair in children, I mean it is somewhat high, and whether it is a good or a bad thing is very difficult to actually conclude and say. You've seen for pediatric requests we did not particularly request studies for Advair. We requested study for fluticasone and not for the combination product, because we do not think that use of Advair in very young children is something which should be really routine because there are very difficult to titrate the combination products, you actually have one product. And we thought in children it's not really very appropriate drug to use. But we also know that Advair is very, very commonly used, and is actually quite commonly used in children and there are three dose strengths available. And often physicians and patients may not go down on the dose when their asthma is controlled.

So I think we have put down enough information in the label, and also there have been some dear doctor letters and some of the public forums where we have spoken about it, and we discourage the use of particularly high dose Advair

if it's not necessary, and also not to use the combination products in very young children where you want to titrate the dose. So I think it is adequately recognized.

But again, going too much on the other side is also a risk because that can lead to decreased use of this quite effective controller therapy. If you look at the U.S., it's approximately thought about that about half of the patients who should be on controller therapy actually are on controller therapy. If you look at Europe, it's actually much more high. So even in the U.S. with continued education, continued awareness, the use of controller therapy is not where I think where experts want. So in that context, putting too much of a cautionary note may actually lead the pendulum swinging in the opposite directions. This is a tight balance, and I mean you can give European and they like to hear that, but we think that balance is quite well struck.

MS. DOKKEN: Just one comment. I mean I think we talked a lot in the last two days about

that issue of balance. And I guess my own belief is that there may be a way to inform and empower families so that what I talked about yesterday, so that they are aware of the risks and can truly be part of the risk/benefit analysis. And I ultimately don't think that that will lead to panic, and you know, restricting use of medications from patients who need them. But I think it could lead to more informed decision making.

But also, families are part of the monitoring system, and if they're not always aware of what they're looking for, then they can't be very effective monitors.

DR. CHOWDHURY: It is a very good suggestion, and thank you for the suggestion, and we really take the suggestions very seriously from the public meetings. Just to let you know that when there are public advocacy groups and also family groups, one of them which is pretty active in the family field is Mothers of Asthmatics. And they're actually very much aware of what has been happening with the FDA. And many of those

meetings, they actually come, and they make presentations. So they are actually very much in line, and the persons who head up that group, we have lot of discussions with them, and as far as we could tell, they're pretty satisfied where the balance is right now, but again, your suggestion is very well taken, and thank you for that.

DR. CHESNEY: Dr. Fant and then Dr. Nelson.

DR. FANT: Just a couple of questions to fill in a couple of gaps on background for me. One, is there any data that points to--the decline in mortality has been commented on a couple of times. Does the data suggest that the use of the corticosteroids contributes to that, or--I'll let you answer that and then I'll just ask my second question after that.

DR. STARKE: The data on mortality comes from coding, primary coding for hospital discharge or death, and that's collected annually by the CDC. So this data, it's difficult to extrapolate any or interpret what the meaning of that data is compared

to the use of controller therapy. I don't think you can make any specific comments on the relationship.

DR. FANT: We know from studies that the use of corticosteroids is the most effective controller or one of the most effective controllers, but we don't know for sure if it is the major contributor to the decline in mortality; is that correct?

DR. STARKE: That's correct.

DR. CHOWDHURY: Let me make a comment here. I mean usually--I mean you can't really make a conclusion regarding an intervention and outcome which is mortality because in aspect it's still a very heavy event, so it's actually very, very difficult to make that conclusion. It's probably a combination of all. But if we take surrogates, for example, which is exacerbations of asthma, or hospitalizations because of asthma, which usually are surrogates of even worst outcomes, I mean usually with controller therapy all of these actually goes down, and I would not really pick out

one class of drug over the other as more contributing than the other.

DR. FANT: No, no. I'm not trying to pick out any. I'm just trying to get a better sense to help me sort of understand the complexity of this in weighing--

DR. CHOWDHURY: It is, and I think one can reasonably say--Dr. Starke mentioned that the better outcome that you're seeing is a combination of a lot of things, including better views of controller therapy. But other factors are also playing a role.

DR. FANT: My second question relates to Advair specifically and the adverse events that seem to be associated with that. Is there any data or information that looks at similar events that occurred when similar--the same two classes of drugs were used separately but in combination? Is it something that seems to be unique to Advair? Is it something that clearly seems to be an interaction between a long-acting beta agonist and steroids? Does it seem to be a beta agonist issue

only? Do we have any information that may help kind of provide hints and what may be the underlying problem, if there is one?

DR. CHOWDHURY: That's a very tricky question and maybe even a very tricky study to do, and the bottom line is the data is not available. And there are no studies long term looking at outcomes. What we have long term is the use of a beta agonist alone versus placebo, and you have probably heard about that study. But there is nothing such available comparing an Advair arm concomitantly taken, so that data is not there.

DR. FANT: Or adverse events that have been reported and in the narrative certain things get blamed, like--

DR. CHOWDHURY: Adverse events are there with fluticasone, adverse events are there with Advair, and as you have seen, with Advair the adverse events are just more, and they're higher, they're more serious. So that signal is there. But, I mean, there is no controlled studies that can go into the explanation whether it is from

Advair or whether it's something else confounding which is contributing to that. Those controlled studies are not available.

I don't think it really is a very useful information either because it's quite well known that Advair is taken by patients who are more sick and, therefore, having an adverse outcome coming out of a sicker patient population is not a big surprise, and also with the new beta agonist study we know that routine use of beta agonist leads to worsening asthma and increased death. And that's already in the product labeling for Salmeterol and also for Advair. So the information already is in a way known that routine use of beta agonist--

DR. FANT: But if you have a sicker patient who's getting treated with a drug that puts him at increased risk, if there's an interaction effect, that certainly is a patient I would really want to--really would not want to elevate that risk anymore.

DR. CHOWDHURY: Again, there is--

DR. FANT: You know, I'm not--

DR. CHOWDHURY: No, these are important discussions to have because it's actually quite important for, I think, everybody in the country to be aware of this. It is an increased risk of adverse outcome, but the risk is actually very, very small. If you look at the black box language which was put up very briefly, the number of deaths is like in two digits out of a 16,000 patient population. This is a very small signal. And I don't think really for the small signal one should not use the drug. The drug is very effective. There's no question about that. And it's also pretty safe. And the signal, which is a serious signal, is not very common. So I don't think--it is really, again, a balance. The signal is really coming out of a very small number of patients. And the more studies going through to the NIH initiatives trying to identify who those patients may be who actually would have the risk, that has been partly identified with the short-acting beta agonist. The studies which have been published--there's a large study which shows the biomarkers

associated with that. And in the future, there will be studies coming out trying to identify patients who are at risk.

DR. FANT: Thank you.

DR. CHESNEY: Dr. Nelson?

DR. NELSON: I'd just like to highlight two issues that are raised by the Flovent exclusivity studies, which I realize may be impossible to talk about today but might merit further conversation in the future.

One is the choice of control group. Those particular trials included children who had been receiving symptomatic treatment two times a week which meets NHLBI criteria for the provision of anti-inflammatory; but, nevertheless, a third of them were randomized to placebo. So the question would be: What is the current thinking about appropriate control groups when you have actually treatment guidelines that, in fact, a third of the population did not receive?

The second point is this was the study that also then had misallocation of study drug, and

so you end up with the irony--and they also were then granted exclusivity, and I don't know if that's because the written request was not ironclad enough to not give them exclusivity, or if, in fact, it was felt that they weren't to blame for the misallocation. But either way--and I realize each of these issues merit debate in their own right, but if you sequence them together in the most unfavorable light--which is not necessarily what I'm going to argue for, but some might--you have a study that withheld effective medication from a third of the kids in the study that didn't get done right, resulted in useless data, and they got the money anyway.

DR. CHOWDHURY: Let me take the questions very, very briefly, because you told it very correctly, these are really larger discussions.

The first issue is regarding placebo in these trials. There are two things to consider. They're actually placebo-controlled but not really without any drug treatment arm. These patients can take rescue medications as necessary and actually

can drop out of the studies if their asthma becomes uncontrolled.

The second thing is that in a short-term study taking off control therapy has not been shown to affect asthma in the longer term. There's CAM(?) studies out there going for quite some time, which does not show that if you do not use a control therapy for a short term, then the lung function of those children is reversibly damaged.

So there is some gain to obtained from some study, and withdrawing control therapy for a short time period with the proper rescue medications available is, again, a reasonable risk/benefit for the study.

And the second issue regarding, I would say, misallocation, whatever the reason being, of having drug in the placebo, is not something that I would--GSK did not want that to happen, neither did we, and the reason it happened is not really very clear. And you are totally right. Because of this, drug levels in the plasma, the studies were not useful. And whether exclusivity should have

been granted or not, I will defer to Dr. Murphy on that. It's a tricky issue.

DR. CHESNEY: Before Dianne comments, we may be looking at the same study. I can't tell. But Dr. Buckman's Slide 18, which was the--is that the same study?--where they found levels in the placebo and really couldn't come up with any conclusions at all, and your first thought is: Why was exclusivity granted when this study really on paper doesn't look very good?

Dianne?

DR. MURPHY: Between ShaAvhree and I, our memories are not clear enough to give you a factual answer. So we think it's because we weren't--you know, but one of the problems with exclusivity is that there's a short-term--we have to determine the exclusivity before the complete analysis is performed. And we will get back to you. I think this is one of the action items we need to get back to this committee at the next meeting about why was exclusivity granted in this situation. But our hazy combined recall--maybe Peter can help us. We

didn't know at this point.

DR. CHOWDHURY: Let me also chime in on this. The studies for pediatric exclusivity comes into a supplement to the NDA, and we have a time clock for reviewing the studies because it involves a lot of analysis, often going into the data and all, and the time frame is six months for pediatric studies. And exclusivity is granted or denied very early on.

DR. MURPHY: It's within 90 days, so--

DR. CHOWDHURY: So when the application comes in, we file the application, and then the exclusivity is granted based on whether the study was done fulfilling the criteria set forth in the written request. And the analysis goes on. So, I mean, one is happening before the other.

DR. MURPHY: What is determined, just again, for what we can tell you, is: Did they do the studies that we asked them to do? And so when the division comes to the Exclusivity Board, they bring the written request and basically a check item. They go through every item. Did they do 2,

randomize? You know, now, you could say it wasn't well controlled, but the division answers as best it can without having completed the analysis. And, therefore, the finding of some of these things, particularly some of the compliance issues and the scientific investigation issues are not available frequently until literally towards the end of the analysis.

DR. NELSON: Just a quick comment. I can appreciate the systems issues in my approach working in an ICU, this is all CQI systems issues. And if, in fact, it's the simple existence of a 3-month difference between one decision versus another and the data gets analyzed, then maybe we need to look at that as an issue. But I think certainly the intent of the exclusivity is to have interpretable data. And maybe there needs to be a fix. Whether that's a regulatory fix or a legislative fix--I realize you can't advocate for legislative fixes, but it just seems to me a gap that ought to be examined, and this would, in my mind, be a sentinel event. If I had something

happen in my ICU, we would look at it as a sentinel event and say, How do we close that gap?

DR. MURPHY: Actually, it used to be worse because we didn't have all of them on six months. And so the system was even more likely to have a problem, is what I was trying to say. We were hoping by having the six months versus the 90 days that we would have less events, but clearly we still have them.

DR. STARKE: Let me see--I'll try to answer the question as best as I can. I was the medical officer who reviewed the studies and presented to the Pediatric Exclusivity Board at the time. If I'm not mistaken--I'd have to go back and look, but I believe it was a 10-month clock for this that had preceded that. And the Pediatric Exclusivity Board met early in the analysis process. It was only later in the process that we found these events had occurred in the biopharmaceutical portion of the study.

DR. MURPHY: That's what I was referring to. Until the recent legislation, there were even

longer dates. Thanks for clarifying that.

DR. O'FALLON: Well, who is responsible for doing those biochemical, whatever, analyses? Is that supposed to be the investigator who put-- the company that gives it to you and you're supposed to look at it? Or is the FDA supposed to run it?

DR. CHOWDHURY: You're asking who is responsible for analysis of the results? It is the company or the company's contractor who is doing the study is supposed to do the analysis. And I'm pretty sure when the submission of the (?) was made, the company knew that there was some problem with placebo arms having active drug.

DR. O'FALLON: And they didn't share that information, they didn't give that to you?

DR. CHOWDHURY: It was there in the whole submission. That's the reason we know about it, and we did not approve the application. But if you go back to what was discussed earlier, the exclusivity determination is made very early on in the chronology of events. And in that time, that

formulation, that placebo had drug. I mean, it was not identified, and even if it was identified, you actually had to look at the cause of what happened and can still the study be salvaged anyway? And that takes time. And because of that, we have this six months versus ten months of clock to go through all of these. And by the time exclusivity is granted, it's basically based on was the study done based on what was asked. Analysis just cannot happen at that time because it requires time.

It is a system that, Dr. Nelson, as you pointed out, really as a--noting as a case.

DR. CHESNEY: The newest legislation is for six months, not 90 days anymore?

DR. MURPHY: No, for the review. All pediatric applications now are considered six-month reviews.

DR. CHESNEY: Any other questions or comments from the committee?

[No response.]

DR. CHESNEY: Let's turn to the question then which we have been asked specifically to

address. Based on the presentations you have heard today regarding drugs containing fluticasone or budesonide, do you have any concerns about the use of these drug products as labeled? If you do have concerns, could you please raise your hand?

[A show of hands.]

DR. CHESNEY: I believe with the members of the committee who are still here we have a consensus that we do not have any concerns about the use of these drug products as labeled based on the very comprehensive reviews you've presented to us.

x All right. Well, let me then just try to summarize what we have--the discussions we participated in this morning. The first had to do with the review of the Subpart D Pediatric Ethics Subcommittee summary, which was presented by Dr. Nelson, with some very good discussion by the committee. The committee had two additional recommendations for the summary, the first of which was to assure that no stimulants were provided within some reasonable period of time before the

study was initiated, and the second was that a comment be added to the consent form regarding the available NIMH information that only four of 3,000 patients who have had MRIs had any significant findings. Do I have that correct? Thank you.

Second, the committee understands that there will be no further reporting required for the four drug products presented mid-morning: ofloxacin, alendronate, fludarabine, and desloratadine.

The third point, there was significant discussion regarding adverse event reporting for drugs either approved or not approved for use in children, and I think not new to this particular committee hearing is the perception that we need better databases; particularly we need better databases that involve children. We also need better denominator data that involve children, and I don't think there was a lot of discussion reviewing the potential need for active surveillance for better documentation of adverse events.

And just to emphasize again the importance of having information from controlled clinical trials in order to better assess adverse events.

Finally, on the last issue with regard to budesonide and fluticasone, we were presented with very comprehensive data regarding the linear growth assessments, the HPA axis suppression, and regarding postmarketing adverse event reporting. And the committee--first of all, there was a recommendation that a MedGuide be provided for pediatric family caregivers with respect to the new labeling for Salmeterol and Advair label changes. And, secondly, a concern which was discussed in some detail today and yesterday, which I think overall we could say has to do with the quality of the studies requested for exclusivity, and I think we understand the process, but as Dr. Nelson pointed out, what we've come up against may be totally a process issue. And we understand better the reasons for why some of--why exclusivity is granted when the clinical trials may not necessarily seem to us to have been designed as

well as they might have and the results turn out not to be very helpful.

Any other summary comments that I have neglected with respect to the committee?

[No response.]

DR. CHESNEY: And, finally, in response to the specific question we were asked to address, we do not have concerns about the use of these drug products with respect to budesonide and fluticasone as currently labeled.

And, finally, just to thank particularly the FDA speakers who spoke this morning. I just have this fantasy that you rehearse these things for days and days beforehand and that somebody oversees them and tells you exactly when were going to have mental questions because you address them. At least as soon as they come in my mind, you address the issues. So we're just extremely grateful for how much you respect our time and for how comprehensively and well you review the topic. That is just very much appreciated.

Thank you also to Jan Johannessen, who has

done an incredible job of keeping everybody on track for the past week. This has certainly been a long trek, more so for you than for us for sure.

To thank all the panel members who are still here who raised always very stimulating and thoughtful questions from my perspective.

To thank Skip for chairing the first-ever Pediatric Ethics Subcommittee.

To thank Dianne, as always, for overseeing this whole operation; Solomon for his always comprehensive presentations.

And, finally, I think this is Dr. Ebert's last meeting and Dr. Maldonado's last meeting. Am I correct? And anybody else?

[No response.]

DR. CHESNEY: So I think they both got recognized at the June meeting of the old committee, but in any case, thank you from my perspective for coming back and joining us for this meeting and for being a part of this committee.

I'll let Dr. Murphy have a follow-up--oh, one more thing. Before we finish officially, I

wondered if the committee could stay for just one minute. We had suggested potentially at the June meeting writing up some of the--well, I'll address it right now--some of the issues that have come up over the years, and I am here to tell you that Dr. Laurel Leslie, who I understand in the pediatric community is known as a writing machine, has already written up a potential manuscript based on her review of what happened yesterday. And she's very interested in finalizing this and submitting it to a journal, and I would appreciate your thoughts, which we could do after we officially finish the meeting, as to who should be included in that, what journal you might consider that that should go into. She's thinking about Pediatrics, but I wonder, as we discussed in June, if there might be a more comprehensive audience if she thought about something like JAMA. But if you wouldn't mind at the end in a few minutes just giving me your thoughts about that, I would be very appreciative.

So, Dr. Murphy, to finalize?

DR. MURPHY: How many ways can I say thank you? That really ought to be the question. I know you guys have been--ladies and gentlemen, excuse me, have been through a grueling four or five days. I think what was interesting to hear this discussion this afternoon, which very much paralleled the questions that came up yesterday with the antidepressants where you have, you know, an adverse event that's part of the disease, if you will, and how you dissect that out and when do you not say the labeling is sufficient, because the division is certainly--they also do the labeling.

So I think it's a real compliment to you and the division that this committee, which has been trained, mandated, and working on labeling, you guys have done a good job. So I want to really comment. I wasn't sure what they'd say. Again, we look very much forward to the ongoing activities, and particularly, Dr. Nelson, to the immense amount of work that you put into condensing that entire day's ethical discussion and synthesizing it so well for this group that they had as few questions

and recommendations that they did, and the ones that they had were very thoughtful and very good. I just look forward to working with you guys in the future.

Thank you.

DR. CHESNEY: And is my understanding correct that our next meeting is a week from today? Is that--

[Laughter.]

DR. MURPHY: I wanted to say one last thing. Jan had no idea he was getting two committees. He thought he was getting one. And we are trying to make it so that you all don't have to have residences here in Washington, though I understand some universities do that. But we'll try to be reasonable in our future requests on your time.

Thank you.

[Whereupon, at 1:10 p.m., the meeting was adjourned.]

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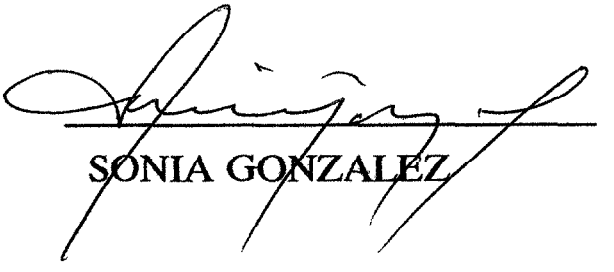

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