FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ADVISORY SUBCOMMITTEE

OF THE

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

8:06 a.m.

Wednesday, October 29, 2003

The Ballrooms
The Hilton Hotel
620 Perry Parkway
Gaithersburg, Maryland

ATTENDEES

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEMBERS: (Voting)

STEVEN E. EBERT, PHARM.D.
Department of Pharmacy
Meriter Hospital
202 South Park Street
Madison, Wisconsin 53715

MARY GLODE, M.D.
Professor of Pediatrics
The Children's Hospital of Denver
University of Colorado Health Sciences Center
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DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE MEMBERS: (Voting)

ROSELYN EPPS, M.D.
Chief, Division of Dermatology
Children's National Medical Center

SHARON RAIMER, M.D.
University of Texas Medical Branch

THOMAS TEN HAVE, PH.D.
Department of Biostatistics and
Clinical Epidemiology
University of Pennsylvania School of Medicine

SPECIAL GOVERNMENT EMPLOYEES-CONSULTANTS: (Voting)

ELIZABETH ANDREWS, M.D.
Vice President
RTI Health Solutions

PATRICIA CHESNEY, M.D., Meeting Chair
Professor of Pediatrics
University of Tennessee College of Medicine

DAVID DANFORD, M.D.
Associate Professor of Pediatrics
University of Nebraska Medical Center

ATTENDEES (Continued)

SPECIAL GOVERNMENT EMPLOYEES-CONSULTANTS: (Voting) (Continued)

ROBERT FINK, M.D.
Chairman, Department of Allergy and Pulmonary Medicine
Children's National Medical Center

NORMAN FOST, M.D., M.P.H.
University of Wisconsin Hospital

RICHARD GORMAN, M.D., FAAP
Pediatrician
Pediatric Partners
Ellicott City, Maryland

VICTOR SANTANA, M.D.
Associate Professor
Dependent of Hematology/Oncology
St. Jude's Children's Research Hospital

BRUCE SCHNEIDER, M.D.
Associate Professor for Clinical Research
Association of American Medical Colleges

FEDERAL EMPLOYEES: (Voting)

DON MATTISON, M.D.
National Institute of Child Health and Human Development, NIH

CONSTANTINE STRATAKIS, M.D.
National Institute of Child Health and Human Development, NIH

BENJAMIN WILFOND, M.D.
Bioethics Research Section
National Institutes of Health

ATTENDEES (Continued)

FOOD AND DRUG ADMINISTRATION STAFF:

SHAAVHREE BUCKMAN, M.D.
DENISE COOK, M.D.
SOLOMON IYASU, M.D.
CLAUDIA KARWOSKI, PHARM.D.
BEVERLY LINDSAY, M.D.
DIANNE MURPHY, M.D.
BINDI NIKHAR, M.D.
THOMAS PEREZ, R.PH., M.P.H., Executive Secretary
JEAN TEMECK, M.D.
ANNE TRONTELL, M.D.
JONATHAN WILKIN, M.D.

ALSO PRESENT:

JERRY ROTH

C O N T E N T S

CLINICAL RISK MANAGEMENT OF HPA AXIS SUPPRESSION
IN CHILDREN WITH ATOPIC DERMATITIS
BEING TREATED WITH TOPICAL CORTICOSTEROIDS

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C O N T E N T S (Continued)

SECTION 17, BEST PHARMACEUTICALS FOR CHILDREN ACT
ADVERSE EVENT REPORTING

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P R O C E E D I N G S

(8:06 a.m.)

DR. CHESNEY: I think we are ready to begin. My name is Joan Chesney, and good morning. I would like to welcome the committee members, the consultants, the guests, and the members of the FDA.

Just briefly, today and tomorrow we will be reviewing two classes of drugs which have been approved for use in the treatment of atopic eczema topically: the topical corticosteroids and the topical immunosuppressants which inhibit the enzyme calcineurin.

Even with topical use often, when used inappropriately, the corticosteroids can cause suppression of the hypothalamic-pituitary axis and the immunosuppressants have been associated with lymphoproliferative disorders when given orally to patients and with lymphoma and follicular cell thyroid adenomas in rodents when given orally, and mouse photocarcinogenicity studies have been associated with cutaneous malignancies.

We are being asked today and tomorrow to provide feedback to the FDA regarding two specific issues. Number one, what are the specific risks of each event associated with each drug? And secondly, how should risk management programs be conducted for, number one, the prevention of HPA suppression with corticosteroids and,

number two, with the topical immunosuppressants, how to design long-term registry programs to evaluate the potential cancer risk from exposure to these topical immunosuppressants?

As always, the FDA has provided us with excellent written materials to review and superb consultants to assist us with the discussion of these two questions.

If we could now turn to the introduction of the individual introductions of the people at the table, and I guess we'll start with Dianne.

DR. MURPHY: I'm Dianne Murphy and I'm the Office Director for the Office of Pediatric Therapeutics and also for the Office of Counter-terrorism and Pediatric Drug Development.

DR. WILKIN: I'm Jonathan Wilkin, Director of the Division of Dermatologic and Dental Drug Products.

DR. TRONTELL: I'm Anne Trontell, the Deputy Director of the Office of Drug Safety in the Center for Drugs.

DR. DANFORD: I'm David Danford, a pediatric cardiologist at the University of Nebraska Medical Center and Creighton University School of Medicine in Omaha and a member of the subcommittee.

DR. SANTANA: Good morning. I'm Victor

Santana. I'm a pediatric hematologist/oncologist at St. Jude's Children's Research Hospital in Memphis, Tennessee.

DR. GLODE: I'm Mimi Glode. I'm a member of the subcommittee. My background is pediatric infectious disease, and I work at Children's Hospital, University of Colorado School of Medicine in Denver.

DR. EPPS: I'm Dr. Roselyn Epps, the Chief of the Division of Dermatology at Children's National Medical Center, Washington, D.C.

DR. FOST: Norm Fost, Professor of Pediatrics, general pediatrician, and Director of the Bioethics Program at the University of Wisconsin.

DR. CHESNEY: I'm Joan Chesney. My field is infectious diseases, and I'm at the University of Tennessee in Memphis and St. Jude Children's Research Hospital.

MR. PEREZ: I am Tom Perez, Executive Secretary to this meeting.

DR. EBERT: I'm Steve Ebert. I'm a pharmacist in infectious diseases at Meriter Hospital and Professor of Pharmacy at the University of Wisconsin, Madison.

DR. GORMAN: I'm Rich Gorman. I'm engaged in the private practice of general pediatrics in Ellicott City, Maryland and a member of the subcommittee.

DR. SCHNEIDER: I'm Bruce Schneider. I'm Associate Vice President for Clinical Research at the

Association of American Medical Colleges in Washington, D.C. I'm a clinical endocrinologist, formerly a medical officer at FDA, and before that Professor of Medicine at Albert Einstein College of Medicine in New York.

DR. FINK: Bob Fink, pediatric pulmonologist at Children's Medical Center in Dayton, Ohio, and Professor of Pediatrics at Wright State University.

DR. TEN HAVE: Tom Ten Have, Professor of Biostatistics, University of Pennsylvania, and member of the Dermatology Advisory Committee.

DR. ANDREWS: I'm Elizabeth Andrews. I'm a pharmacoepidemiologist. I'm Vice President of RTI Health Solutions at Research Triangle Institute in North Carolina.

DR. RAIMER: I'm Sharon Raimer. I'm a pediatric dermatologist from the University of Texas in Galveston, Texas.

DR. WILFOND: I'm Ben Wilfond. I'm a pediatric pulmonologist with the Department of Clinical Bioethics at the NIH and also with the National Human Genome Research Institute.

DR. MATTISON: Don Mattison. I'm at NICHD. My clinical training is in obstetrics.

DR. CHESNEY: Thank you.

Next on the agenda is the meeting statement by Tom Perez, our Executive Secretary.

MR. PEREZ: Thank you.

The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at the meeting.

The subcommittee will discuss the risk assessment and possible risk management strategies for hypothalamic-pituitary-adrenal axis suppression in children who are treated for skin disorders with topical corticosteroids.

The topic of today's meeting is an issue of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

All special government employees have been screened for their financial interests as they may apply to the general topics at hand. Because there have been reported interests in pharmaceutical companies, the Food and Drug Administration has granted a general matters waiver to Dr. Richard Gorman, which permits him to participate in today's discussions.

A copy of the waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30 of the Parklawn Building.

Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each member and consultant. FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

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 product they may wish to comment upon.

Thank you.

DR. CHESNEY: Thank you.

Our first speakers, who will make opening comments, are Dr. Dianne Murphy and Dr. Wilkin. Dr. Murphy is the Director of the Office of Counter-terrorism and Pediatrics and the Director of the Office of Pediatric Therapeutics. Dr. Wilkin is the Director of the Division of Dermatologic and Dental Drug Products of the FDA. They

will be providing us with an introduction and overview.

DR. MURPHY: Good morning and welcome to the lousy weather we have in what should be a glorious autumn, but unfortunately you will mostly be locked up in this room with us. So I guess it doesn't matter as much.

But we are delighted to have the committee meet and help advise us. We have combined the elements of our Pediatric Advisory Subcommittee and members of the Dermatology Advisory Committee, and we look forward to your recommendations to us today.

The good news is that we are bringing these questions to you today because we have conducted trials in children. We had this information brought to us because we asked for these studies to be done. The information, some of it or much of it, is the result of trials that were conducted in response to a written request which the FDA sent to sponsors, and if sponsors respond to these written requests and conduct the trials as we have asked them to do, they are awarded additional marketing exclusivity. This has been a tremendous motivator for the conduct of trials in children, which have been very necessary because, as we all know, the products are being used anyway. So like all things, once you get information, being mostly scientists here, it just tends to generate more questions, and that is exactly what has happened here.

You will hear over the next two days about two different classes of products that are used in diseases that can be serious, not life-threatening, but for which children need options. So these products, over the next two days, are linked. They are linked because they're treating similar diseases. They are linked because they're topicals, and they're linked because they, again, bring forth questions from the studies that have been conducted. And they're particularly linked -- and I think this is going to be the challenge to you over the next two days -- because they are, in essence, options for parents and children and physicians. If one can't use one, one may need to use the other. Yet, what we are asking you to help us with is how do we appropriately advise the people who are both prescribing these products and the parents who are using them when we are not able to clearly delineate the level of risk. That is really what you're going to struggle with over the next two days.

You are going to hear what we think the risk is, but not only what additional studies do we need, but how are we going to develop a risk management program that will not, in essence, limit options and yet clearly inform so that the selection of the product will be that it will be used in the safest manner until we are better informed about what the true risk is. As I said, you will also be

asked questions about how to help us identify additional studies that might define this risk. So it's, I think, a very difficult task that you have in the next two days.

You're going to hear about risk management programs that we have and various approaches to risk management, but I think the real quandary to you is we're asking you to help us say when we don't have an absolute certainty on the risk, it is not completely defined, how do we best manage these risk management programs.

Thank you and we look forward to your discussion.

DR. CHESNEY: Dr. Wilkin?

DR. WILKIN: I'd be happy to make my very brief comments from here. I'd like to first echo Dr. Murphy's welcome.

I'd like to point out that we have pediatric dermatologic reviewers in our Division of Dermatologic and Dental Drug Products who will be looking forward to how the committee responds to the questions later in this day, but I would like to point out that they spend a lot of time looking over the transcripts for the entire meeting because what you say and discuss in each section is actually just as meaningful as specific fill-in-the-blank answers that come later in the day.

Dr. Murphy has given an overview of both days.

I would like to say just a couple of words about what we'll think about today.

Topical corticosteroids have really been the workhorse for many dermatoses. Most dermatoses are, in fact, inflammatory and many of the dermatoses in children are inflammatory and respond to topical corticosteroids. There has been a lot of success and advantage from this group of products over the last four decades.

We have recognized for many years the potential for adrenal suppression with some of the topical corticosteroids, especially when used over larger body surface areas and in smaller children with a somewhat larger surface-to-volume ratio, and there may be some additional factors also in the younger children.

It's a difficult area to really think about. There is some uncertainty. There aren't many post-marketing reports of adverse events. On the other hand, we have substantial evidence for adrenal suppression with the testing that Dr. Murphy has described that we have been able to obtain from the different products during product development. I think by first principles, the agency has gotten to the stage where we believe that there are certain things we need to say in labeling about risk management, and we'll share with you where we are on this. But we're looking for the committee and for the experts to give us

advice on are we where we need to be.

Again, adrenal suppression is silent. It's like hypertension or osteoporosis. I think the usually statement about osteoporosis is the first warning sign is there isn't any. It's a fracture. And that my be the case with adrenal suppression. It's either hidden from view until there is sepsis or some major traumatic event or it's really not detected.

Alvin Feinstein, who coined a lot of words, is the Yale clinical epidemiologist. One word that probably should have gotten picked up more and didn't was he used the word "lanthanic" for these kinds of conditions. It comes from Greek lanthanos, hidden from view, or lanthanine, to escape notice. You may recall from chemistry the lanthanide series of elements, the rare earth elements, the ones that were very difficult to detect. I think that's what we're talking about, a lanthanic kind of condition in Feinstein's terminology.

So, again, there is this kind of uncertainty and we would like to share this uncertainty, the first principles, how we've been thinking about it, how we've been crafting our statements for risk management, and get the sense of the committee, are we on target, are there other things we need to do.

Thank you.

DR. MURPHY: We depend on Jonathan to give us a new word.

(Laughter.)

DR. CHESNEY: I was thinking of laudanum. There must be a derivative there somewhere.

Our first formal presentation is by Dr. Nikhar, and Dr. Nikhar is a medical officer with the Division of Dermatologic and Dental Drug Products and a board certified pediatrician. She will present an overview of atopic dermatitis, its clinical course and therapeutic options.

DR. NIKHAR: Good morning. My talk this morning covers atopic dermatitis, its clinical course and therapeutic options.

Starting off with a brief introduction, atopic dermatitis is a chronic inflammatory disease of the skin, primarily seen in the pediatric age group. It is characterized by dry skin, pruritus, erythema, edema, scaling, excoriations, oozing, and lichenification. However, dry skin and pruritus are invariably present all stages of the disease. It is a multi-faceted disease showing increasing prevalence and rising costs, and together with asthma and allergic rhinitis, it forms part of the atopic triad.

Going on to epidemiology, currently about 10 to 20 percent of children in industrialized countries develop

atopic dermatitis, and for reasons that are unclear, this number seems to be increasing. Environmental factors such as urbanization and development may be contributory factors. It is commoner in higher socioeconomic groups and in children from smaller families. The overall clearance is about 50 to 60 percent and 80 percent of children with severe disease continue to have lifelong exacerbations.

Considering morbidity, it has an impact on the quality of life at all ages, and this is due to psychological problems from visible skin lesions due to stigmatization, the itch-scratch cycle that is aggravated during flare-ups, sleeplessness, lack of concentration at school or work, and distress over repeated treatments, time involved, and financial costs.

Atopic dermatitis can cause a considerable drain on financial resources of patients and health services. The costs increase with disease severity and they're highest in the first few years, after which there's a decrease indicating a learning effect in the treatment of patients. And while the FDA does not consider pharmacoeconomic issues in drug approvals, we do recognize that cost is an important factor in drug availability.

Going on to clinical manifestations, atopic dermatitis is a condition of early infancy and in 50 to 75 percent of cases, the age of onset is 6 months or younger.

A clearance rate of 60 percent is expected by age 16. However, relapses can occur in adulthood. A worse prognosis is indicated by severe childhood disease, early onset, concomitant or family history of asthma or allergic rhinitis, and a biparental history of atopy.

There are three main age-related stages. Dry skin and pruritus are associated with all stages. The skin barrier function is decreased and this may lead to increased absorption of topically applied treatments. However, this usually improves with adequate treatment.

The infantile phase is from 0 to 2 years of age. The onset can be around 3 months of age, and under 6 months, the face and scalp are commonly involved, while at an older age, the limb folds and hands may be involved. Red, scaly, crusted, weeping patches with excoriations may be seen on both cheeks and extensor surfaces of extremities, and typically the course is chronically relapsing and remitting.

These pictures, courtesy of the University of Erlangen, illustrates the features just described. The infant on the left has typical facial and upper chest involvement and probably has a body surface area involvement of about 20 to 25 percent, while the infant on the right has facial and extensor surface involvement as is again typical in this age group and probably has a body

surface area involvement of about 30 to 35 percent.

The childhood phase is from 2 to 12 years of age. Here papular areas in flexural regions are common, and in areas of chronic involvement, persistent rubbing and scratching lead to lichenified plaques and excoriations.

The adult phase is from puberty onwards, and here flexural lichenified eczema with facial involvement in periorbital regions may be seen. The upper trunk, shoulders, and scalp may be affected, with chronic remissions and exacerbations.

In this picture, this young child shows flexural involvement, which is again typical of this age group, and probably has a body surface area involvement of about 35 to 40 percent.

The first picture on the left shows lichenification which is seen in areas of chronic involvement. The picture on the right on the top shows periorbital involvement. The young man on the left in the picture on the bottom shows impetigo, which is a complication that may be seen with atopic dermatitis, while the picture on the right shows typical flexural involvement.

The following are some of the reported immunological features of atopic dermatitis. There is increased IgE production with specific IgE to multiple

antigens, increased basophil spontaneous histamine release, decreased CD8 suppressor/cytotoxic number and function, an increased expression of CD23 on mononuclear cells, chronic macrophage activation with increased secretion of granulocyte macrophage colony-stimulating factor, PGE2, and interleukin 10, an expansion of interleukin 4 and 5 secreting Th2-like cells and decreased numbers of interferon-gamma-secreting Th1-like cells.

The diagnosis of atopic dermatitis requires the presence of three or more major and three or more minor criteria, as defined by Hanifin and Rajka, which is a commonly used method. The major criteria include pruritus, lichenification, chronic or chronically relapsing course, and personal or family history of atopy. There are 23 minor criteria that have not been mentioned in this presentation.

As far as the management of atopic dermatitis, there is no single ideal treatment available. Each patient should have a flexible plan tailored for their need taking into account the severity of the illness, the resources available, the compliance of the patient, and so on.

Dietary history is important, but dietary manipulation remains controversial. Infants are most likely to benefit from this, in which case their nutritional status should be closely monitored.

Family education is important regarding atopic dermatitis and its clinical course, while measures to reduce exposure to allergens such as house dust mites, animals, and clothing should be discussed.

Going on to general treatment guidelines, moisturizers are the cornerstone of therapy in atopic dermatitis. Their frequent use, together with avoidance of drying bathing products, is important because atopic dermatitis is often accompanied by dry skin. Creams, ointments, or lotions can be used depending on individual needs.

Itch control is another important aspect. It can be a very distressing symptom leading to skin breakdown, infections, and lack of skin healing. Oral antihistamines, often of the sedating variety, are used to try and break the itch-scratch cycle.

Patients with extensive atopic dermatitis are often colonized with Staph. aureus. A course of oral antibiotics, plus or minus topical antibiotics, may be needed for lichenified, excoriated lesions not responding to treatment. Viral infections, for example, warts, eczema herpeticum, may be seen in these patients and should be appropriately managed.

The selection of treatment depends upon the disease severity, the age, the compliance, the efficacy and

safety data, and treatment costs.

The following -- that is, the first three -- are some of the prescription treatment options available. Topical corticosteroids are currently the mainstay of first-line therapy of atopic dermatitis and will be discussed further. Topical immunosuppressants. This group of calcineurin inhibitors has been introduced as second-line therapy for treatment of atopic dermatitis and will also be discussed. Systemic corticosteroids are useful for severe, acute cases of atopic dermatitis. However, chronic use can lead to serious side effects and they should be used with caution.

The following are then the off-label and other treatment options available.

Photochemotherapy has been tried mainly in adults.

Cyclosporin was the first in the class of immunosuppressants to be introduced for recalcitrant atopic dermatitis. However, it can lead to serious systemic side effects such as hypertension, renal toxicity, and a propensity for malignant tumors, and this has limited its use.

Azathioprine, thymopentin, and interferon-gamma therapy have all been tried.

Traditional Chinese medicine has also been

tried. However, liver function abnormalities and interstitial renal fibrosis has limited its use.

Gamma-linoleic acid in the form of evening primrose oil has also been tried.

Now going on to review topical corticosteroids. These were first introduced in the 1950s and are currently the mainstay of prescription therapy for atopic dermatitis. They are safe and effective when used as recommended. The weakest steroid that will keep the eczema under control should be used, and potent steroids should be used in short pulses, generally about 2 to 3 weeks.

The following are some of the factors to consider when prescribing topical corticosteroids. First, the type of preparation, that is, the base and the potency. The base can be an ointment, cream, emulsion, gel, or lotion, and this is important because that can affect the efficacy. The potency is classified from group I, which is the most potent, to group VII, which is the least potent.

Second, acute or chronic eczema.

Third, the age of the child. More potent steroids should be avoided in younger children.

Then the site to be treated, for example, the face and scalp need special attention in choosing potency of steroids.

Next, the extent of eczema. A higher body

surface area involvement would lead to increased absorption.

And lastly, the method of application. For example, steroids used under occlusion would lead to increased absorption.

As far as the mechanism of action of topical corticosteroids, there are three effects.

The first is the anti-inflammatory effect. Topical corticosteroids affect inflammatory cells, chemical mediators, and tissue responses which are all responsible for cutaneous inflammation.

Second, the antiproliferative effects. Topical corticosteroids may reduce mitotic activity in the epidermis leading to flattening of the basal cell layer and thinning of the stratum corneum and granulosum.

And thirdly, the atrophogenic effects. Topical corticosteroids can promote atrophy of the dermis through inhibition of fibroblast proliferation, migration, chemotaxis, and protein synthesis.

Now considering the systemic effects of topical corticosteroids. If a topical corticosteroid is absorbed percutaneously in significant quantities, it can cause systemic adverse effects similar to systemically administered corticosteroids. And this is discussed under adverse effects, and so the adverse effects can result from

the drug substance or the vehicle which can potentiate problems.

The following are some of the systemic adverse effects of topical corticosteroids. Suppression of hypothalamic-pituitary-adrenal axis, atrogenic Cushing's syndrome, growth retardation in infants and children. And these effects are usually associated with a large body surface area use of potent topical corticosteroids and will be discussed further in the next presentation by Dr. Temeck.

The following are some of the risk factors for systemic adverse effects. Young age, especially infants and children, liver and renal disease, the amount of steroid applied, the extent of skin disease treated, the frequency of application, the length of treatment, the potency of drug, and the use of occlusion. It is not established whether catch-up growth in children will occur when steroids are discontinued.

These are the local side effects of topical corticosteroids. Epidermal atrophy leading to wrinkled skin with prominent vasculature, pseudoscars, striae, or purpura; steroid dependence or rebound; glaucoma and cataracts; and an increased susceptibility to bacterial, fungal and viral infections.

Now going on to the next class of drugs,

topical immunosuppressants, these will be discussed in brief today and in further detail tomorrow. This is the newest pharmacological class for atopic dermatitis. These drugs were introduced in this decade. They have a direct immunosuppressive action in diseases with an immunological basis. There are two currently FDA-approved products: tacrolimus, FK506, the trade name being Protopic; and pimecrolimus, SDZ ASM 981, the trade name being Elidel.

Now reviewing their background. Protopic ointment was approved in December of 2000. There are two strengths available. The .03 percent ointment was approved for children 2 to 15 years of age, while the .1 percent ointment was approved for adults. The indication in both age groups is short and intermittent long-term therapy of patients with moderate to severe atopic dermatitis.

Systemic tacrolimus, or Prograf, was first introduced for prevention of allograft rejection and is now used in kidney, liver, and heart transplantation.

Elidel cream 1 percent was approved in December of 2001. It is indicated for patients 2 years of age and older for short and intermittent long-term therapy in the treatment of mild to moderate atopic dermatitis. Both drugs were not approved for use in children less than 2 years of age. And systemic absorption can take place in both adult and pediatric age groups from the topical

application of both drugs.

And further, pediatric patients enrolled in clinical studies of tacrolimus and pimecrolimus had an increased frequency of certain adverse events, for example, viral infections compared to vehicle, and currently the effects of topical immunosuppressants on the developing immune system are unknown.

Thus, the indication for use, as mentioned, is second-line therapy in the treatment of atopic dermatitis. Both Protopic and Elidel are indicated for patients in whom the use of alternative, conventional therapies are deemed inadvisable because of potential risks or in the treatment of patients who are not adequately responsive to or are intolerant of alternative, conventional therapies.

Lastly, I wish to acknowledge Diepgen, Yihune, et al., and the Dermatology Online Atlas for the pictures used in this presentation. And that brings me to the end.

DR. CHESNEY: Thank you very much.

I understand we'll have time for asking questions of the speakers after our next three speakers.

Next, Dr. Jean Temeck, who is a medical officer in the Division of Pediatric Drug Development and a board certified pediatrician and pediatric endocrinologist, will present an overview of the hypothalamic-pituitary-adrenal axis suppression secondary to the use of topical

corticosteroids.

DR. TEMECK: Good morning and welcome. Thank you all for coming today to help us sort out some very difficult issues.

The topic of my presentation is hypothalamic-pituitary-adrenal axis suppression following topical corticosteroid administration. I'm going to be covering the following topics in this presentation: the regulation of glucocorticoid secretion, the spectrum of hormonal effects of exogenous glucocorticoids on the HPA axis, the spectrum of clinical manifestations of adrenal insufficiency, the importance of diagnosing it, the tests which are used to diagnose it, and the risk factors for HPA axis suppression.

This slide depicts the regulation of glucocorticoid secretion. The hypothalamus secretes corticotropin-releasing hormone, or CRH, which stimulates the pituitary gland to synthesize and secrete ACTH. The ACTH, in turn, stimulates the adrenal gland to synthesize and secrete cortisol. As cortisol levels rise, they suppress the secretion of ACTH and CRH.

Exogenous glucocorticoids may have variable effects on the HPA axis. They may not suppress the HPA axis at all or they may suppress the secretion of ACTH and CRH, and this is termed secondary or central adrenal

insufficiency.

The degree of this suppression is variable. It may be mild or partial or it may be complete. If suppression is mild or if it is short-term, only the pituitary ACTH response to stress may be impaired. Both the basal ACTH and cortisol levels may be normal, as well as the adrenal cortisol response to stress. If suppression is severe or prolonged, then adrenal cortical atrophy may occur, and in this circumstance, the basal cortisol levels are low and the entire HPA axis is suppressed.

The clinical manifestations of adrenal insufficiency are variable. Some patients are asymptomatic but their HPA axis is suppressed by hormonal testing. This hormonal suppression is not just an abnormal laboratory finding. It is clinically relevant because when the HPA axis is suppressed, the patient is at risk for an acute adrenal crisis during periods of stress. Other patients with adrenal insufficiency may be symptomatic and the symptoms are generally nonspecific and subtle, such as weakness, lethargy, or decrease in appetite, and they may be insidious in onset. Other patients with adrenal insufficiency may present with an acute adrenal crisis, and this is generally triggered by stress, stress of a febrile illness, for example, trauma or surgery. It is characterized by fever, severe hypotension and shock which

may progress to coma and death unless the patient is treated emergently with supplemental glucocorticoids.

This slide reinforces the concept that all patients with HPA axis suppression, regardless of whether they have symptoms or not, are at risk for an acute adrenal crisis during periods of stress.

The true prevalence of glucocorticoid-induced adrenal insufficiency is unknown, and this may be because of several factors. One, there may be lack of clinical suspicion. There may be failure to recognize that topical corticosteroids are systemically absorbed, and therefore they can cause HPA axis suppression. In addition, because the signs and symptoms of adrenal insufficiency are so subtle and nonspecific, clinical suspicion is not aroused and therefore diagnostic testing is not performed or attribution is made to other causes.

For example, if a child with HPA axis suppression secondary to topical corticosteroid use for atopic dermatitis sustains major trauma from a car accident, the ensuing shock may be attributed solely to the car accident without recognizing the contribution of the adrenal insufficiency to the shock.

Another reason that the true prevalence is not known is if the period of suppression induced by the steroids is short so that the short period of suppression

goes undetected.

Finally, if a hormonal test with low sensitivity is used for diagnosis, one may get a false negative test result and therefore the adrenal insufficiency is not diagnosed.

Identifying patients with adrenal insufficiency even if it is mild, is important because these patients are at risk for life-threatening hypotension during periods of stress, and the condition is totally preventable if supplemental glucocorticoids are administered before or early in the course of the stress.

The following slides will describe the tests that are available to make the diagnosis. Basically there are two types of tests which are available: the basal hormonal tests and also the dynamic tests.

The dynamic tests fall into two groups: those which test the integrity of the adrenal gland only and those which test the integrity of the entire HPA axis.

There are two basal hormonal tests which are available for diagnosis: the plasma cortisol level and either single or multiple measurements may be obtained; and also the 24-hour urinary free cortisol test.

Plasma cortisol levels are only helpful if the level is either very low or very high. For example, a level cutoff usually used is less than 3 micrograms per

deciliter, which is drawn early in the morning around 8:00 a.m., that is soon after the peak cortisol surge occurs, or if the level is very high, greater than or equal to 20 micrograms per deciliter, and that can be obtained at any time of day. Unfortunately, measurements of plasma cortisol usually fall between these two extremes, and therefore they are not diagnostic.

Likewise, the 24-hour urinary free cortisol level is often non-diagnostic because normal individuals may have low cortisol excretion rates and also there may be difficulty in obtaining a complete 24-hour urine, especially in infants.

Due to the low sensitivity of these basal tests, most patients do require dynamic testing for diagnosis. And the advantage of the dynamic testing is that it provides information regarding the function, the reserve capacity, and hence the ability of the adrenal gland or of the entire HPA axis to respond to stress.

There are four dynamic tests which are available to make this diagnosis. Two of these tests, the high-dose and the low-dose cosyntropin stimulation tests, assess only the ability of the adrenal gland to respond to exogenous ACTH. The other two tests, the insulin tolerance test and the CRH test, assess the ability of the entire HPA axis to respond to stress.

This concept can be described graphically. With the cosyntropin tests, exogenous ACTH is administered and this stimulates the adrenal gland to release cortisol. So the cosyntropin test directly assesses the ability of the adrenal gland to release cortisol.

With the CRH test, exogenous CRH is administered and this directly stimulates the pituitary gland to release ACTH.

With the insulin tolerance test, one administers insulin and then subsequently you get a hypoglycemia. The hypoglycemia is a potent stress stimulus for the release of both CRH and ACTH. So then you can see that the ITT and the CRH tests directly assess the ability of the pituitary gland or also of the hypothalamus to release ACTH and CRH, respectively.

Remember that secondary adrenal insufficiency, secondary to exogenous glucocorticoid administration, means that the pituitary ACTH reserve capacity is impaired. As I just pointed out, the ITT and the CRH tests directly assess pituitary ACTH reserve, and therefore these tests are very sensitive for diagnosing secondary adrenal insufficiency.

The cosyntropin stimulation test will also be sensitive for diagnosing secondary adrenal insufficiency if it is chronic or longstanding. The chronic ACTH deficiency leads to adrenal gland atrophy and this is the basis for an

abnormal cosyntropin test. However, if the ACTH deficiency is of recent onset, then adrenal gland atrophy may not have had time to develop and therefore the cosyntropin test will be normal although secondary adrenal insufficiency is present.

Likewise, if the ACTH deficiency is mild, there may be sufficient secretion of ACTH to prevent involution of the adrenal gland. So then again the cosyntropin test will be normal although secondary adrenal insufficiency is present.

Therefore, if secondary adrenal insufficiency is of mild or recent onset, the cosyntropin stimulation test may yield a false negative result, and additional testing may be needed in such circumstances if the patient is symptomatic or if there is a high index of suspicion of adrenal insufficiency.

The next few slides will describe each of these four dynamic tests which are available to diagnose adrenal insufficiency.

The high-dose cosyntropin test is the one that is most commonly used to make this diagnosis. A supraphysiologic dose of synthetic ACTH is administered either IV or IM. The cosyntropin label states that this dose is usually 250 micrograms, but that a dose of 125 micrograms may be sufficient in a child who is 2 years of

age or younger. Serum cortisol levels are obtained at baseline and at the completion of the test. The advantage of this test is that it is simple, fast, and inexpensive. It can be performed at any time of day as an outpatient and you can complete the test in an hour or less.

The cosyntropin label refers to both the 30-minute cosyntropin stimulation test, as well as the 60-minute test. Since as you will hear from Dr. Denise Cook's talk that the clinical studies that were performed generally use the 30-minute test, it's the 30-minute test that we will predominantly focus on now.

There is controversy regarding the criteria that should be used to define a normal cortisol response. The cosyntropin label mentions three criteria. A basal cortisol level should be greater than 5 micrograms per deciliter. The peak cortisol level should be greater than 18 micrograms per deciliter, and the increment, which is the difference between the baseline cortisol and the peak cortisol levels, should be greater than or equal to 7 micrograms per deciliter. However, the label does specify that since this test can be performed at any time of day and since it is only the peak level which is not dependent on the time of day, the peak cortisol level is sufficient in and of itself to make the diagnosis of adrenal insufficiency.

I would also like to mention that use of the increment may be problematic because the increment is inversely proportional to the basal cortisol level, so that the higher the basal cortisol level, the lower the increment. Therefore, most endocrinologist use a peak cortisol level of greater than 18 micrograms per deciliter to denote a normal response to the 30-minute test.

The disadvantage of this test has already been mentioned. You can get a false negative test when the secondary adrenal insufficiency is mild or is of recent onset. Additional testing may be needed if the patient is symptomatic or there is a high index of suspicion of adrenal insufficiency.

The next test for discussion is the low-dose cosyntropin stimulation test. This is a newer test, and a physiologic dose of ACTH, either 0.5 microgram per meter squared or in other circumstances 1 microgram per meter squared -- those are some of the ACTH doses which have been used as reported in the literature in children -- is administered intravenously, and then blood samples are obtained at baseline for cortisol measurement and then serially post ACTH administration. Because such a low dose of ACTH is being administered in this test and ACTH has a very short half-life, this test requires frequent, carefully timed blood sampling because you do not want to

miss the peak cortisol response.

Some have reported that this is a more sensitive test than the high-dose test to detect mild secondary adrenal insufficiency because you are administering a physiologic dose of ACTH and therefore only mobilizing the cortisol that is available in the immediate release pool. However, results of studies on this issue have been conflicting.

In addition, there is no standard method of performance for this test either with regard to the dose of ACTH that should be administered or the frequency or the timing of the blood samples post ACTH administration.

In addition, this low dose of ACTH is not commercially available, and therefore dilutional errors can occur. There can be variability in the amount of the ACTH that is administered from test to test, and there is at least one report of adherence of part of the ACTH to the plastic tubing of the vein delivery set.

This slide compares the low-dose to the high-dose ACTH test. Again, with the low-dose test, this dose is not commercially available, but the 250 microgram dose is. Low-dose, you're administering a physiologic ACTH dose; with the high-dose test, you're administering a supraphysiologic dose. The low-dose test, as we said, requires frequent, carefully timed venous sampling, while

with the high-dose test, only a single cortisol level needs to be obtained at the end of the test and it does not have to be precisely timed. While there is no consensus on method of performance of the low-dose test, the method of performance with the high-dose test has been standardized. And while with the high-dose test there is no consensus regarding what constitutes a normal cortisol response, with the high-dose test, it is generally accepted that a peak cortisol level greater than 18 micrograms per deciliter with a 30-minute test constitutes a normal response. So as you can see, on balance, the high-dose test offers a number of advantages over the low-dose test.

The next two slides will describe the insulin tolerance test. As we mentioned before, hypoglycemia is a potent stress stimulator for the release of CRH and ACTH. This test involves administration of intravenous insulin after an overnight fast. Plasma cortisol and glucose levels are obtained before and at 30, 45, 60, and 90 minutes post insulin administration. A normal response is a peak cortisol level of greater than 18 to 20 micrograms per deciliter at 60 to 90 minutes post insulin administration, with a concomitant serum glucose level of less than 40 milligrams per deciliter.

Although this test provides a direct and definitive assessment of HPA axis integrity, it is a very

high-risk test, and there has been significant neurologic morbidity and also mortality has been reported with conduct of this test in children. Therefore, this test is rarely, if ever, used. Safer diagnostic alternatives are available.

The next three slides will discuss the CRH test. This test is a newer test, and as we said, the physiologic basis for this test is that CRH stimulates the release of ACTH and hence of cortisol.

A 1 microgram per kilogram dose of CRH is administered intravenously, and plasma ACTH and cortisol levels are measured periodically for 90 to 180 minutes post CRH administration. This test has been used to differentiate primary from secondary from tertiary adrenal insufficiency. With primary adrenal insufficiency, basal ACTH levels are high, and they increase with CRH administration but cortisol levels do not. Both secondary and tertiary adrenal insufficiency are characterized by low levels of ACTH basally. With secondary adrenal insufficiency, you get a flat response to CRH administration, while with tertiary adrenal insufficiency, you get an exaggerated ACTH response to CRH. However, I would like to point out that the distinction between secondary and tertiary adrenal insufficiency is not important here because we're talking about adrenal

insufficiency secondary to exogenous glucocorticoid administration.

The advantages of this test are several. The CRH test provides a direct and definitive assessment of HPA axis integrity. There are also reports that the CRH test has equivalent diagnostic value to the insulin tolerance test, but unlike the insulin tolerance test, the CRH test is safe and it can be conducted as an outpatient.

There are a number of disadvantages to this test. First, it is expensive and it does require performance of multiple blood samples. There may be errors in blood collection and storage, and this is because ACTH has a short half-life. It's readily inactivated by proteases so that when you're collecting the samples for ACTH, you have to collect them in pre-chilled containers and then the specimen should be kept frozen to minus 20 degrees Centigrade until ready for assay.

In addition, the normal responses of ACTH on cortisol are laboratory-dependent, and so there is no consensus regarding what constitutes a normal response.

Also, FDA has not approved the CRH test as a diagnostic for adrenal insufficiency. It has only approved it for the use of the differential diagnosis of Cushing's syndrome, whether the ACTH hypersecretion is from the pituitary or from an ectopic source.

Additional studies are needed to confirm the usefulness of this test as a diagnostic for adrenal insufficiency.

We'll now discuss risk factors for HPA axis suppression. Again, to remind you, there is individual susceptibility. HPA axis suppression is variable as is time to recovery. Therefore, the diagnosis of adrenal insufficiency does require performance of hormonal testing.

Nevertheless, there are a number of risk factors that may influence the development and the degree of HPA axis suppression. Certainly the higher the potency of the steroid used and the longer the half-life, the greater the risk of suppression. Also, the vehicle or base used, that is, whether the preparation is a cream, a lotion, or an ointment, may also be an influencing factor, and Dr. Cook will discuss this in her talk.

The greater the extent of absorption, the greater the risk of suppression. Absorption of topical corticosteroids is increased by thin stratum corneum such as found in the face in the intertriginous areas. Absorption is also enhanced in areas of heat and moisture, such as found in the intertriginous areas. And likewise, absorption is greater when the steroid is applied to abraded or inflamed skin as opposed to if you had an intact skin barrier.

Also, the greater the amount of steroid used, the greater the risk of suppression. With topical corticosteroids, the dose administered is a function of the concentration of the steroid in the base vehicle and the percent of skin surface area that is covered. We know that infants are particularly susceptible or vulnerable to HPA axis suppression. It's postulated that this is due to the higher ratio of skin surface area to body mass.

In addition, the longer the contact time of the steroid with the skin, the greater the risk of suppression.

The cumulative dose is a function of the dosing interval and the duration of treatment. The more frequent the application, the less the chance of HPA axis recovery between applications so that continuous application would be expected to be more suppressive than intermittent application.

With regard to duration of treatment, if a topical steroid is used for, let's say, a week or 2 or less, one would anticipate less chance of suppression and if it did occur, there would be more rapid recovery.

These next three slides will summarize the main points of this presentation.

First topical corticosteroids are systemically absorbed and therefore they may cause secondary adrenal insufficiency.

The symptoms of adrenal insufficiency may be subtle and nonspecific, and therefore the diagnosis may not be suspected clinically or attribution is made to other causes.

Patients with secondary adrenal insufficiency are at risk for an acute adrenal crisis regardless of the degree of suppression or the presence of symptoms. An acute adrenal crisis is preventable if supplemental glucocorticoids are administered before or early in the course of stress.

Although risk factors for HPA axis suppression may be present, individual susceptibility is variable.

Hormonal testing is required for the diagnosis, and basal hormonal tests are often nondiagnostic. Therefore, the majority of the patients do require dynamic hormonal testing.

Dynamic tests of HPA axis integrity are more sensitive for the diagnosis of mild or recent onset secondary adrenal insufficiency than are tests which measure only adrenocortical reserve.

A negative cosyntropin test may warrant additional testing, particularly if the patient is symptomatic or if there is a high index of suspicion of secondary adrenal insufficiency.

When HPA axis suppression is diagnosed,

treatment should follow standard medical practice and the patient should be followed to document full recovery of the axis.

Thank you.

DR. CHESNEY: Thank you very much.

Our next speaker is Dr. Denise Cook, who is also a medical officer and board certified pediatrician in the Division of Dermatologic and Dental Drug Products. She will present data on HPA axis suppression from the clinical studies for various topical corticosteroid drug products.

DR. COOK: Thank you. I'd just like to make one correction. I'm a board certified internist and dermatologist, although I'd love to claim to be in the field of pediatrics also.

DR. CHESNEY: We're glad to have you join us even if name only.

(Laughter.)

DR. COOK: With that, good morning, everyone.

I'm going to speak today on topical corticosteroids and HPA axis suppression. This presentation will outline the history of where the FDA has been and where we are presently as it relates to HPA axis suppression and the use of topical corticosteroids. I'll examine the history of labeling as it relates to systemic safety and topical corticosteroids. I will briefly speak

about the regulation and legislation relevant to this topic. The large majority of the talk will focus on specific drug products data. Information presented will come from labels and trials to help us examine the relationship between topical corticosteroid use and HPA axis suppression. Since this is a Pediatric Advisory Committee meeting, the main focus of the talk will be on pediatric patients.

As mentioned by Dr. Nikhar, topical corticosteroids were first introduced in the 1950s and have been the mainstay of treatment of atopic dermatitis for approximately half a century.

Before I get started, for understanding I will briefly mention the classification of these drug products. Topical corticosteroids are divided into seven classes. Class I is the superpotent topical steroid of which Temovate is the drug most known. Class II is the high potency topical corticosteroids. Class III through VI are mid-potency, and those steroids are divided into high mid-potency and low mid-potency. And Class VII is the low potency for which hydrocortisone acetate is the prototype.

The classes are determined by a vasoconstrictor assay in which caucasian patients are used and medication is applied to the skin with bracketing of known drug products, and then the amount of blanching is determined as

compared to products in certain classes. And that's how the class is determined for that particular drug product.

I am going to begin with a label dated in the early 1970s as a 30-year history should suffice to show the progression of labeling.

Lidex gel is a class II high potency topical steroid that was approved in 1971. At that time, the safety information in labels was very brief, and it stated in the precaution section, if extensive areas are treated, the possibility exists of increased systemic absorption and suitable precautions should be taken.

In the 1980s, labels become somewhat more sophisticated. The safety update information was expanded. In the precaution section for Temovate cream and ointment, which was approved in 1985, it stated: Temovate is a highly potent topical corticosteroid that has been shown to suppress the HPA axis at doses as low as 2 grams per day. A pediatric use section was now in the labels, and it stated that use of Temovate cream and ointment in children under 12 years of age is not recommended.

The claims in the label were supported by the following two trials. These trial were done with Temovate ointment and they were open-label trials.

Trial 1, there were 6 adult patients with psoriasis who applied the medication to 30 percent of their

body surface area for 7 days at a dose of 7 grams per day. In this trial, the ACTH stimulation test was performed at baseline and two post-treatment AM cortisols were obtained. They found in this study that 3 of the 6 patients, or 50 percent of the patients, exhibited decreases in cortisol production.

The second trial objective was to determine the largest dose that could be used over a 7-day period that would not cause significant suppression of the adrenal gland. Three doses were used: 7 grams per day, 3.5 grams per day, and 2 grams per day. Suppression in this trial was determined not by the cosyntropin stimulation test, but by just determining the basal AM plasma cortisol levels and urinary corticoid concentrations. It's interesting that none of the psoriasis patients suppressed, but at doses as low as 2 grams per day, marked suppression of cortisol secretion occurred in patients with atopic dermatitis. That led to the label that I discussed earlier.

Now that we had documentation of HPA axis suppression, class labeling was adopted for topical corticosteroids in 1990. It primarily affected the precaution section and the pediatric use section. I will go over each of these sections.

First, the precaution section. In the general part of the label it stated, systemic absorption of topical

corticosteroids can produce reversible hypothalamic-pituitary-adrenal axis suppression with the potential for glucocorticoid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

It went on to say that patients applying a potent topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, AM plasma cortisol, and urinary free cortisol tests.

Further, it stated: if HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticoid insufficiency may occur requiring supplemental systemic corticosteroids.

The pediatric use section also had an update and was part of this topical class labeling. If no trials had been performed in pediatric patients, which was usually the case at the time, then the statement "safety and

effectiveness in children and infants have not been established" was used. Because of a higher ratio of skin surface area to body mass, children are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. They are therefore also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment.

Further, it stated: HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include low plasma cortisol levels to an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

One regulation and two pieces of legislation improved the agency's ability to examine safety of new and existing drug products in the pediatric population, and I will speak briefly about them. The first one was the Pediatric Rule in 1994. The second one was section 111 of the Food and Drug Administration Modernization Act approved in 1997, and the final one was the Best Pharmaceuticals for Children Act passed in 2002.

In the Pediatric Rule, it allowed for extrapolation of adult efficacy data to pediatric patients, when appropriate, plus additional safety, PK, and/or dose-ranging studies in the targeted pediatric population.

Section 111 of FDAMA introduced the written request where sponsors are offered 6 months of exclusivity for their chemical moiety if they fairly respond to the agency's request for pediatric studies.

The Best Pharmaceuticals for Children Act had several important edicts, two of which are relevant to this talk. It establishes additional mechanisms for the study of both on-patent and off-patent drugs. Pediatric supplements are now priority reviews.

The following portion of the talk will examine individual drug products and the trials that were undertaken in an attempt to provide additional safety data regarding their use. So I hope you had a healthy dose of caffeine as we delve into all of this data.

(Laughter.)

DR. COOK: There are 10 drug products that we're going to speak about, although more have been done. Eight are topical corticosteroid products, and two that I will speak about are combination drug products. Eleven studies will be discussed. The patients ages range from 3 months to adult, and all of the studies evaluating the

function of hypothalamic-pituitary-adrenal axis were open-label studies.

As mentioned earlier by Dr. Temeck, the cosyntropin stimulation test is the most frequently used to assess adrenal function. As you will note, varying criteria over the years have been used by the agency to define adrenal gland suppression via this test. We are currently in the process of drafting a consistent approach to the evaluation of HPA axis suppression.

The first drug that I'm going to speak about is Dermatop, a class V steroid that was approved in 1996, and a pediatric atopic dermatitis trial was performed. In this trial, there were 59 pediatric patients enrolled, and there were two targeted populations. Patients between 1 month and 2 years and patients between 2 years and 12 years of age. 10 patients were less than 2 years old. 49 patients were greater than or equal to 2 years old.

The treatment criteria for this trial was that greater than 20 percent of the body surface area had to be involved, patients had to use the drug twice daily for 21 consecutive days. In this trial, it did not matter if the patient's skin disease had cleared. They continued to use the drug for 21 consecutive days.

The ACTH stimulation test was used. Cosyntropin was administered at baseline and day 22.

Patients who were greater than 15 kilograms received .25 milligram IV, and patients less than 15 kilograms received 0.125 milligram IV. This happens to be the case for all of the studies except the Cutivate study in which they divided the dose according to age.

The criteria per protocol for a normal adrenal response to ACTH stimulation at 30 and 60 minutes was that the post-stimulation serum cortisol had to be greater than 20 micrograms per deciliter. Also, if the pre-stimulation serum cortisol level was already greater than 20 micrograms per deciliter, then an incremental increase greater than 6 micrograms per deciliter in serum cortisol was required.

The outcome was that 3 patients according to the protocol criteria were suppressed. 2 patients, 1 an 18-month-old, had a peak response of 5 micrograms per deciliter change from baseline. 1 patient had a post-stimulation cortisol value that actually decreased after stimulation.

At that time, the agency agreed with an outside endocrinologist that since these 3 patients had a post-stimulation response that was already greater than 20 micrograms per deciliter, although they didn't have the required incremental rise, they would not be suppressed. This led to the current label for Dermatop which reads that none of the 59 patients showed evidence of HPA axis

suppression.

The next drug is Cutivate cream which is also a class V steroid. It was approved June 17th, 1999. When I talk about approval, I am not speaking about the approval of the drug product itself, but the approval of the pediatric supplement that came into the agency.

There was a pediatric atopic dermatitis and psoriasis trial. However, in the trial only patients with atopic dermatitis were studied. There were 43 patients who were evaluable, all with moderate to severe atopic dermatitis. When I say evaluable, that means that at baseline the patients did not show any evidence of adrenal suppression on cosyntropin stimulation.

29 of the patients were 3 months to 2 years old, and 14 patients were 3 years to 5 years old.

The treatment criteria for this trial was that at least 35 percent of the body surface area would be involved and treated. There would be twice-a-day application for 3 to 4 weeks. In this trial, patients were required to use the drug continuously for 3 weeks. If they continued to have disease at that point, they could use an additional week of drug product. Patients up to 2 years of age were limited to 120 grams per week, and patients 3 to 5 years of age were limited to 180 grams per week.

I just want to put into perspective about using

the drug for the required 3 weeks even if the disease had cleared. In this study, there were 46 patients who were enrolled, and 23 of the patients, or 50 percent, had a decrease of body surface area improvement of 50 percent by 2 weeks. 20 percent had a decrease of 50 percent BSA involvement by 3 weeks, and 9 percent had a 50 percent decrease of BSA involvement by 4 weeks. So this kind of shows that most of the patients still had some evidence of disease throughout the trial.

The cosyntropin stimulation test was used. The test was administered at baseline and end of treatment, and again, in this trial the younger age group had the smaller dose and the older age group had the larger dose.

A normal response in this trial was a serum cortisol level greater than 18 micrograms per deciliter at 30 minutes post stimulation.

2 out of the 43 patients experienced adrenal suppression. 1 was a 5-year-old who had 95 body surface area, and over the course of the trial improved to about 26 percent BSA involvement, used the drug for 4 weeks, used 561 grams, as mom continued to apply the drug to 95 percent BSA, although the requirement was just 35 percent BSA. You can see that the post-stimulation cortisol was 11.8. However, 2 weeks after treatment when there was no medication used, the patient recovered with a post-

stimulation of 19.8.

The second child was a 2-year-old who only had 35 percent BSA involvement, used a much smaller amount of drug over 5 weeks, 176.5 grams, and was suppressed at the end of treatment with a serum cortisol of 9.4 micrograms per deciliter. Unfortunately, he was lost to follow-up, although several attempts were made to locate the patient, so we don't know about that patient's recovery.

This led to a labeling change for Cutivate cream where the indication stated that children as young as 3 months of age could use the drug for up to 4 weeks, and safety update information was included in the precaution section's general and pediatric use sections.

The next group of drugs that I'm going to speak about are the betamethasone propionate drugs approved in 2001. These drugs range in class potency from a class II steroid high potency to a class V steroid. Lotrisone cream and lotion will also be discussed here because it also includes betamethasone propionate.

The betamethasones heralded, with extra divisional input, an internal change in policy regarding what constitutes HPA axis suppression using cosyntropin stimulation. That included that now for normal HPA axis response, we must follow the Cortrosyn label, and failure of any one of three criteria would indicate suppression of

the HPA axis. Stimulation should also occur at baseline and end of treatment in any future trials.

Those criteria at the 30-minute post-stimulation, which you have heard earlier, are that the control plasma cortisol level should exceed 5 micrograms per 100 milliliters. The 30-minute level should show an increment of at least 7 micrograms per 100 milliliters above the basal level. The 30-minute level should also exceed 18 micrograms per 100 milliliters.

The first drug I'm going to speak about is Diprolene AF cream. In this trial, there were 60 evaluable patients, ages 1 to 12 years, with moderate to severe atopic dermatitis. The mean body surface area involved was 58 percent. Patients in these studies used the drug per the product label. They used the study drug twice a day for 2 to 3 weeks, and they were limited to 45 grams per week. Again, they used it for 2 weeks, and if they needed an additional third week because there was still significant disease present, they used it for 3 weeks. So the test could either occur at the 2-week point or at the 3-week point.

In this study, 32 percent of these patients showed evidence of HPA axis suppression. Of the 19 patients who suppressed, 11, or 58 percent, had a post-stimulation plasma cortisol value of less than 18

micrograms per deciliter. 6 patients failed to have an incremental change of at least 7 micrograms per deciliter, and 11 percent had a pre-stimulation cortisol less than 5 micrograms per deciliter. I should also mention that most of the cosyntropin testing was done in the morning, AM, 8 o'clock.

Now, if we look at suppression by age group in Diprolene AF cream, we will find that the younger the patient was, the greater the proportion of subjects who suppressed. For example, in the 9-year to 12-year group, 17 percent of patients suppressed, and in the infant group, 3 months to 1 year, 50 percent of the patients suppressed.

Regarding recovery of normal HPA axis function, 4 patients were retested 2 weeks post treatment, and 3 of the 4 recovered normal function of the HPA axis.

Now, the statistical analysis in the development of HPA axis suppression for Diprolene AF showed there was no correlation between amount of drug used, body weight, age, or sex and the incidence of adrenal gland suppression. There was a statistical relationship between body surface area and risk of HPA axis suppression such that for an increase of 1 percent BSA involved, risk of HPA axis suppression increased by 4.4 percent, and that should be p is less than 0.01. This latter statistical fact, in the absence of a correlation with amount of study

medication used, may be related to the increased BSA to body mass ratio in young children and infants.

This study led to a labeling change for Diprolene AF cream such that the cream was restricted to patients who were 13 years of age and older, and clinical safety information was updated in the appropriate sections of the label.

The next drug is Diprosone ointment. In this study there were 53 evaluable patients with atopic dermatitis. Their age range was 6 months to 12 years old. Medication again was applied twice a day for 2 to 3 weeks, and there was a mean body surface area involvement of 58 percent.

In this study, 28 percent of patients showed evidence of HPA axis suppression. Of those 15 patients who suppressed, 53 percent had a post-stimulation plasma cortisol value of less than 18, and 47 percent failed to have an incremental change of at least 7 micrograms per deciliter.

If we look at this drug at suppression by age group, we will see the same thing. The younger the patient, the greater the proportion of subjects that experienced suppression, ranging from 17 percent in the 9-year to 12-year-old group to 36 percent in the infant group.

The statistical analysis, however, did not show a significant effect for drug usage percent BSA involvement, weight, or age. However, there was a higher proportion of males than females who developed HPA axis suppression.

In the recovery of HPA axis function, there were 2 of 15 patients who were suppressed that were retested, and there was 100 percent recovery at 2 weeks.

A labeling change for Diprosone ointment also added an age restriction of 13 years and older, and clinical safety information was updated in the clinical pharmacology, the precautions, general and pediatric use sections of the label.

Diprosone cream had 43 evaluable patients with atopic dermatitis in its trial. The age range was 1 year to 12 years old. The mean body surface area involvement was 40 percent. The medication was applied twice a day for 2 to 3 weeks.

In the Diprosone cream trial, 23 percent of patients showed evidence of adrenal suppression. Of those 10 patients, 50 percent had a post-stimulation plasma cortisol value of less than 18 micrograms per deciliter. 30 percent failed to have an incremental change of at least 7 micrograms per deciliter, and 2 of the 10 patients had a pre-stimulation cortisol less than 5 micrograms per

deciliter. In all of these trials, there were some patients who failed actually on more than one criterion.

If we look at HPA axis suppression by age in this study, there again was a progression the younger that the patient was, except in this trial, for some reason, no infant suppressed.

The statistical analysis did not show a statistically significant effect for number of days treated, weight, or age.

There was a statistical significance found for this particular drug product in the mean amount of drug used. Those who suppressed used 81 grams versus 37 grams in those who did not suppress.

There was a numerically higher percent of body surface area involvement in those who suppressed, and numerically more males developed suppression.

In the recovery of HPA axis function, 2 of 10 patients were retested, and 1 of the 2 patients recovered HPA axis function at 2 weeks.

The labeling change for Diprosone cream was also the same in the indication where age restriction of 13 years and older was placed. Clinical safety information was updated in the appropriate sections of the label.

The last solitary betamethasone propionate product that I will speak about is Diprosone lotion. In

this trial, pediatric patients were to be enrolled in a step-wise fashion beginning with the oldest age group. If significant suppression was not observed, then progressively younger age groups could be enrolled. This is a class V corticosteroid. There were 15 evaluable patients with atopic dermatitis. The age range was 6 to 12 years old. The mean body surface area involvement was 45 percent. The medication was applied twice a day for 2 to 3 weeks.

In this trial, 73 percent of patients showed evidence of HPA axis suppression, and of those 11 patients who suppressed, 91 percent had a post-stimulation plasma cortisol value less than 18 micrograms per deciliter. And 1 of the 11 patients failed to have an incremental change of at least 7 micrograms per deciliter.

When you look at suppression by age group, you see, because there was such a high percentage of patients who developed adrenal suppression, there were no patients less than 6 years of age who were enrolled in the study.

When you do a numerical analysis -- we only did a numerical analysis because the numbers were so small -- it showed that subjects exhibiting HPA axis suppression had a larger mean amount of drug used, had a slightly higher percent of body surface area involved, had lower mean weights at visit 1 and 4, but the differences with respect

to age and days of treatment were minuscule.

In recovery of HPA axis function with Diprosone lotion, there were 6 of the 11 patients retested, and 67 percent recovered their HPA axis function at 2 weeks.

This led to a label change for Diprosone lotion where the age restriction was of 13 years and older and the appropriate clinical safety information was updated in the label.

Now, if you look at a comparison of HPA axis suppression criteria of the betamethasone dipropionates, whether you use all three criteria as per the label or whether you just use greater than 18 micrograms per deciliter, you will see that the Diprolene AF cream, the Diprosone ointment, and the Diprosone cream all tended to clutter around the same ball park in their ability to suppress the adrenal gland. However, Diprosone lotion stands out by itself with a high rate of suppression. This led us to believe that the actual vehicle in which the chemical moiety is in may play a role in the amount of absorption into the systemic circulation of the chemical moiety.

Lotrisone cream is the last betamethasone diproprionate product that I will speak about. This also includes clotrimazole and is approved for the treatment of dermatophytosis. The two studies were a tinea pedis study

and a tinea cruris study. Both studies were in the adolescent population, ages 12 to 16 years. The medication was applied twice daily. In the tinea pedis study, it was applied for 4 weeks. In the tinea cruris study, it was applied for 2 weeks.

In this study, 39.5 percent of patients demonstrated adrenal suppression in the tinea pedis study and 47 percent demonstrated adrenal suppression in the tinea cruris study.

This led to a label change for Lotrisone cream and also for lotion by extension of the betamethasone lotion study that was done which showed significant suppression. An expanded indication section was developed. It added an age restriction to only patients 17 years and older. It also recommended that effective treatment may be obtained without the use of a corticosteroid for noninflammatory tinea infections. They updated safety information in the appropriate sections of the label.

The last drug product that I will speak about are the clobetasol propionate products. These are class I steroids, the superpotent steroids. I will speak about Clobex lotion and Temovate E cream.

This was done under Clobex lotion. There were three studies, two adult studies, one in psoriasis and one in atopic dermatitis. There was one pediatric study, ages

12 to 17, in atopic dermatitis.

The construct of the HPA axis evaluation was the control plasma cortisol levels should exceed 5. The 30-minute level should show an increment of at least 7 micrograms, and the 30-minute level should exceed 18 micrograms per 100 milliliters.

In these trials, however, there were some exceptions. The plasma cortisol levels were drawn at 60 minutes post stimulation. In the adult studies, subjects were stimulated with cosyntropin weekly.

In the adolescent study, there were 24 evaluable patients, 14 treated with Clobex lotion and 10 treated with Temovate E cream. They had moderate to severe atopic dermatitis. They had to have at least 20 percent body surface area involvement. Medication was applied twice a day for 2 weeks. There was a 50 gram per week limit. This is because the trial had to follow the Temovate E labeling.

In this trial, HPA axis suppression was noted in 64 percent of the subjects treated with Clobex lotion as compared to 20 percent of the subjects treated with Temovate E cream, again suggesting that the vehicle, which is a lotion, may play a role in the absorption of the chemical moiety into the systemic circulation.

In the statistical analysis the mean percent

body surface area treated was higher for patients with adrenal suppression, 32 percent versus 27 for Clobex lotion and 35 percent versus 25 for Temovate E cream.

In the recovery of HPA axis function, 1 of the 4 patients retested, who were treated with Clobex lotion, remained suppressed after 2 weeks. The 1 patient who was retested with Temovate E cream recovered.

In one of the adult studies, there were 18 evaluable patients, 9 in each arm, moderate to severe atopic dermatitis. Their mean body surface area treated was approximately the same for both drugs. Medication was applied twice a day for 2 weeks, and there was a 50 gram per week limit.

In this trial, 56 percent of the subjects treated with Clobex lotion suppressed, and 44 percent of the subjects treated with Temovate E cream suppressed.

Of the patients who were retested, 1 out of the 3 patients on Clobex lotion failed to recover function 7 days post treatment. Both patients who were retested on Temovate E cream recovered function 7 days post treatment.

In the final adult study, there were 20 evaluable patients, 10 treated with Clobex lotion and 10 treated with Temovate E cream. The patients had moderate to severe plaque psoriasis. They had approximately the same body surface area treated, 16.2 percent for Clobex

lotion and 17.9 percent for Temovate E cream. Here the medication was applied twice a day for 4 weeks. Temovate E allows for 4-week treatment to small areas of body surface area involvement in psoriasis. The gram limit again is 50 grams per week.

In this study, 80 percent of the subjects treated with Clobex lotion suppressed compared to 30 percent of subjects with Temovate E cream.

In the recovery of their HPA axis function, 1 of the 2 patients treated with Clobex lotion remained suppressed after 8 days. None of the patients on Temovate E cream were retested.

The label for Clobex lotion that was developed stated the drug would be restricted to patients 18 years or older. It could be used for 2 consecutive weeks, not to exceed 50 grams per week. Moderate or severe psoriasis for localized lesions less than 10 percent body surface area could be treated an additional 2 weeks. And safety information was included in the indications and usage, in the precautions, general and pediatric use, and in the dosage and administration sections.

In summary, just a few salient points. HPA axis suppression does occur with the use of topical corticosteroids. The adrenal suppression is not limited to the superpotent class of topical corticosteroids. The type

of vehicle may contribute to the extent of absorption of the active chemical moiety. The suppression appears in most cases to be reversible upon cessation of drug usage.

In conclusion, there has been progress in acquiring safety information in the pediatric age group for the use of topical corticosteroids as it relates to systemic safety, in particular, the function of the HPA axis. The Pediatric Rule of 1994, section 111 of FDAMA, and the Best Pharmaceuticals for Children Act have certainly spurred this process in obtaining information for specific drug products to aid healthcare professionals in their risk-benefit analysis. Yet, there are more questions that remain to be answered and hopefully will be answered by this committee today.

Thank you.

DR. CHESNEY: Thank you very much for presenting a lot of technical information in a way that kept us all alert. We had enough coffee.

Our final formal presentation of the morning is by Claudia Karwoski, who is a safety evaluator team leader with the Division of Drug Risk Evaluation in the Office of Drug Safety, and she will present the adverse event reports of HPA axis suppression among children treated with topical corticosteroids.

DR. KARWOSKI: Good morning. I'll first

provide an overview of AERS, including its strengths and limitations. I'll touch upon the potency classification system for the topical corticosteroids, and then I'll discuss the methods for case selection, the results of our evaluation of the cases, and finally provide an overall summary of our findings.

The Adverse Event Reporting System is a spontaneous, voluntary surveillance system of adverse events for U.S.-marketed products. Reporting by healthcare professionals and consumers is voluntary. Reporting by manufacturers is mandatory.

There are currently about 3 million reports in the database. It dates back to 1969 with the implementation of the Spontaneous Reporting System. SRS was replaced in November of '97 with AERS. At that time, all the reports were migrated from SRS into AERS. AERS contains reports for all human drug and therapeutic biologic reports except for the vaccines, which is a separate database.

Spontaneous reporting systems such as AERS have several limitations. The quality of the reports are variable and often incomplete. Because reporting is voluntary, AERS is subject to under-reporting and therefore the true numerator of adverse events for a specific product is unknown. Reporting biases exist. An example is

increased reporting that often occurs following publicity of a safety issue.

Although we often use drug usage data to estimate exposure, the exact denominator or number of patients exposed to a product is unknown. And because we don't know the true numerator or denominator, we cannot use spontaneous reports to determine incidence of an adverse event.

Duplicate reporting also occurs and matching duplicates can be difficult particularly when the information is incomplete.

Despite its limitations, AERS does have several strengths. It allows for early detection of events not seen in clinical trials. It is especially useful for detecting serious rare events such as hepatic failure or aplastic anemia. Often one or more well-documented reports can trigger further evaluation. And a case series evaluation may aid in identifying adverse event trends such as events that occur when a product is used for a specific indication or in a specific patient population such as children or the elderly. And lastly, AERS is relatively inexpensive compared to alternative surveillance strategies.

The topical steroids are classified by potency, and you've seen this slide before. Generally the class I

includes the most potent and VII includes the least potent. The characteristics of the concentration of the product, as well as the vehicle, will influence the potency, and the potency is determined by the drug's ability to induce vasoconstriction.

We searched AERS for all adverse events reported for the topical steroids in children from 0 to 16 years of age. This was done in 2001 to provide an overall safety review of these products in that population. We also searched AERS and the medical literature for case reports of adrenal suppression, Cushing's syndrome, and growth retardation in children.

This graph depicts the leading adverse events as a percentage of all adverse events in children treated with topical steroids. The most commonly reported events are local irritation and application site reaction, which represents about 27 percent of all adverse events. This is followed by lack of effect, skin discoloration, and skin atrophy, which represent about 12 to 13 percent of adverse events. Among the top events are Cushing's syndrome, adrenal suppression, and growth retardation.

Our search for cases of adrenal suppression, Cushing's syndrome, and growth retardation identified 24 total cases in AERS and the published literature. We excluded two because one turned out not to be an event of

interest and in the other the use of a topical corticosteroid was reported. Of the remaining 22 cases, 8 reported adrenal suppression, 13 reported Cushing's syndrome, and 10 reported growth retardation. Some of the cases reported more than one of these events, and six were published in the literature.

The children's ages ranged from about 6 weeks to 15 years of age and the median age was 3.

9 of the adverse events occurred in pediatric patients younger than 3 years and 5 occurred in infants. There were over twice as many reports in males than females.

And the duration of therapy ranged from 22 days to 7 years. In 7 cases, use of the topical corticosteroids continued for over a year, and it's only clear in 1 of the 7 reports that the use was intermittent.

Slightly more than half of the cases are foreign, and these reports span just over 20 years, with the first being reported in the literature in 1980.

10 patients were hospitalized and 2 patients with Cushing's syndrome died. 1 death was secondary to respiratory infection, and the circumstances in the second death were not provided.

A variety of indications were reported. 7 reported being treated for atopic dermatitis or eczema. In

6 cases the children received topical steroids to treat diaper rash and 2 were being treated for hair loss.

The site of application includes the diaper area in 7 cases. 2 reported the use of a topical steroid to the entire body, and 3 reported use in more than one location on the body.

Clobetasol, mometasone, and betamethasone-containing products were the most frequently implicated. In 4 cases, the patient was treated with more than one topical corticosteroid product.

The patients presented with one or more of the following. 12 patients presented with weight gain or other Cushingoid features. 10 presented with growth retardation. 1 infant presented with acute adrenal insufficiency after a possible acute illness, and 1 child presented with skin striae and depigmentation.

I'll now present select cases that provided laboratory evidence of adrenal suppression. The first is of a 4-month-old boy who presented with accelerated weight gain, obesity, and diaper dermatitis that was unresponsive to topical corticosteroids. At 2 months of age, he was prescribed hydrocortisone which was to be administered three to four times daily for a week. This was continued by his mother and she additionally used clobetasol. A total of eight tubes of hydrocortisone and six tubes of

clobetasol were used within a 2-month frame.

On presentation, his laboratory evaluation included decreased levels of ACTH, cortisol, and 24-hour urinary free cortisol. A low-dose cosyntropin test showed no increase in cortisol levels. His parents were instructed to reduce the frequency of the applications to prevent adrenal crisis. After 2 months, a low-dose ACTH test was repeated and showed a significant cortisol response.

The second case involves a 4-and-a-half month old who presented with a history of increased weight and body fat. It was discovered that his mother had been applying clobetasol for diaper rash for over 2-and-a-half months. The infant had received approximately 8 to 10 25-gram tubes within that time frame. His morning and evening cortisol levels were low. He was discharged on physiologic oral replacement with hydrocortisone. At his 2-month physician visit, an ACTH stimulation test showed continued suppression. A normal response was seen after 6 months, at which time his hydrocortisone was tapered and eventually discontinued.

The third case is of a 1-year-old male infant who was brought to a baby clinic with a history of sudden increase in weight and increasing fat deposits. It was discovered that his mother had used approximately seven

tubes of clobetasol for diaper rash for over 2 months. His serum cortisol was low. He was placed on physiologic oral replacement with hydrocortisone. An ACTH stimulation test 2 months later showed a serum cortisol of 2.8, 20, and 23 before, 30 and 60 minutes after ACTH injection. Hydrocortisone was tapered and stopped. On subsequent visits, his Cushingoid features gradually improved and his weight decreased to a normal range.

The fourth case involves an 11-year-old male with an 8-year history of atopic dermatitis who developed Cushing's syndrome and adrenal suppression secondary to long-term whole-body application of a topical betamethasone-containing product. He presented with amnesia, somnolence, moon face, and low height and obesity. His serum cortisol was low and he had a low ACTH level. A rapid ACTH test showed adrenal suppression. He had concomitantly received betamethasone-containing tablets at some point in his treatment. However, the dates of administration and duration were not provided. Upon discontinuing his topical steroids, neurological status improved. His cortisol levels and ACTH test 5 months later were normal.

The last case I'll present involves a child who was hospitalized at 15 months of age with Cushing's syndrome. He developed an Abken rash at 5 months of age

and was prescribed clobetasol cream. Treatment was continued without medical supervision for the next 10 months. The parents noticed an increased weight and hypertrichosis for 3 months before his admission. On exam, he was found to be Cushingoid. His morning and evening cortisol levels were low. Following discontinuation of clobetasol, the morning cortisol rose to 2.9 micrograms per deciliter after 12 days and 14.2 after 17 days. A synacthen test was performed 3 weeks after he initially presented, which showed an increase in cortisol response 30 and 60 minutes after an injection. 2 months after initial presentation, he was well, with a decrease in body weight. His examination was unremarkable except for some mild Cushingoid features.

The factors affecting absorption of topical steroids are multifactorial and one or more of these factors were present in many of our cases. One factor is the size of the area being treated. In two cases the topical steroid was used or applied to the entire body, and three cases reported application in more than one location on the body.

Longer duration of treatment is another factor. The duration of treatment was 3 months or longer in 11 cases and over a year in 7 cases.

Increased penetration can occur with the use of

occlusive dressings. An occlusion of a topical steroid by a diaper occurred in 7 cases.

Small children are at increased risk of topical steroid absorption because they have a higher ratio of skin surface to body weight. 40 percent of our cases were in children less than 3 and 5 were in infants.

The site of application may have been a factor in some cases. Penetration of the steroid is related to the thickness of the stratum corneum and the vascular supply to the area. The are regional differences in absorption and the diaper area, which was the site of application in seven cases, has a greater absorption relative to other sites such as the arms and legs. There was also one case where the product was applied to second degree burns which were devoid of epidermis.

Other contributing factors were present in some cases. 15 reported the use of a superpotent or a potent topical corticosteroid product. In four cases, more than one topical corticosteroid product was used simultaneously, and in four cases use of a topical corticosteroid product occurred without medical supervision. Two reported concomitant or prior use of a systemic corticosteroid product.

In summary, there are a small number of post-marketing cases of adrenal suppression, Cushing's syndrome,

and growth retardation given their long marketing history and probable large exposures. This is probably due in part to under-reporting which is a known limitation of spontaneous reporting systems. And as Dr. Temeck had alluded to earlier, there may be a lack of suspicion, including a failure to recognize that topical corticosteroids may be systemically absorbed; an assumption that the adrenal suppression is unusual and therefore routine testing is not done; and that the signs and symptoms may be subtle and nonspecific, therefore attributed to other causes.

DR. CHESNEY: Thank you very much, Dr. Karwoski.

We have 15 minutes on the agenda now for questions from the committee and the consultants for the speakers. Dr. Fink.

DR. FINK: I had several questions. One was how often is decreased growth velocity associated with adrenal suppression, or is that known? Because obviously a clinical marker of adrenal suppression would be much easier to use in reality than just laboratory assessment.

DR. CHESNEY: Were you addressing anyone in particular?

DR. FINK: No. Anyone who has data.

DR. TEMECK: Certainly growth suppression would

be associated with chronic use of steroids, and we're talking here basically about short-term use. The cases, therefore, that Dr. Karwoski was referring to regard misuse of the products because these are really basically labeled for 4 weeks or less. So you would not really expect to see an effect on growth as opposed, for example, if you were treating an asthmatic patient with an inhaled steroid and you would need a long period of treatment, then you would start to see the growth suppression.

DR. FINK: Actually that leads into my second question which is, is anything known about the interaction of topical corticosteroids with inhaled corticosteroids or pulse oral steroid therapy since in these atopic individuals, many of them will have concomitant asthmatic symptoms with chronic low-dose inhaled corticosteroid and will that potentiate the intermittent use of topicals?

DR. TEMECK: You're asking if the patient is on multiple topical inhaled systemic. Yes, you would certainly expect a potentiation of effect.

DR. CHESNEY: Dr. Gorman?

DR. GORMAN: I have another general question which is at the risk of making my nephrology and hematology friends upset because I'll mangle their data. Do we have any idea how much adrenal suppression is necessary before clinical symptomatology becomes available? In the

hematological world, you can use a lot of your particular clotting factors before you see any abnormality in clotting on a clinical basis. Do we have such data? Can you lose 20 percent of your reaction and still have no problems or 40 percent or 80 percent?

DR. TEMECK: Yes. I mean, it's very variable. You can have some patients that may not have as much suppression as another patient and yet they will have symptoms. So there's no specific cutoff value, if you will, of degree of suppression that is associated with symptoms that I'm aware of, unless Dr. Stratakis or Dr. Schneider have information to the contrary.

DR. SCHNEIDER: If I could comment on that. That question might apply more aptly to primary adrenal insufficiency in which there is loss of mineralocorticoid function and patients are much more susceptible to shock and hyperkalemia and so on.

The manifestations of pure secondary glucocorticoid insufficiency are really more protein and may be much more subtle, which is really part of the problem. It's very hard to characterize degree of loss in terms of percent loss of adrenal function in secondary adrenal insufficiency, as well as loss of ACTH function. So I think it's a difficult question.

DR. STRATAKIS: I agree. This is also the

problem with defining the cutoff criterion for the peak stimulation value. Although most people agree that 18 micrograms is what the cutoff criterion should be, at the NIH we usually use anything above 16 as an indication of adequate stimulation. Other people might say that normal is only above 20. So 18 is a nice compromise, but there's no good data as to whether 18 is the actual normal value.

DR. GORMAN: If I can be forgiven a follow-up question. So 18 or 20 or 16 was picked because it's a statistical number that meets some criteria, or does it have a biological analog that's measurable?

DR. STRATAKIS: There are simply no good studies addressing this particular question. It's clinical experience from about 30 years of use of this test now that have defined 18 as the criterion. But as I said, it's a compromise really.

DR. CHESNEY: Dr. Danford.

DR. DANFORD: To follow up on that question about the stimulation test, I have some concerns about whether stimulation testing is valid in the very young infant. I'm picturing how this test is being done. Taking your standard 18-month-old and hauling them off and trying a few times to get some blood or maybe starting a heparin lock might be a stress in itself and may have either predictable or unpredictable effects on either the changes

in cortisol levels you will get or in baseline or response.

I wonder, have control studies been done of normal individuals of that age, performed in the way that these tests might have been done in testing of the dermatologic products to show that this test tells us anything in this group performed in that way?

DR. TEMECK: Yes. I think that there is a significant amount of published data with performance of the cosyntropin test in infants. Certainly if they're going to be stressed, you will expect, therefore, a higher basal cortisol level than you would if you did the test in an unstressed individual. And just the fact that they can elevate their cortisol level, if you have a basal level of 18 or 20, which you can very well get in a crying infant, that certainly is evidence that the patient does not have axis suppression. So, therefore, there are standards in that age group with regard to performance of this test, so it's not really problematic doing this test in young infants. We have sufficient normative data.

I don't know if Dr. Stratakis or Dr. Schneider want to add to that.

DR. CHESNEY: Dr. Stratakis.

DR. STRATAKIS: I'm glad you made the comment. There is an additional factor here that the adrenal cortex does not assume its normal adult configuration until the

end of the first year of life. So we really don't know what the effect of an ACTH stimulation test would be in an incompletely developed adult adrenal cortex. So the adrenal cortex during fetal development has the fetal zone which normally involutes by the end of the first year of life. So unlike mouse, for example, there's continued development of the fetal adrenal cortex into the adult adrenal cortex for the first year of life. It finishes by 18 months or so.

So we really don't know. There are really no good studies on addressing what ACTH does to cortisol secretion in a continuously developing adrenal cortex and on an involuting fetal adrenal cortex. We certainly don't know what the effects are of exogenous steroids on a developing adrenal cortex.

DR. CHESNEY: Dr. Glode, did you have a question?

DR. GLODE: I did. I just wanted to ask Dr. Temeck if you thought there was any possibility of identifying a surrogate marker that would be easier to measure than the stimulation test. I wondered about if you had someone of these drugs for 3 or 4 weeks, that you could monitor, that would say it's being absorbed and this is the surrogate marker for suppression like a total lymphocyte count or a total eosinophil count or a CD4 or CD8 or

something. Is there anything that anybody has looked at that might just be --

DR. TEMECK: I'm not aware of a surrogate marker.

DR. SCHNEIDER: I can just say as an endocrinologist, I'm not either aware. The best tests are the biochemical tests that we have, and I think that they're pretty good. We know a lot about them and what they correlate with at this point.

DR. GLODE: But it just seems that they would be potentially more cumbersome to use. I'm in infectious disease. If we have someone on an antibiotic for 4 weeks, we do a weekly CBC, a weekly BUN, creatinine, a urinalysis and that's our markers for interstitial nephritis and bone marrow maturation arrest, and they're easy to measure and it's a simple blood test. It's just nice to have instead. The stimulation test is pretty. It can't be done in the dermatologist office, for example, I don't think. Or is it?

DR. SCHNEIDER: It could be done in the dermatologist's office.

DR. GLODE: Oh, is it done in a dermatologist's office?

DR. SCHNEIDER: An ACTH stim test can done practically anywhere at any time of the day, and so that's

of great usefulness. Of course, also the cortisol assay is excellent at this point. So we have a lot of data in support of it.

The question is, what do we do with the information? Whom do we test and so on? This will come out later in the discussion.

DR. TEMECK: Just to add to that, you could do a simple 8:00 a.m. basal cortisol level and certainly, as I said, if it's elevated, then you're okay. You don't have to do a dynamic test like the cosyntropin test. But unfortunately, many times that's not the case.

I don't know. Dr. Stratakis, did you want to add further to the response to this question?

DR. STRATAKIS: No. I think the comment was appropriate.

DR. TEMECK: It's adequately covered?

DR. STRATAKIS: Yes.

DR. CHESNEY: I have Dr. Epps and Dr. Santana, and then I had a question.

DR. EPPS: One quick comment. Dermatologists aren't going to do stimulation tests.

(Laughter.)

DR. EPPS: My questions were regarding the adverse event reporting. Some of the adverse events can occur regardless of the medication. For example,

hypopigmentation can be post-inflammatory. Some people have stinging or redness regardless of what is applied. Even bath water can make you sting. So I guess my question -- two of them. One is regarding is there any estimation of the real numbers that really are due to the medications.

I think the cases that were presented clearly were secondary to inappropriate use. I think the ages were inappropriate, the amount of medication was inappropriate. The body surface area, the location. I wasn't really surprised that side effects could have occurred with those extreme cases. But a lot of the other ones are hard to determine because the underlying condition can result in stinging and redness and some of the things that were reported.

Also, is there a way to differentiate when things are reported as an adverse event whether it's due to the medication or the use, or is that broken down?

DR. KARWOSKI: I think your first question was could we tell exactly how many reports there actually are. No, I don't think so. It's been estimated that the FDA receives somewhere between 1 to 30 percent of adverse event reports, but there's just really no way of knowing what we're receiving. I think what we do have is probably the worst cases where there was clear recognition of symptoms.

As far as causality goes, we can never be

totally clear that it was attributable to the actual product. It becomes even less clear when there are confounding factors such as use of systemic products, but for many of the cases, I think it was relatively clear that it the use of the topical steroid, and as you stated, it was an overuse or misuse of the products in these cases.

DR. CHESNEY: Dr. Santana.

DR. SANTANA: I have two questions for you, Dr. Temeck, and Dr. Cook can help me. It appeared to me in looking at the data that was presented on the pediatric studies, that the majority of patients recovered HPA function when these products were used in the quasi-acute setting, that is, for a defined period of time of 3 or 4 weeks. But I think in reality we know that these products are used repeatedly in many patients who have exacerbations over long periods of time. So is there any data on the incremental risk of suppression with intermittent chronic use? That's one question.

And then the second question is, when do you test for the first time? These patients were all tested within 3 to 4 weeks, but I got no sense, based on the data. If you could give us some indication of when would be an appropriate recommendation to test these patients.

DR. COOK: I'll answer the second question first. That's probably why we're having the advisory

committee meeting.

(Laughter.)

DR. COOK: Because that is a question about when is the appropriate time to test these patients who obviously have a chronic remitting and relapsing disease.

In the second question where I think you -- remind me of the second question.

DR. SANTANA: Is there an incremental suppression risk when you do repeated therapy intermittently over months or over years?

DR. COOK: We don't have data for that. These are the trials that we were able to convince the sponsors to do on a short-term basis. But we do actually have a question as to what does happen even with chronic intermittent suppression of the adrenal gland. Is it a problem? We don't really know. Dr. Temeck was stating how you need long-term use before you get actual growth suppression with adrenal suppression to get growth suppression, and the question is, is there a problem and can you get growth suppression over long-term intermittent use of topical corticosteroids for years? And we just don't have that answer.

DR. CHESNEY: Dr. Wilkin.

DR. WILKIN: Dr. Cook may actually have more information on this. But it's been my recollection in the

data sets that have come to our division that we always like the HPA axis suppression tests done during drug development on the higher body surface area children, and as a consequence those kids are very likely to have had their atopic dermatitis for a substantial period of time. It's not uncommon for us to see kids who at baseline, that is, before they actually get treated with the corticosteroid that's being tested, that they're already suppressed. They have the signals of suppression at baseline. So I think we have some hint of that, but we have nothing very quantitative that we could say after X number of months of intermittent use.

DR. CHESNEY: Good point.

Dr. Wilfond.

DR. WILFOND: I have two questions that are related to sort of a benefit-risk ratio. We've been focusing mostly on risks, and I have a couple questions about benefits.

My first question really has to do with whether or not -- it's part of a dermatologic question -- early and aggressive use of some drug could actually change the course of atopic dermatitis, in particular, whether there's any additional efficacy even from systemic steroids in that regard.

My second question, which is more of a labeling

question, is that in the more recent products that have been labeled to be fairly restrictive of being only used in adults or older children, is the purpose of that because it's believed that it's not appropriate to use that in young children or just that there's an interest in not having the companies aggressively marketing that for young children? I'm not clear about that.

DR. CHESNEY: Dr. Wilkin.

DR. WILKIN: I'll pick up on your second question. That's right. We've really tried to achieve some balance in labeling. What we've done in the indications section is we will say something like indicated for age 13 and above. That's not the same thing as contraindicated in 12 and under. And then there will be the pediatrics use section and precautions, and it will describe the material that you've seen generally in our labeling that speaks to HPA axis suppression. Because we recognize that dermatologists and pediatricians and other clinicians from time to time will make wise clinical choices to use these products outside of the 13 to above. So I think we're trying to hit a fine line on that.

DR. MURPHY: Let me just say that you brought up a subject which is very difficult because the one thing you do not want to do is to de facto give an indication when you don't want to give an indication. In pediatrics,

we are constantly in this balancing act. If you talk to our marketing people and other policy people, we shouldn't be putting anything in the label if they don't have any indication. In other words, we haven't proved it's safe and efficacious.

There are times when we say it's been proven to be efficacious but here are the restrictions because of the safety issue. There are other times when it has not been proven to be efficacious. We know people are using it, and we're trying to put safety information in there.

There are a variety of situations that arise, but you don't want to be giving the indication because you're putting information in the label. That's the problem. Yet, at the same time, you're trying to achieve that communication of what the safety issues are. So it is often very difficult to balance that.

DR. CHESNEY: I think Dr. Fost wanted to comment on the same issue and, Dr. Andrews, I think maybe you had your hand up.

DR. FOST: Well, a couple questions on the same issue. First, I'd be interested in hearing from the dermatologists how much of this problem is due to inappropriate use of the more potent steroids. That is, is that sort of the general practice now not among obviously excellent dermatologists but among pediatricians or others

who are taking care of these children? Is there an overuse of the more potent classes?

Second, what do we know about the marketing, particularly CME activities, and distribution of samples that's pushing that? That is, how much of this problem is due to inappropriate use of excessively potent steroids? How many of these children could be well cared for with less potent uses and how much of that is being driven by CME or other marketing efforts?

DR. CHESNEY: No one wants to answer that.

(Laughter.)

DR. RAIMER: I will. I think that the pediatricians are almost overly cautious with topical steroids, so I don't think it's the pediatricians who are using the high potency steroids. If you look at the reports, several of these are foreign reports, and one of them where steroids are more available over the counter. Mothers can get them and use them inappropriately. So dermatologists I don't think are using high or super potent steroids in young children very often, and I don't think it's the pediatricians. So I don't think it's being done terribly often in the United States, frankly.

DR. COOK: I'll just make a quick comment just from the study data that was presented. I just want to make the point that it's not all super potent topical

corticosteroids. As I pointed out, there are steroids in class V that also can cause significant adrenal suppression.

In these studies, at least -- I can't speak for how people practice -- most of the topical corticosteroids are going to be used for 1 to 2 weeks, 2 weeks to 3 weeks. In the studies, most of them were used for 2 weeks. I tried to point out that children still had some disease left for some of the drugs that were used because these weren't efficacy studies, of course. They still had some evidence of adrenal suppression with appropriate use of a topical corticosteroid.

So the question is not just those who we know the drug is being abused, and that answer is very easy. It's what do we do with those who are using it appropriately and are getting intermittently suppressed.

DR. CHESNEY: Dr. Andrews, and then I think Dr. Schneider has his hand up, and then Dr. Gorman. Dr. Andrews.

DR. ANDREWS: My question is really in follow-up to the question about what do we know about actual use patterns for these drugs? Evidently they are used repeatedly. And what do we know about recovery of adrenal function following repeat suppression? And maybe we don't know it for these particular drugs, but I wonder if there

are some analogies from patients with inhaled steroids for asthma. It may be a question for Dr. Schneider.

DR. SCHNEIDER: I'd just like to make a comment. If you look at this quantitatively, it seems to me that if you're giving, let's say, 50 grams of a preparation which is .something percent active ingredient, but if it's a very highly potent steroid, you're giving maybe several hundred milligrams of that steroid over a small period of time. Now, we really don't know what percent of that material gets systemically absorbed in patients with active skin diseases. We suspect, of course, that it's higher than in patients who have intact skin. If you just sort of look at this quantitatively, much of this suppression of the HPA axis is entirely predictable on the basis of the pharmacokinetics. For example, you can suppress the entire axis with a milligram of dexamethasone given by mouth at night. It's a common dex suppression test. So that it's not surprising to me that there is this degree of HPA axis suppression as evidenced biochemically. Of course, our task later on will be to figure out what to do about this and how to label for it. But it's clear that there is a high prevalence of axis suppression, and it seems to me that this is quite predictable and it shouldn't be surprising.

I had one question and that has to do with the

language used to describe recovery. I see over and over and over again in these labels, in general HPA axis suppression recovers promptly. I see the word "promptly" over and over and over again and with data, 2 out of 3 recovered, 1 out of 4 recovered or didn't recover and so on.

What this really means, of course, is that the patients recovered responsiveness to exogenous ACTH 1 to 24 stimulation. That doesn't mean that the entire axis has recovered, and it certainly doesn't mean that the patient would respond appropriately to stress. Has anyone looked at that? Has anyone done further examinations of patients who have recovered to 1 to 24 stimulation to see if they can respond to material pollen or ITT?

DR. COOK: I'm not aware of any such studies. In these studies, they were just required to follow the patients out until they had an appropriate response to cosyntropin. Actually the data, as I showed it, we really didn't get all of the patients retested either due to lost to follow-up or a discrepancy in the criterion of what really constituted adrenal suppression. So that's what we have.

DR. SCHNEIDER: So accordingly, these patients would still be vulnerable during stress of surgery or accidents or whatever, at least according to generally

acceptable practice in the adult population.

DR. COOK: If they have a normal response to ACTH, then you would assume that they could respond appropriately.

DR. SCHNEIDER: You can't assume that in all patients.

DR. COOK: Therein lies the problem.

DR. SCHNEIDER: Right.

DR. CHESNEY: Dr. Gorman, Dr. Ten Have, Dr. Fink and myself have questions, but I don't know that we answered Dr. Andrews' question which I think was what about recovery after repeated insults, another example of which would be asthma. Does anybody have an answer to that? Dr. Fink.

DR. FINK: Well, with asthma, it's definitely clear that with repeated pulses of oral steroids, if they are closer together than 4 to 6 weeks, you will get a cumulative effect on adrenal suppression, but that's really oral corticosteroids with a 4- to 6-week break. It's less clear with inhaled corticosteroids.

DR. CHESNEY: So you do get a cumulative suppression. I mean, you're not just suppressed with each episode, but each one is additive to an overall suppression?

DR. FINK: You're more likely to see

suppression in a child who's had multiple courses of oral corticosteroids separated by less than 4 to 6 weeks. Probably once you get beyond about 8 weeks, you're safe or you appear to be clinically safe.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: This is a question to the FDA. The classification of steroids in my simple clinical head deals with how effective are. And now I know they're generated by this vasoconstrictive test. Is there any consideration being given to creating another scale of the risks or the TPA suppression? Because the data showed pretty elegantly this morning that the classes of steroids don't correlate with their TPA suppression. So there may need to be a new rating of steroids, topically or orally, that deal with what their risk of suppression is as well as their potential for efficacy.

DR. WILKIN: Well, if we could achieve that, I think it would truly be wonderful. I think one of the difficulties -- and maybe I should just speak to the classification. It really isn't a classification about the corticosteroid moiety. It's really about the product because you can have an individual moiety that can be in a different class based on its concentration or the vehicle in which it is presented. Because there is so much noise in extracting this signal of HPA axis suppression, I would

think that there would really have to be a whole series of head-to-head studies literally of steroid A versus steroid B to really figure out what the groupings might be.

You have seen the numbers. Many of the HPA axis suppression testing are in numbers that are sufficiently small that the confidence intervals are somewhat difficult for us to say this has a precise eventual risk estimate at 4 weeks of, say, 40 percent of the population is going to be suppressed. We have the confidence interval problem plus we have a lot of different body surface areas of involvement, different frequencies of use. I think the quantitative aspects of this -- it would be nice if we could do that. I just think it's close to insurmountable unless we had really large numbers and head-to-head studies.

DR. CHESNEY: Dr. Ten Have?

DR. TEN HAVE: I have two epidemiological questions, one for Dr. Cook regarding whether or not we can use the age trend data to provide us any hints of any long-term effects of cumulative use of corticosteroids. I noticed you had consistent downward trends across age, and if these post-infant children are using steroids cumulatively, would you expect an increase across age if there was a long-term cumulative effect?

DR. COOK: I'm not sure I know the answer to

that. Even though in the betamethasones, it showed that there was an increased proportion of children who became suppressed the younger they were -- so I guess the natural progression is you would think that there may be some effect over time in those children -- it didn't seem to be the case for all of the drugs. That's part of our problem. When we saw the statistical analysis, it also didn't necessarily bear it out.

DR. MURPHY: Just to follow up on that, I think the thing that is interesting is when you look at the data for the tinea pedis. These are adolescents. Of course, you had the lotion issue that you need to consider, but we felt we had some confounding information here, that certainly in one area it looks like you have this trend, but overall, when you look at this data, we didn't feel as comfortable that you could make those sort assessments.

DR. CHESNEY: Dr. Ten Have, you had another question.

DR. TEN HAVE: Yes. I'm sorry. I didn't quite understand your answer. In adolescents there's a --

DR. MURPHY: There was a high percentage of suppression, yes, a 60 percent I believe in one of the slides. Denise, is that right? 47, yes. So, again, when you took that adolescent group and looked at it, you got a different type of answer. There are other issues there,

but I'm just saying it didn't look quite as clear as it did with the one product.

DR. TEN HAVE: Thank you.

The second question I had was for Dr. Karwoski. I'm wondering if we can get anything from the -- even though we had a small sample of reports of adverse events in terms of adrenal suppression, in that registry data we had, I think it was, about 42 cases, but the timing of those reports was interesting in table 10 where you had data going all the way back to 1980 with I believe 2 cases in 1980 and '81 and then the real cluster of cases starting in 1995, about, prior to the introduction of the AERS reporting system. I'm wondering if we can get anything from that in terms of whether or not there's a corresponding increase in corticosteroid use for atopic dermatitis.

DR. KARWOSKI: Unfortunately, we didn't actually look at the drug use data, so we didn't actually look at trends over time. But we do know that reporting has increased over time, so that could account for just the increased number of reports that we've gotten after 1985 or whenever it was.

DR. CHESNEY: I think Dr. Mattison was next on our list.

DR. MATTISON: Two questions. I think the

first may have already been answered. I'm confused about actual use by age and given especially that the products are available both over the counter and by prescription.

But the second thing that I'd appreciate some information on is efficacy. When we talk about characterizing risk, it's also helpful, I think, to understand efficacy and benefit. So if there could be some description of that, and perhaps that will come in the discussion of risk and benefit later in the day.

DR. COOK: Well, on the issue of efficacy, I think topical corticosteroids have shown over the decades that they're quite efficacious in treating atopic dermatitis. As far as the potency of the drug, according to the vasoconstrictor assay, as far as efficacy, I think that you can rely on that scale and the amount of efficacy you're going to get for a given severity of the disease. Like the class V lotion product, for example, is not as efficacious in moderate to severe atopic dermatitis as, say, clobetasol which is in class I. That may have something to do with the fact that the chemical moiety doesn't stay in the epidermis as long and somehow gets into the systemic circulation. That has been a thought since we got this new data. But the drugs are highly efficacious in treating atopic dermatitis over short periods of time in getting the disease under control.

DR. CHESNEY: I think we'll plan to take a break in 5 minutes. So I have two more people on the list. Dr. Schneider and Dr. Wilfond.

DR. SCHNEIDER: I may have missed this, but have you redone the statistics, the correlation statistics, using the single criterion of 18? And do the data look any different at all or any cleaner or not?

DR. COOK: Well, I only looked at it for the betamethasone products. I showed that chart there. Even though we used three criteria, I looked at the 18, and as you saw, it was pretty consistent with using the three criteria. And if you look through each one, I tried to point out even though that the failure of one would do it, most of the ones who suppressed did have a cortisol level that was less than 18.

DR. CHESNEY: Dr. Wilfond.

DR. WILFOND: I also have a question for Dr. Cook that's related to what Dr. Mattison asked also. It's not so much efficacy only but just the efficacy-risk balance. I just want to clarify. I'm assuming that the reason why these drugs are used is that even though there are side effects, it's viewed that the benefits far outweigh the side effects in some circumstances. Like in chemotherapy there are horrible side effects, but we still think it's appropriate to use them because the benefits are

substantial and necessary. That's why I just want to clarify that because this may be less of an issue if we actually think that these are really necessary interventions.

DR. COOK: Well, yes. I don't think we're here to advocate that topical corticosteroids not be used in atopic dermatitis. It's just that we discovered that something else is going on and we're trying to get a handle on what's the best way to make physicians and the public aware that there is this potential and that there may be a need for something to be done on the short term.

DR. CHESNEY: Dr. Wilkin.

DR. WILKIN: Yes, I agree with Dr. Cook's response and would just add to it. Of course, these topical corticosteroids are not curing. They're suppressing. I think there's a lot of information especially in the dermatologic literature and the guidelines that the AAD, the American Academy of Dermatology, has.

The goal of therapy is to treat early and, if there's a lot of inflammation, to use something towards the upper end of potency to achieve control, and then fairly rapidly move to things that are lower down or even drop off the corticosteroid list and maybe go with moisturizers. A dermatologist doesn't just offer corticosteroids to the

patient with atopic dermatitis. They talk about the soaps that they're using and a variety of other things, the humidity in the bedroom, which is where one spends one-third of the time as a child.

So I think that yes, it really does fit very well with a good risk-benefit calculus. These products are really safe and efficacious when used appropriately.

DR. CHESNEY: One last question before the break. Dr. Ebert.

DR. EBERT: I think you kind of touched on my question which is it appears that when these agents are used, they are used in a fixed dose and in a fixed frequency throughout the course. Is there ever the determination that you might want to use these drugs similar to what you might do with a systemic steroid in a more aggressive manner early and then taper and use it, say, as a once-a-day administration over a longer period of time, whether that might be a means to reduce some of the effect that you're seeing on the HPA axis.

DR. WILKIN: Well, there are actually two committee members that are in the trenches and actually do these sorts of things, and they probably want to comment. But certainly that point of view is well established in the dermatologic literature, that one wants to get on top of the situation promptly, so it's treat as soon as possible.

Sometimes that means even giving a patient an early clinic visit or some other arrangement to ensure prompt treatment.

DR. CHESNEY: I think we will take a 15-minute break now, and if everybody could reconvene at 11 o'clock, we'll move on to the second part of the morning's program.

(Recess.)

DR. CHESNEY: Our next speaker is Dr. Anne Trontell. Dr. Trontell is the Deputy Director of the FDA Office of Drug Safety. She's a pediatrician and an epidemiologist with experience working at the CDC and HCFA/CMS. She will present a framework for risk assessment and management.

DR. TRONTELL: Good morning. I'm going to be giving what might be lightly termed some risk management 101. This will really reflect FDA's experience to date with risk management programs across a broad array of drug products. I'll also be touching upon the risk management practices that are currently under development within the agency.

It should come as no surprise that FDA has been involved in risk management for many years. We simply haven't been using that term. As part of our approval of drug products, we weigh risks relative to benefits.

It was in 1999 when the FDA Commissioner issued the Report on Managing the Risks of Medical Products, that

the term "risk management" came into widespread use within the agency.

It was under PDUFA3 that FDA's role in risk management became formalized when the agency was called upon to develop three interrelated guidances for industry on risk management and to do so by September 30th next year. The topics for these three guidances included pre-marketing risk assessment, post-marketing risk assessment through pharmacovigilance or pharmacoepidemiology, and the third, risk management per se. In that capacity, I'm privileged to serve as the chair of the joint working group between the Center for Drugs and the Center for Biologics to develop that guidance, and some of my remarks will be based upon some of that work.

FDA developed some preliminary concepts about risk management for each of these three topic areas and published them and then presented them in a public forum in April of this year. This was as concept papers and the opportunity was used to solicit comments at that meeting and subsequently. Based upon those concept papers and the commentary that was received, FDA expects to issue draft guidances later this fall.

In this presentation, I'm going to focus on FDA's experience with risk management in a wide variety of drug products. I will draw upon some of the concepts that

were articulated in the concept paper entitled Risk Management Programs, but I need to remind you that as such I'm talking about a snapshot of what is truly a very rapidly evolving field and approach to drug safety.

The Risk Management Programs concept paper focuses on risk minimization efforts. These efforts were termed risk management programs in the concept paper issued in the spring. The risks that we discussed and the minimization efforts are, in fact, identified using practices outlined in the other two concept papers dealing with risk assessment in the pre-marketing and in the post-marketing arena.

The concept paper indicates and reminds all that safety in some sense is relative, that when FDA determines that a product is safe and effective, it means that the beneficial actions outweigh the likelihood of harmful or undesirable side effects and shouldn't be construed to mean that risks are absent.

Turning now to some of the definitions that we established in the concept paper on risk management programs, we defined them as being strategic safety efforts that involve an effort to reduce risk and having at least one or more risk reduction goals and the use of one or more interventions, sometimes called tools, other than the package insert to reduce risk. The package insert may be

known to you by many different names, sometimes called the PI or the professional labeling, sometimes known as the FDA-approved labeling. This has really been the cornerstone of industry and the FDA in speaking to clinicians and to the public about the safe and effective use of drug products. These were considered not to be risk management programs per se.

To define the goals of a risk management program, the concept paper stated that these would be tailored to the specific risk concerns and that they would describe the ideal product use scenario or the desired end result of the risk management program. Borrowing from the management literature, you might use a term such as a "vision statement" to refer to it where you would look for the optimal drug use scenario. Examples probably are better illustrative than the definitions. In the case of thalidomide, a known teratogen, one goal might be stated as no fetal exposures, or for the drug product clozapine, no agranulocytosis.

The concept paper attempted to address when a risk management program might be appropriate. It said certainly in terms of timing, that this could occur at any point in the product's life cycle when a risk reduction need emerged. So it could occur pre-marketing or post-marketing. This could be done at the initiation of the

drug company or upon FDA's suggestion. The language stated in the concept paper was: "when the number or severity of a product's risks appears to undermine the magnitude of benefits in an important segment of actual or potential users."

The challenges, however, to determine exactly when that point might occur -- and the concept paper indicated this was a complex task. There is clearly no simple formula that will compare risks to benefits. These are measured in different units and there are different types, so that the best FDA could state, at least in the concept paper, was that they anticipated that this would be a matter of case-by-case judgments done jointly by the drug company/sponsor, as well as FDA, on whether or not a risk management should be developed, submitted, or implemented.

We did state, however, in our concept paper that our mainstay of risk communication, the package insert, would probably suffice for the vast majority of products, so that formal risk management programs are, in fact, things that we expect to apply to a limited number of drug products.

To define risk management program tools a little further, these were defined as processes or systems intended to enhance the safe use of a product by reducing risk, and the choice of tools would be influenced by the

severity, reversibility, or rate of the risk that was being avoided.

I'll now turn to some discussion of FDA's experience in various types of tools which we've put into three broad categories with probably some fuzzy boundaries, the first being education and outreach; the second, so-called guiding systems, which I'll elaborate upon; and the third category being restricted access programs.

Education and outreach, as defined in a risk management program context in this concept paper published to date describes those efforts again that go beyond the package insert that's traditionally used. These might, for example, entail the mailing of Dear Healthcare Practitioner letters or other public notices of risks. It could include training programs or continuing education and may, in fact, use various forms of patient-oriented labeling, such as medication guides and patient package inserts, which I'll now elaborate upon.

Medication guides are one form of FDA-approved patient labeling regulated since 1999 under the federal regulation described here. Medication guides are distinctive in that they are required to be dispensed with each prescription to a patient, most commonly by the pharmacist, but this can also be done by the physician.

These were intended primarily for outpatient

drug products that could pose serious and significant public health concerns, and at the time that this authorization was passed, it was anticipated that about 5 or 10 products a year might fall into this category.

There are now approximately 13 medication guide texts concerning again approximately 22 products. It depends on if you're a lumper or a splitter in your counting. The risks that they cover are wide. They include but are not limited to hepatotoxicity, teratogenicity, abuse and diversion, or overdose.

The text of this slide may not be well legible, but this lists the 13 broad categories. I have a second slide that lists those where pediatric safety or exposure concerns were part of the contents of the medication guide or in some instances some of the motivating reasons for their being written. The committee has been given a copy of a sample medication guide which they may wish to refer to since I'm going to walk through some of the specifics of it in a minute.

Back to the medication guides requirements. Since this is to be used in a judicious manner, three triggering criteria were set forth in federal regulation, at least one of which needed to be met, the first being that patient labeling in fact could make a difference in preventing the occurrence of serious adverse events. The

second was that there might, in fact, be serious risks relative to benefits about which a patient should be informed in terms of making an informed decision about whether to initiate or continue use of that product. And the third criterion was instances where patient adherence to the directions for use of the product were considered crucial to the product's effectiveness for a serious or life-threatening condition. And the medication guide regulations in fact go so far as to describe the content areas and format for this material, as well as even the font size that should be employed.

I'll go through this quickly. If you wish to refer to the example, please do. Basically the medication guide follows something known to many of us who use the internet, the frequently asked questions format. So after describing the title, brand name, and established name, it starts with a bolded topic sentence saying, well, what is the most important information I should know about this product. This is typically the section of the medication guide that describes the health concern that in fact prompted the medication guide being issued.

Subsequent sections will talk about what is the drug where we typically then take the indications and disease states that are associated with that drug product and describe them in lay terms.

Contraindications are again expressed in lay language in the section that says who should not take the drug product.

Then a subsequent section, how should I take the drug, is where dosing instructions are typically found.

Precautions or special population concerns are addressed in the section which says what should I avoid while taking the drug product.

Side effects and general information on safe and effective use are also included.

Another form of FDA-approved patient labeling is patient package inserts. These, in the case of estrogen-containing products, are in fact required to be distributed, under a different federal regulation. In some instances, these patient package inserts are being used as the basis for the brief summary in direct-to-consumer advertisements, and in that case again, they're subject to our oversight under regulation.

These days, in fact, the distinction between patient package inserts and medication guides may be somewhat artificial. Many of the patient package inserts now in fact follow the medication guide. That's the agency's recommendation since we know that has been generally well accepted, and we would like to promote consistency in FDA-approved patient labeling.

In instances were products are packaged in unit-of-use packaging with the PPI included, these may operate quite similarly to medication guides in that each patient would receive one with every prescription. But just to be quite clear, the distinction really relates to this requirement on whether or not the product needs to be accompanied by this patient information. Medication guides are required. PPIs are optional with the exception of the estrogen products.

The other thing to bear in mind, if generic products exist or are anticipated, the requirements for a medication guide readily transfer to the generic products from the innovator.

Turning now to the second broad category of tools, those that may guide prescribing, dispensing and use. The purpose of these tools are really to assist individuals in following what are considered to be appropriate prescribing and use practices. Alternatively stated, they're really designed to make it difficult for individuals to forget important safety processes or precautions. A variety of reminders or prompts may be used in these systems, as we've described them.

One example may include patient agreements where a patient is given information about the product, its risks, and the patient signs that to assure communication

and education has occurred. In some instances, practitioner certification has been required. In other instances, special conditions have been attached to the dispensing of the product or in some instances the packaging. Packaging may be constrained in a certain way. There may be a limitation on the supply allowed at any one time or refills may be barred for certain products. In some instances, certain pharmacy checking mechanisms have been put into place to assure that appropriate prescribing is done, and I'll give you a few examples that may make this clearer.

Lindane may be a useful example of special packaging. Earlier this year, this product's labeling was modified, and at that time the volume that was available to any patient was reduced to being either 1 or 2 ounce aliquots. This was done out of concern for seizures and deaths that had been reported to the agency on occasions where individuals had used this product excessively or reapplied it.

Some additional guiding systems were used with Lindane. The package insert, the cornerstone of risk management for the agency, was in fact revised to include a boxed warning about its second-line use and about concerns for its reuse, as well as highlighting the risk to children and to individuals of low body weight. A medication guide

was issued for Lindane, and that's in fact the example we've provided to the committee. It instructs about the risks and how to use the product appropriately.

Also the FDA issued a public health advisory to make these changes salient to practitioners and to patients.

Two other products with guiding systems are alosetron and isotretinoin. Very broadly stated, each of these have a patient agreement that's to be signed, and in each instance, the physician is asked to attest to having either necessary knowledge to prescribe the product or test the patient. This attestation is the mechanism whereby that clinician obtains stickers which are then placed on the prescription itself. Those stickers are to be used to indicate in fact that, depending on the product, the physician has the necessary expertise or has made the appropriate decisions in selecting the patient for this therapy, or in some instances, that the physician has done the appropriate testing to make sure the product is being safely used.

When the patient takes these prescriptions to the pharmacist, the pharmacist is asked to check for the presence of this sticker to make sure in fact that all the safe conditions of prescribing have been followed.

Turning now to the last category of tools, at

least as we have categorized them, they are those that we call restricted access systems. These are systems that link drug product access to compliance with risk management program elements. And for those of you who know the drug product clozapine, a pharmacist is not allowed to dispense that to a patient unless in fact they're presented with a CBC indicating an adequate white count. The moniker for that is "no blood, no drug."

In these restricted access programs, typically prescribing and dispensing is limited to a select population of clinicians and pharmacists. In some instances they require documentation of safe use conditions as in the case of clozapine producing a laboratory test result before the product can be dispensed to the patient.

An example of a restricted access program is the drug product thalidomide, which has the system for a thalidomide education and prescribing safety, abbreviated STEPS. I'm presenting only a portion of what's a complex system, but just to hit some of the key features, this product thalidomide is only shipped to registered pharmacists and those pharmacists are only to dispense thalidomide to patients who are registered and who have prescriptions from registered physicians. There is a central authorization process where information is centrally placed from both the provider and from the

patient to assure that the woman is not pregnant at the time that she receives her prescription.

Turning back to our concept paper, FDA set forth several considerations to industry and to itself in terms of how tools might be selected or put together in a risk management program. One important consideration was to seek input from stakeholders on the feasibility and acceptability of tools that are proposed for use. So this would certainly, at a minimum, include prescribers, pharmacists, patients, and third-party payors, as well as probably many others.

The FDA also stated the value of seeking consistency and using risk management tools that were already in existence and had documented acceptance, the idea being we wanted to avoid confusion and burden on the medical system by creating numerous customized programs.

FDA also stated value in using tools that had been documented to be effective in the past either in a similar drug product or in a similarly related health objective.

Public comments to FDA were generally supportive. We were reminded of the importance of preserving patient access to benefits in the discussion of risks, and also again asked to be sure to seek to avoid confusion and burden to the medical care sector and to

pharmacy practice by creating multiple customized programs.

FDA in its concept paper had one additional important point that it feels is a substantial departure from its practices to date which was the importance of measuring the effectiveness of a risk management program as developed, and that was to assure in fact that the program is effective and that its tools add value in achieving its stated goals. To that end, FDA recommendedm wherever possiblem to look at the health outcomes of interest to see if in fact there's a change in their occurrence or to go to the next best available surrogate for that health outcome. The intent of gathering information on the effectiveness of programs was to allow modification of these programs, perhaps either to make them more stringent or more lenient, as the case may call for based upon the data.

Evaluation can take many forms. I won't elaborate on that here. There is some overlap with other concept papers, in particular, the one addressing pharmacovigilance and pharmacoepidemiology, if evaluation is to take some form of active surveillance for outcomes or adverse events.

So let me summarize our experience to date with risk management programs at FDA and as we are developing guidance on this topic. Risk management programs are intended in FDA's mind to be applied sparingly and are

intended to be used to minimize identified drug risks. These risk management programs should be goal-oriented and should use tools that are commensurate with the risks and benefits of the products, and that any program, if instituted, should consider evaluation to assure effectiveness in achieving its stated goals.

Let me give you again a quick digest of the three broad categories of tools that I've presented, the first category being education and outreach. It probably comes as no surprise to many of you education and outreach can take many forms. There can be general information or highly targeted information. This has been applied to many drugs, probably more than we would be able to count in terms of the amount of information that has been issued in the form of brochures. Certainly over the years, the agency and drug company/sponsors have issued many Dear Healthcare Practitioner letters.

This category of tools based on our feedback and experience is perceived by many to be limited in terms of how intrusive they are upon conventional prescribing, dispensing, and use of drug products. Data on the effectiveness of these educational interventions are in fact limited, and some data that have been collected to look at changes in physician behavior in response to Dear Healthcare Practitioner letters and labeling changes have,

in fact, shown quite mixed results in terms of limited or small changes in response to these forms of education.

The second category of tools, what I abbreviated as guiding systems, are used on a more limited number of products. I can't give you an exact number, but we're probably talking tens or twenties of products. These are perceived to be somewhat moderately intrusive on conventional prescribing, dispensing, and use. To date, we actually don't have within the agency any evidence on the effectiveness of these programs, but evaluations are in fact planned for the two drug products with sticker programs that I described to you in my presentation.

Turning to the last category of restricted access systems which in the definition I used really have a very tight linkage between release of the product and compliance with risk management processes, we in fact have probably the smallest number of drug products that fall in this category. My count is about six or seven products. These have to date largely been applied for products where the condition has limited therapeutic alternatives and where in fact may be limited options for those people, and the products themselves in fact pose significant risks. As such, the user populations for this very restricted category of drug products is typically small. These systems, not surprisingly, are perceived as being the most

restrictive on prescribing, dispensing, and use. The name in fact tells you they do restrict access.

Those systems that register all the components, patients, providers, pharmacists, in fact give us some of the best data that we have in terms of effectiveness, and it is encouraging the data that the agency has received do support their effectiveness in risk minimization, again within these very specialized populations to which they've been applied. But there is other information as well that suggests that the imposition of such systems may, in fact, limit product uptake or slow product uptake or in some instances may lead to substitution of alternative drug products, sometimes with unintended consequences if those substitutions may themselves impose risks.

This committee will be considering today and tomorrow, as Dr. Murphy indicated, two broad categories of drug products that are often used for the same indication, and decisions made in fact relative to one class of drug products may have impacts on how that other class of drug products is also used.

Thank you.

DR. CHESNEY: Thank you very much.

Are there questions for Dr. Trontell while she's still at the podium?

(No response.)

DR. CHESNEY: I have one. You mentioned early on that the real challenges to determine when the need for an RMP is appropriate. Could you give us maybe just a little bit of the thought process behind when you decided that you had to put restricted access on that very small number of drugs? It seems intuitively obvious, but there must have been a whole process behind doing this for thalidomide, say, or the other five drugs.

DR. TRONTELL: It's sometimes difficult to talk about our rationale because the agency truthfully is learning in the process of executing these programs and there is some history of time over which those restricted access programs have been developed.

My own interpretation, which won't necessarily reflect the historical record, is that again these have been instances where the agency may have, in some instances, felt it had little choice in terms of approving the drug product without some severe restrictions because of the magnitude of the public health risk that was seen. In the case of clozapine, the rate of agranulocytosis in clinical trials was in fact quite high. So the concern was that this product represented a meaningful therapeutic alternative for patients who might have been refractory to other forms of antipsychotic therapy. So it was approved with conditions around the manner in which it would be

used. It had second-line use and this attempted to look at the rate of agranulocytosis.

I think probably the next major significant restricted distribution system to come out of the agency was the one involving thalidomide where clearly there's a long history and very high concern about the risk of pregnancy exposures to that drug product. In fact, that system and its clarity in terms of its goals informed some of our decisions and thinking about the concept paper. The goal was very clearly articulated with that product given its history of previous use that they wanted to design a system that would avoid, at all possible costs, the risk of fetal exposures in recognition, however, that there was a strong cry within the medical community for this product for certain indications.

So they've tended to be decided by the agency on a case-by-case basis. In fact, we still are largely making these decisions on a case-by-case basis, and sometimes the particular benefits and risks, as they're interpreted in different areas of the agency, may have slightly different emphases placed.

So that's as close as I can come to a rationale. These are products that you might think you wouldn't approve if you didn't have a very compelling reason to put them on the market.

DR. CHESNEY: Any other questions for Dr. Trontell? Dr. Danford.

DR. DANFORD: The discussion of risk management that you just gave us focuses a great deal on the risks of bad events coming from use of a product, and the more aggressive you get with the restriction of the use, the more likely you are to uncover the risks of not being able to effectively treat the disease you're trying to approach in the first place. It looks to me as though the monitoring for the effectiveness of your risk management focuses on just looking at the minimization of the risks caused by the drug and it might be blind to the risks we encounter by restricting use of the drug to people who might benefit from it.

Is there an effective way to monitor the reduction of benefits that might occur with the implementation of risk management, which I think is probably harder than looking for the risks of the use of the drug in the first place?

DR. TRONTELL: That's an excellent question. I had anticipated your asking about unintended consequences, but on the benefits arena, I know certainly in the instances of some drug products, the agency certainly hears from patient groups and clinicians when drug products in the worst case scenario are withdrawn from availability.

That's really a case where we have the most obvious loss of potential benefits as well as of potential risks.

In terms of systematically accounting for benefits lost, I actually don't think we have stated an explicit process for that. In the case of the drug product alosetron, that product's reintroduction into the marketplace was in part in recognition of the benefits of that product's use prior to its temporary withdrawal from the patient community and probably an increased recognition on the part of the agency about symptomatic disease having profound impacts on daily functioning.

So I think we would rely on information volunteered to us, but in terms of looking at benefits foresworn, I think that's a much more challenging thing to address.

DR. CHESNEY: Questions for any of the other speakers? Dr. Fink.

DR. FINK: This is really more a comment than a question. Earlier it was stated that it was thought that the AERS database contained the severe reactions. My concern would be that with HPA axis suppression, it is so far below the clinical radar screen that I'm not sure that it's adequate to say that the database really reflects severe reactions.

Thinking about it, I consult frequently in the

ICU. Topical products are typically not asked for in the medication history by physicians in practice. They are not included in ICU databases such as Apache. And the critical question that would have to be looked at is does topical use of steroids predispose children or adults to increased ICU admissions. And I don't think that can be done easily retrospectively. Yet that is really the key issue because without that data, we really don't have a handle on the risk. You have data that says here's what we can measure with a clinical test that would not be easy to implement on a wide scale basis, and we don't really know whether this risk is clinically significant and causing significant harm to patients in an unrecognized manner.

DR. CHESNEY: I think certainly that's one of the points Dr. Cummins made to me on the phone call that we routinely have to discuss the content of the meeting, is that we really don't know. For example, how many children come in with bad RSV and we incidentally notice that they have eczema, but really don't make that association. Certainly I've had patients several years ago come in and say they were on Protopic, and I said, what is that? I've never heard of that. So as a non-dermatologist, I think we routinely, even people in academic medical centers, don't pay any attention to topical medication.

Dr. Fost.

DR. FOST: Yes, I think that is at the core issue. I mean, we have all these very scary numbers of high incidence of HPA suppression, but we have no idea whether that's just bad numbers or really a clinical problem. But I'm wondering how hard it is to study that retrospectively. If you went to a database like Kaiser which must have thousands if not tens of thousands of kids on topical steroids and could also tell you how many had herniorrhaphies or were admitted to ICUs and so on, I wonder if it wouldn't be possible to do a retrospective study and get at least a preliminary handle on it.

DR. MURPHY: Joan, I had a question for Dr. Gorman before we get to the questions later. One of the important issues which you all have discussed is we really don't know what the risk is. The simple way of putting it is we don't have bodies saying this adrenal axis suppression related to this product is why this is happening. We just don't have that. We have facts. We all know adrenal axis suppression is bad. We know what you're supposed to do if you diagnose it, but the whole point that is being put forth today is that we think that people may not be asking the right questions and how do we find out what the real risk is. That's really the crux of the question. But to get to the real risk, some of it is the use, both appropriate and misuse, of products.

I wanted to ask Dr. Gorman to say something because having been in charge of a large ambulatory care setting for pediatrics, I am concerned about as much as people try to counsel and appropriately define use of products, what his perception of some of the issues are with use of these products because despite all the efforts of the physician, we don't always control what happens with that product once it leaves our pen onto the pad. So I'd like Dr. Gorman to make some comments along that line.

DR. GORMAN: I guess this is because I practice in a trench like my dermatology colleagues that sit around the table.

You used an analogy at the end. I just finished reading three books that examine the history of the world, one through salt. Salt has determined the history of the world. And the second one was olives determined the history of the world. And the third is codfish determined the history of the world. They all make very convincing arguments. I often wondered whether the prescription pad has determined the history of the world, but I haven't seen that book yet.

I think there's a lot of different factors that sort of intersect in how people use medicine. One of it is how available it is. So we try to control that with prescription versus nonprescription. But this class of

medicines that we're discussing is available both ways. So I think sales numbers become important.

There's another factor, at least in the "velvet valley" of Ellicott City that I practice in. It's the quest for perfection. And the quest for perfection in the dermatology world I think is very explicit. People don't want wrinkles. So they use the wrinkle cream, and now they use Botox, the first biological weapon developed, but now we're using it to take care of wrinkles in people's skin. Accutane was developed for severe nodular cystic acne, if I've got the label correct, but now if you have two zits and you're 45 years old, you go to your dermatologist or your internist and you ask for a prescription. I know now you've got a sticker system, but there's this quest for perfection.

When a mother looks at their baby's bottom and sees redness, they put goop on it.

(Laughter.)

DR. GORMAN: Now, they put goop on it that I prescribe. They put goop on it that they get over the counter. We had a presentation this morning that says genetics has something to do with this. So atopic kids come from atopic parents, so they use the goop that I give them and then they give this stuff that they've been given themselves. They add that to the stuff that they get over

the counter.

These agents, as Dr. Fink says are not thought about by clinicians. I think really carefully -- and I check the chart before I refill a prescription on one of my attention deficit medicines. I never look at the chart before I refill WestCort or Lotrimin or Lotrisone. I had data presented this morning -- that's something I don't even think about doing when a 17-year-old with athlete's foot calls me about giving them a prescription for athlete's foot medicine may, in fact, have some significant risk for these kids. It's not over-the-counter, but it's a non-physician visit, so it's not going to be captured in a lot of the databases that we use because I'm going to prescribe that with a phone call. I suspect I'm not alone in that particular prescribing pattern.

I'm trying to think about clinical ways that I've seen steroid overuse. I have never, fortunately, made the diagnosis after I've admitted someone to the ICU. But there have been many times when I've had discussions in my office mainly under the diaper area of this is atopy. I'm sorry. This is now disease caused by our medication, not disease that was there before where their skin becomes atrophic. This thinness and redness and purpura that you're seeing is because of the medicine you've been using and not because of the disease that started it.

So I don't think this is as simple as I am a well-trained pediatrician and I prescribe appropriately. I think there's a lot of other themes that come in, and I suspect parents are using these medicines because of their perceived safety and their very generous availability in the home. These things never go bad. As long as you can squeeze it out of the tube, you're going to use it. I know you put an expiration date on it, but they never go bad.

(Laughter.)

DR. GORMAN: And parents don't throw this stuff out.

I don't think there's an epidemic that's clinically significant to the point where you don't respond to shock out there. I think we might have seen that. But I think there's an epidemic of use of these agents in ways that we don't understand.

There's one piece of data. A fellow did a research study where he wanted to count the number of ointments or salves that were put on a baby by the age of 4 months, and the average number was 27. This has been a long time since I looked at that data, just the number stunned me. That means one new stuff every 3 days gets put on a kid, a baby, who we think of as safe. I don't remember the data whether they were prescription or not.

DR. MURPHY: And I always look to Dr. Gorman to

give me a fact I never had before. Thank you.

(Laughter.)

DR. CHESNEY: Dr. Wilkin has his hand up but Dr. Epps has read another book on the history of the world and she wanted to discuss that with you.

DR. EPPS: Well, not that much detail certainly.

One was a question I guess briefly for Dr. Cook. Are fluorinated topical steroids still considered to be more of a problem than non-fluorinated?

DR. WILKIN: There are corticosteroids that typically have fluorine or one of the other halogens at the 9 alpha carbon, and what that does is it is slower to metabolize and so it lingers longer at the active site and it becomes more potent that way. But the pharmaceutical companies have been very good at figuring out other ways of adding potency to the basic steroid nucleus by esterifying, putting some long chain thing onto the carbon 17 or carbon 20 or carbon 21.

Actually that's one of the points I wanted to make back to Dr. Gorman. The hydrocortisone that is in the class VII, which is the only one that really is over the counter, is substantially different from the hydrocortisones that are in those higher classes because they're not truly hydrocortisone. They are esters of

hydrocortisone, hydrocortisone valerate, hydrocortisone butyrate. Once again, if you esterify the steroid nucleus, that's a way to make it more potent independent of adding halogens to the 9 alpha or some other site.

I think Dr. Gorman, Dr. Fost, and others have touched on one of the key pieces we would like to hear back from the committee today. Everyone has been up-front I think from FDA in conveying that there's a lot of uncertainty here that we're saying with you our inference structure on why we think it might be prudent in the short term, in the absence of having definitive information, that we do have some kind of risk management. We'd like to know from you if that inference structure is reasonable and if the risk management approaches that you've seen embedded in labeling, if they seem to be somehow appropriate. And I think we've heard of some examples of maybe ways where we can go and explore and find out is there really a problem out there.

But our fundamental concern is that we see a substantial amount of signals for adrenal suppression during drug development, and that's the only time we would see that, when we ask for it and get it prospectively. This is again one of those lanthanic conditions where there are no signs or symptoms. Our thought is that a patient may have to have some additional event, major trauma or

sepsis, for this to become clinically important.

My first year after medical school was not as a dermatologist. I was a first year resident in obstetrics and gynecology, and I know that year I didn't ask about topical products in the pre-op list. My wife is an anesthesiologist so I have contact with a small number of anesthesiologists, and none of them routinely ask for topical products. They do ask for injectables in addition to oral products.

My thought is all of the signs and symptoms one would see in the setting of sepsis or major trauma you could ascribe to the sepsis or the trauma. This is really something that requires a high index of suspicion.

So I like the comment that we may need to go with one of these controlled third party groups where the outpatient care and the emergency inpatient care might somehow get into the same system and maybe that's the source. But if there are any other suggestions on how we may actually tease out whether there is a signal, we would be very grateful in hearing that.

DR. FOST: Wouldn't Kaiser have a complete database of all prescribed topicals?

DR. EPPS: Not everybody stays in the system.

DR. FOST: You'd have enough that you could do a case control study of children who are on topicals, and

there must have been a large number of them who come in for anesthesia or for surgery or for trauma other things and look at outcomes.

DR. EPPS: It's better than most, but certainly I'm not participating in Kaiser and a lot of people pay to get what they want if they can't get it from Kaiser, especially in dermatology. They may have one dermatologist for a huge region, and so if they don't achieve satisfaction, then they opt out. That is one thing that people will pay for is dermatology services. If you can't get it within your HMO or your plan, then you go to who your friend goes to or your mom says.

DR. TRONTELL: I can speak a little bit. The Kaiser system in California, which operates more in the closed model, staff model HMO, may in fact give you the opportunity to look at drug exposures and outcomes. The issue would have to be clarity on the outcome you want to look at. You might be able to look grossly at issues like ICU admissions relative to RSV, for instance. You might also consider prospective forms of data collection where you may want to capture even a random cortisol in situations of sepsis and trauma, where typically lines are being placed and bloods are being drawn. Again, this is more in the nature of an investigation to try and assess the impact of it. But the challenge in observational data

is many factors that might lead an individual to an ICU still may not be well captured by the data systems that we have in place.

DR. CHESNEY: Dr. Schneider.

DR. SCHNEIDER: Yes, just to step back a moment. The way I look at this is that after the data that we heard this morning, we know that a substantial proportion of patients exposed to these drugs are in a situation which I would consider to be at risk, that is, that they have abnormal Cortrosyn stimulation tests. The clinical manifestations of that situation -- that is a precarious situation. We know that if that continues down the road, patients will get into trouble one way or another. We also know from adverse event reports, of course, there is a small number of patients who have either had adrenal insufficiency or frank Cushing's syndrome associated with the use of these agents and that apparently the adverse events were reversible on withdrawing the drug. We don't know in that situation if it continues for a little while, there are other adverse events not all that serious that are associated with this sort of intermediate situation, and that may be psychological changes. No one has brought up osteoporosis, for example, which can occur rapidly in children exposed to steroids and so on.

We do know that down the road some people will

be at extreme risk. We know that patients who are admitted to ICUs who cannot mount an adequate ACTH and cortisol response endogenously don't do as well. So we know that there will be a small number of patients who will be at risk or will actually develop these serious adverse events or death.

I don't know how well one could do a formal study to examine this, and given what we know now about the effects of systemic steroids -- and I really don't see much difference here. I take a more quantitative view of this. I think we have a good idea clinically what the risks are. We know that these patients are now at risk after 3 or 4 weeks, and if it continues, they will be more at risk. If you stop it, probably most of them, if not all, will recover, and no one will wind up in the ICU.

DR. CHESNEY: Dr. Gorman and then Dr. Fink.

DR. GORMAN: This is responding to the question of suggested ways to look at this. It can be looked for as a confounding variable for hospitalizations in ongoing clinical trials, knowing that I just probably broke four FDA regulations. But I can think of several recently approved drugs that hospitalization was one of the outcomes to prove efficacy and perhaps it could be looked for as a confounder whether or not they use topical steroids.

DR. CHESNEY: Dr. Fink.

DR. FINK: It seems like if we look at risk management programs, one concern I would have is obviously education about this is potentially beneficial, but it also strikes me that education about this problem is also potentially very harmful in that if this is widely publicized, you may see the medical community reacting to this with the sense that anytime a child who's on topical steroids has a cold or an illness, they get put on systemic steroids to cover them for the risk of HPA axis suppression. So you could have an RMP program that actually increased the risk of the side effect you're trying to avoid because of the way physicians would tend to react.

And it really is an issue of perceived risk. If I have an asthmatic who's been on systemic steroids in the last 6 months, I always get called by an anesthesiologist before anesthesia even though, if it's 4 months ago, there's really no risk. You rarely get called for other things. So I think it is an issue of perceived risk, but I am concerned that an intervention here, particularly education, unless it is really well done, could actually increase the risk of children being exposed to adrenal suppression by an inappropriate response to the educational program.

DR. CHESNEY: Dr. Trontell.

DR. TRONTELL: I think those are very legitimate concerns and it gets at the difficult area of unintended consequences. How do you know what you don't know in advance? Some of the stakeholder input that I alluded to in the selection of tools in fact -- the concept paper, in fact, suggests that you may try pretesting, particularly in the educational arena. Again, there are challenges in trying to assess what people learn versus what they do. But it may be possible to try and get some assessment before you send out a message whether or not that message might be misperceived.

DR. CHESNEY: Dr. Andrews.

DR. ANDREWS: I had a couple of comments back to the question can you study this association between exposure and outcome. As an epidemiologist I'm always looking to use an electronic database where the data are already existing rather than go out and do a very elaborate study. In this particular case, the use of a database like a Kaiser is very appealing if you could identify the outcome well and if the outcome is frequent enough. So I think you could do that in terms of identifying the outcomes.

Exposure is the difficult part. Because people tend to use these drugs not just within 3 months or a week of when they're prescribed, and they may have been

prescribed to another family member, one might broaden your scope in looking at a fairly long period of time before the outcome, as well as looking at all family members who might have received a prescription. But I think you would also have to supplement that data collection with an interview with a parent to find out what they actually used before the outcome.

DR. CHESNEY: Dr. Fink.

DR. FINK: In terms of risk management programs, the list you had was good. The one that occurs to me that I did not see on the list is liaisons with professional organizations to encourage them to have increased drug information into their recertification and certification exams. As someone who recertifies in pediatrics and pediatric pulmonology and serving on this committee, I'm almost amazed at the lack of drug-related questions on board exams. One mechanism -- if more questions about drug reactions or drug toxicity were put into professional recertification exams, it would force physicians to raise their interest in that subject because I think the average practitioner gets most of their information from the detail person and probably does not read the package insert before they prescribe a drug.

DR. TRONTELL: That's an excellent suggestion. I didn't mean to imply that the tools that I listed were,

by any means, exhaustive. I think in some instances the agency has worked very well in cooperation with professional societies. It's an excellent suggestion.

DR. MURPHY: Actually I think we've mentioned this to the peds committee before. We've been working with the American Academy of Pediatrics to make, as part of their recertification, a certain number of drug-related -- new labels basically that deal with changes that have occurred that we all know that your bedtime reading is not the PDR and nowadays, particularly for some of the older products that we're looking at or being studied, won't be in there at all anyway. But the changes that are occurring to labels because of these studies, both from dosing and safety, you're lucky if you get one or two. We've got 60 new labels now. So I think it really is a matter of having to have possibly multiple approaches.

DR. CHESNEY: We have one more question and then I think we probably need to break for lunch so that we still have a half hour. There are one or two people signed up for the open public hearing, and we want to have lots of time to have open discussion on Dr. Murphy's questions. So, Dr. Glode, would you like the last question or comment before lunch?

DR. GLODE: Thank you. It's a comment I guess and a short question for Dr. Cook. So it's just in the

studies that you reviewed, again without a calculator present, it looked like there were about 57 children less than 2 who have been studied in the 10 or 11 studies you presented. So that's just to point out the scarcity of data in young infants with diaper rashes.

Secondly, I just had a question about study design in most of these studies, because of the 100 and some -- I added up to 113 individuals studied who were suppressed, had evidence of suppression -- only about 26 of those were retested. So were the protocols to retest? And so why did 75 percent of the people get lost to follow-up or refuse to be retested? Or was it not part of the study design?

DR. COOK: Well, no, it was part of the study design that patients who showed evidence of HPA axis suppression at end of treatment should be retested. The problem actually came in the definition of what was HPA axis suppression according to the sponsor versus the agency. So for that reason, there were some patients who by our definition were suppressed and not considered suppressed by the investigator and therefore the test didn't occur. In a few there were some that were like lost to follow-up. So that's why there's somewhat a paucity of data there.

DR. CHESNEY: Thank you.

Tom tells me that there is an area in the dining room that's been set aside for the committee and consultants to eat. I think we need to reconvene in an hour at 1 o'clock for the open public hearing. Thank you.

(Whereupon, at 12:03 p.m., the committee was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:03 p.m.)

DR. CHESNEY: I think we're ready for the afternoon session, if everybody could take their seats please.

This is the beginning of the open public hearing, and the FDA has a new policy which I will read, or a new statement which needs to be read before public hearings.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include a company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise FDA encourages you at

the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Is there anybody who would like to speak at our open public hearing? Is there a Mr. Jerry Roth here?

MR. ROTH: Thank you. My name is Jerry Roth. I am President and owner of Hill Dermaceuticals, which in today's society makes me a dinosaur in the sense of, so to speak, the side effects stop here.

During today I wanted to let you know that every corticosteroid possibly will not fall into the side effect range of what you've seen this morning. There were three things that have been mentioned by every speaker and that is the body surface area, the vehicle, and the volume of use or the amount exposed to. And I hoped that some of these questions would get answered in the safety data that I'm going to present. I will make it very brief since we've been here long, and I'm not used to sitting still this long myself.

First of all, Derma-Smoothe/FS is a fluocinolone acetonide in a peanut oil vehicle. We conducted two independent studies for the treatment of atopic dermatitis in ages 2 to 12, and I want you to

understand that the criteria for atopic dermatitis was greater than 50 percent body involvement. The data that I'm about to show has been approved by the dermatology branch of the Food and Drug Administration.

I might add that you had a pre-conference document and it mentioned fluocinolone acetonide topical oil. It's ages 6 to 12. Since that time, it has been approved for ages 2 to 12.

The study design as an open-label safety study. Once again, the patient criteria was moderate to severe atopic dermatitis involving greater than 50 percent of the body. The dosage was twice a day application to the diseased skin for continuous treatment for 4 weeks. The criteria is what you have heard all day, the cosyntropin ACTH stimulation test and the serum cortisol levels both baseline and post stimulation.

The study design was prior to day 1 and day 29 the pre-stimulation serum cortisol level was assessed, immediately followed by stimulation with cosyntropin, and then the post-stimulation cortisol level was taken after 60 minutes.

The total population was 34 patients. There's a typo in your pre-packet. You had 33. It was 34 patients.

But 18 patients had a body involvement of

greater than 75 percent of the body. 16 additional patients were involved. The body surface area was 50 to 75 percent.

The other question that we'll get answered is the amount of volume of use and the amount exposed. The average patient used in the 30-day -- in the 4-week -- or 29-day level was 9.5 milliliters and I will come back to that in just a minute.

But the baseline cortisol levels did not change from day 1 to day 29. The p value in the first study was .6. The p value in the second study, .376. When you increased or did the stimulation, the increment was no difference from day 20 -- statistical difference between day 1 and day 29.

Just for those who are not physicians, we're talking about a considerable amount of body surface area, your chest, back, front of your legs, back of your legs, arms, and so forth. So once again, I want to point out that it is a significant body surface area.

Study 1, just to review. The baseline from day 1 and 21 on the cortisol levels -- or to 29 was not statistically significant. It was .6. The increment increase in cortisol after stimulation of day 1 and after 4 weeks was not significantly different either.

Study 2 showed pretty much the same. There was

not statistical difference from day 1 to day 29 in their cortisol levels as well as the increment increase.

I mentioned drug exposure. Each patient was dispensed -- and it's been brought up by several of the advisory committee today. Each patient was dispensed a 4 ounce bottle and the average usage was 9.5 milliliters. Now, within this 4 ounce bottle, there are 12 milligrams of fluocinolone. That means that the average patient had exposure of no more than 1 milligram of fluocinolone, and that is not much. I mean, that's infinitesimal compared to what you've seen and the amount of usage in the studies that have been presented today.

The conclusion, of course, 4 weeks, twice daily application of Derma-Smoothe/FS, or fluocinolone acetonide in peanut oil, to diseased skin involving 50 to 90 percent of the body surface area, there was no change in the morning baseline value of plasma cortisol, nor did it affect the cortisol stimulation by the administration of ACTH.

It has been asked several times in here this morning about efficacy, and very briefly, these patients, the 34 patients, greater than 60 percent, actually 67 percent, 23 patients had a 75 to 100 percent improvement.

I want to thank you. I know you've heard a lot of data today. If there are any questions, I would

certainly --

DR. CHESNEY: Any questions for Mr. Roth? Dr. Fink.

DR. FINK: Yes. Analysis of pooled data would hide potentially outliers who had adrenal suppression. Did any of the subjects in either study show evidence of adrenal suppression?

MR. ROTH: Not one patient showed adrenal suppression. I should have said that in the beginning

DR. CHESNEY: Dr. Stratakis.

DR. STRATAKIS: The question I have is again with regard to the test that you used to assess adrenal suppression. So I think it was very nicely put forward this morning that baseline cortisol values are not a good test to assess adrenal suppression. I think that this is evident from your numbers. In one of your studies anyway, you have a baseline value of 10.73 as the average and then you have a standard deviation of 5.1 with a mean value of cortisol of 10.73?

MR. ROTH: That was the range. I think that the accepted standard here and what the agency requires for a test is the baseline cortisol and stimulation before the study. I believe Dr. Wilkin had mentioned that there's not one of these patients that haven't been treated before. At this time, that is the best that the agency has. I'm only

comparing my data to the same test standards that what you've seen this morning.

DR. STRATAKIS: Do you have the numbers of the ACTH stimulated values?

MR. ROTH: Yes. I believe they're on your chart. Is it not? The increment is on there.

DR. STRATAKIS: This is the increment.

MR. ROTH: Yes, the increment.

DR. STRATAKIS: The actual number.

MR. ROTH: The actual increment, yes.

DR. STRATAKIS: The actual peak --

MR. ROTH: It more than doubled on each of those patients, and I believe at 60 minutes the standard range is a double, and I believe that each of those, the increment wasn't more than doubled in each of the patients after the stimulation.

DR. STRATAKIS: Thank you.

DR. SCHNEIDER: Obviously, these results are a little bit at variance with what we've heard earlier. Let me ask you first. The total amount of steroid that the patient was exposed to during this 29-day period was 1 milligram?

MR. ROTH: Per day.

DR. SCHNEIDER: It was 1 milligram per day.

MR. ROTH: Per day. Once again, fluocinolone

is considered a light to mid potency and this vehicle is possibly less because the vasoconstriction is even less than what this same active would be in something else. If you put this amount in an ointment or cream, the amount exposed would be many times more than that 1 milligram to cover the same body surface area.

DR. SCHNEIDER: You mean the amount that was applied.

MR. ROTH: Right. In other words, being in a peanut oil base, you have spreadability. That's why the average -- and we calculated each bottle returned -- was 1 milligram per day. If this same corticosteroid may have been in an ointment or something, you would have to apply a lot more to cover the same amount of surface. Therefore you would be exposed to far more than possibly the 1 milligram per day. It may take three tubes or four tubes.

DR. SCHNEIDER: Do you have any information on differential absorption? For example, if you put the material in peanut oil, is it absorbed less through the skin?

MR. ROTH: Well, we don't get much absorption. This the product on the market in a peanut oil. We didn't do it just for this study. It was previously on the market. It was done. I can't tell you that if you put it in plain mineral oil, it's going to be any different, but

the product was approved way before we did these studies. The product was initially approved in 1988 and it was also approved under a different thing for scalp psoriasis. This has been on the market. It wasn't that we put it in the peanut oil just to check for this study. The vehicle is an NDA and because of the vehicle, it is an NDA drug not a generic equivalent.

DR. SCHNEIDER: I mean, your contention is since the efficacy was the same that you achieved this equal efficacy with less total skin exposure than if you put it in a cream or a lotion and, in addition, that you may also have less systemic absorption.

MR. ROTH: I'm not telling you that this works better than the cream.

DR. SCHNEIDER: Well, you don't have a head-to-head trial.

MR. ROTH: Okay.

DR. SCHNEIDER: But the response was certainly within the range of what we heard earlier for other drugs.

MR. ROTH: Yes. The response was, yes, and that's always been the case. Efficacy studies were done. This was done as an efficacy approval and efficacy was done at many centers for efficacy results besides these 34 patients. This was approved as an efficacy study. Once again, we showed that oil sometimes -- it has been

mentioned many times in here today regarding hydration or whatever, and there have certainly been many studies done on peanut oil with hydration. So that's not our claim in the label though.

DR. SCHNEIDER: Thank you.

MR. ROTH: Okay.

DR. CHESNEY: Dr. Ebert.

DR. EBERT: Your figure of 1 to 2 percent absorption is based on what --

MR. ROTH: That was the general accepted, I believe, in the textbook of corticosteroids by Dr. Maybach. I believe that that's their accepted of what is absorbed through the skin. That I believe is a range. I don't think that's amount. However, with just 1 milligram you certainly have room for a lot more. That 1-2 percent, of course, is higher for more exposure, volume of steroids.

DR. CHESNEY: Dr. Wilkin.

DR. WILKIN: Yes. We in the review division for this product were not made aware of the content of this particular presentation in the open public section, and so I would say that we're in the position of extreme neutrality in terms of the data and the conduct of the trial. We just simply didn't prepare. Had we known and if this is an important thing to discuss, we could have reviewed this efficacy supplement, but we did not realize

this was going to be discussed.

DR. CHESNEY: Any other comments, questions?

(No response.)

DR. CHESNEY: Thank you very much.

MR. ROTH: Thank you very much for your time.

DR. CHESNEY: Is there anybody else who wanted to speak in the open public hearing?

(No response.)

DR. CHESNEY: Dr. Murphy is going to give us the questions for our deliberation for the afternoon.

DR. MURPHY: Can somebody put the slides up for the questions?

We're going to give you first two questions that are slow balls and then we'll get a little harder here. Okay?

(Laughter.)

DR. MURPHY: The first question really has to do with a drug development approach, and it starts out with the statement which is clinical studies of pediatric patients using topical corticosteroids have demonstrated HPA axis suppression during the ACTH stimulation test. I think everyone agrees with that statement.

The next question is, is the cosyntropin test performed during drug development sufficient to determine the risk of potentially life-threatening adrenal

suppression? And if one has other recommendations, are there additional specific tests that the subcommittee would recommend to measure this risk that we would ask sponsors to perform? That's not on this slide, but basically as part of the drug development process. The division is asking in their approach to having these products developed for use in children, is this the best test that we should be using and are there any additional specific tests that we should be asking for.

DR. CHESNEY: Do you want discussion on question 1 and then we'll come to question 2?

DR. MURPHY: I'd like to. I think once we go to question 3, we may be here for a while. So I wanted to try and address these individually first.

DR. CHESNEY: And we have a total of three questions. Correct? Three questions total?

DR. MURPHY: Yes. Well, there are three questions, but question 3 is -- no. Somebody said three pages. No. It's two pages.

(Laughter.)

DR. CHESNEY: I'm trying to make a rough allotment of time. We give 5 minutes to question 1 and then a half hour for each of the others.

So question 1. Any comments as Dr. Murphy has presented it and as we see it on our handout and on the

screen? Dr. Fink.

DR. FINK: I guess the only question is, is there any data available looking at multiple applications of the cosyntropin assay on the same day? Because the clinically relevant issue is does the patient respond appropriately to stress. An impaired adrenal gland may respond to the first supraphysiologic dose of cosyntropin, but if you hit it again 2 hours later, would you see an impaired response that you did not see with the initial stimulation? Or can you count on it responding reliably?

DR. MURPHY: I am going to ask for all endocrinologists in the room to please respond to that.

DR. SCHNEIDER: Actually the adrenal gland is impaired because the pituitary is impaired. So the answer to that is really it won't be impaired. In fact, it will be better. There used to be a thing called the long-term cosyntropin test where you would either drip it in or give it every 8 hours or whatever. This was before ACTH assays were available or reliable, and this would distinguish primary from secondary adrenal insufficiency. So if you take somebody with secondary adrenal insufficiency, and even if they have had a lousy response at the beginning, as you keep hitting them with exogenous ACTH, the gland will wake up, and normally that will take about a day or two. We have a lot of data on that, and the answer is if you

have an impaired gland through secondary adrenal insufficiency, repeated stimulation will only improve cortisol responsiveness.

DR. FINK: Over a short period of time?

DR. SCHNEIDER: Over 24 to 48 hours. I was actually forced to do some of these tests when I was an intern, and it can distinguish the two.

DR. CHESNEY: Dr. Murphy, it occurs to me there are two questions here. One is, is the cosyntropin test sufficient to determine the risk of potentially life-threatening adrenal suppression and I think many of us would be dependent on our endocrine colleagues.

But the other part of the question is should the FDA ask sponsors to do this in future studies of topical corticosteroids?

DR. MURPHY: The second part of the question is if the answer is that we need additional tests, then would you recommend that we ask sponsors to do these during their conduct of trials, when they're looking at the efficacy, to assess safety side of the question.

DR. CHESNEY: Dr. Fost.

DR. FOST: I'm having a little trouble with the phrase "life-threatening" because from what we've heard, I don't know if there's any -- I don't know what the risk of life-threatening is. My impression is it's pretty low, but

we don't know. We talked about ways of getting at that.

So I would feel more comfortable if you phrased the question is the cosyntropin test sufficient to determine the risk of adrenal suppression. My impression is from what I've heard -- I'm no endocrinologist -- it's a pretty good screening test. It's not perfect because of the other elements of the axis, but weighing costs and benefits of assessing the whole axis, not to mention stress to the children who would be in these studies, it strikes me as a reasonable screening test for a problem whose clinical significance we don't know anyway. It's not the ideal test, but it strikes me as a reasonable, middle-ground sort of test to see if there's any effect at all.

DR. MURPHY: So your answer is that as far as looking at the adrenal response, you think it's an adequate test. That's what we're asking.

DR. FOST: That's my impression.

DR. MURPHY: That's what we're asking. You're going to the latter part, the part we really have a hard time defining and brought to the committee. You're correct for sort of taking that out of this part of the question.

DR. CHESNEY: Dr. Stratakis.

DR. STRATAKIS: I agree with what was said, that this is the best screening test we have so far.

I think we have to also agree, however, on how

to use the results of the ACTH stimulation test. In other words, we have to agree on whether the 18 micrograms per deciliter is what we are going to use as the criterion for adrenocortical insufficiency.

There are really not good studies looking at the increment. There are not good studies looking at the baseline value. Although I agree that baseline values and increments can be used in the overall assessment of a test, we think we should prioritize on what we use, if we're going to use it as a screening test, as the best value for that test.

I think that if I were to order, what I would use for this test as a screening test, would be first the peak value, and I would compromise with 18 micrograms per deciliter, which I think is reasonable based on the data that we have so far, number one. Then between the other two, increment and baseline, I would use increment second. And baseline -- I'm not even sure that I would look at it. I don't know whether it should be actually one of the criteria.

DR. CHESNEY: Dr. Wilkin.

DR. WILKIN: I would just like to say that we have that as an action item that we're following up on. We're going to get specific discussion from experts on exactly what criteria to use with the Cortrosyn testing.

We didn't see that as actually a specific question that we would discuss today. I think there are other experts, in addition to some who are here today, that will help us on that.

DR. MURPHY: We appreciate the comment. It's just that we didn't want the committee to get bogged down into that very specific which criteria to use because we are doing additional work on that because we thought could be an extensive discussion unto itself. So it was really using the criteria that had been discussed, does the committee feel that this is an adequate test.

DR. CHESNEY: Would anybody recommend any other specific tests? Dr. Schneider and then Dr. Stratakis.

DR. SCHNEIDER: I'd just like to sort of mix these two things together and make the observation that during drug development, there are early parts and there are late parts of drug development because you asked the question relating to drug development, to what we can learn during this process. There is, or there should be, in the development of a drug an early period in which there is intensive PK/PD studies, and then a later part where there are what are usually termed population based PK/PD. We have a larger population.

During this intensive phase I think sponsors have the opportunity to study the absorption of the drug

itself perhaps in a clinical research center environment and to do some more sophisticated PD studies such as, for example, looking at the timed cortisol levels or the time to ACTH levels or the peaks or whatever to get some idea of how big a problem this is with a new molecular entity. Remember, whether it's an inhaled steroid or a dermatological steroid, the drug is being developed because it will exert its effect locally and the systemic effects will be minimized. So here's a time during development when there is a really great opportunity to get what we would term intensive PK/PD data. In that regard, there are other tests that can be used such as, for example, a temporal profiling of cortisol levels or even cortisol production rates or ACTH levels or whatever. But clearly you couldn't do this with 200 people.

Later on in my opinion, the Cortrosyn stimulation test is really the best screening test that we have. In my opinion, the single peak value of 18 or 20 micrograms per deciliter outweighs the others. The increment I don't think is quite as reliable simply because it's inversely proportionate to the baseline level.

So I think one really should distinguish these essentially two broad phases of drug development. And early in development you do have the opportunity to get some really good information. If it turns out, for

example, that the drug is really absorbed systemically by whatever analytical method you have and that furthermore it has a pharmacodynamic effect, then you've really learned a lot and I think a warning light should go off and you might really look at some of these issues subsequent in development. I know that this came up in our deliberations over inhaled steroids, the same thing. Having said all of that, that would be my answer regarding drug development.

Is the test performed during drug development sufficient to determine the risk of life-threatening adrenal suppression? Again, not absolutely. It can give you some indication but there will always be exceptions and there will always be people whose adrenals will respond but whose hypothalamic-pituitary units will not respond adequately to stress. On a population and a clinical level, it's I think the best that we can do today.

DR. CHESNEY: Dr. Stratakis.

DR. STRATAKIS: I agree with the statements by Dr. Schneider.

I just wanted to add another dimension. When we talk about these compounds, we haven't addressed at all the mineralocorticoid effects that some of the compounds may have. I guess I need some help here whether fluorinated compounds have more mineralocorticoid effects than one would anticipate from the usual hydrocortisone

esters that we have been using. So the question is whether other measures like blood pressure, for example, and other mineralocorticoid effects should be used. I'm asking this more as a question to the pharmaceutical development people here.

With regard to any other tests, other than the blood pressure, which I would like more help with with regard to the mineralocorticoid effects, obviously this morning we talked about the CRH stimulation test. The CRH stimulation test, in theory at least, is a better test than the ACTH stimulation test. However, at this point, because the data are not out there, we can't use those tests. I think we are addressing this issue in question 3, but in the future, more studies ought to be done employing the use of the CRH test in the evaluation of secondary adrenocortical insufficiency, and at least again in theory it may be more practical than ACTH and also more applicable in all situations of secondary adrenocortical insufficiency because as it was pointed out, if you do an ACTH stimulation test within the first couple of days, you won't pick up secondary adrenocortical insufficiency.

So any light on the fluorinated compounds and whether mineralocorticoid effects would be screened more carefully?

DR. WILKIN: I can't really comment on

halogenated versus non-halogenated. But we take your point about considering the blood pressure and mineralocorticoid effects and we'll have those discussions with sponsors.

DR. CHESNEY: Have we answered question 1?

DR. MURPHY: Yes, thank you. I think basically I took a consensus that the cosyntropin test with the three criteria to be ranked later is adequate, that there are some other things that we can look at, both earlier in development on smaller numbers of patients and enrich the database to inform us more about the behavior of the product, and also to answer if there are any other mineralocorticoid type of activities. So I think that's the consensus I took out of what was said.

There's another hand.

DR. SCHNEIDER: Just a question. Does this question include what's appropriate in labeling for the tests that are recommended?

DR. MURPHY: No.

DR. CHESNEY: Dr. Fink has the last word here.

DR. FINK: I guess I would feel comfortable accepting this as a bronze standard, but if you want a gold standard, you need to get adult volunteers who you bleed into shock and see what their response is.

(Laughter.)

DR. FINK: But the real issue here is if you go

with a standard and you say that we want to develop a risk management program, the fact that you've documented some HPA axis suppression may not have a big impact on practitioners. They may say this is just a biological observation, and if you don't tie it to clinical outcomes, it doesn't necessarily move me to make a lot of change in my practice.

DR. MURPHY: I think that that is the crux of really the third question of what are we going to do while we don't have the final answer.

Next question. The questions are a little different on those slides than they are in what I have in my hand. Nothing like keeping us on our toes here.

Just basically I'm saying this for the recorder here. The younger pediatric patients have a larger surface area to mass ratio when compared to adults and may be at greater risk of higher systemic exposure to topically applied drugs. A statement of fact.

Because of this, the FDA has usually requested the sponsor conduct suppression studies in older groups first. If there is no evidence of suppression, to proceed in sequentially younger patients until all groups have been studied or until there is evidence of significant suppression. This is too a statement of fact.

Given the data from clinical trials that were

presented today, does the subcommittee recommend continuing this sequential testing or should the testing be performed concurrently?

We ask you this question because we have had objections to doing it the way we do it, and it has had consequences for some product development. So we're asking what the committee thinks about this approach.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I think dose-ranging studies is something the agency probably has a wealth of experience with. I think using the age criteria, of marching down the age criteria is certainly one way to do it to protect the youngest patients. And other way to do it would be to test them for the suppression more frequently after smaller doses of the drug either by changing the amount of surface area that could be treated or the duration of treatment. There are a lot of ways to do dose-ranging studies that I don't think would necessarily dictate the age march-down, that would perhaps satisfy the sponsor and company, as well as the agency, as well as protecting human subjects as they go through this research process.

DR. CHESNEY: Dr. Santana.

DR. SANTANA: I would actually state that I think in this scenario in which we have some data, although limited, that the studies should be done concurrently.

When I looked at the numbers that Dr. Cook presented, 1 out of every 6 patients in those series were under 2 years of age. So it's already happening. These patients are getting the therapy. So I think we should be studying them concurrently. We shouldn't restrict it to the older age groups first because we already have some evidence in those older age groups that it is occurring in frequency between 30 to 50 percent of the patients have some sort of suppression. So we have some indication that occurs in the older age group. Why not extend it concurrently to the younger age group in which potentially it could be more problematic? Because I heard Constantine say over there that he was concerned that the adrenal is not as mature in the younger age groups, et cetera. I think we need that information early not later.

DR. CHESNEY: Dr. Danford and then Dr. Epps.

DR. DANFORD: I think the answer to this question hinges not in a small amount on the meaning of the word "significant" when it's used in the phrase "evidence of significant suppression." Significant might mean a statistically detectable level or significant might mean evidence of some potentially life-threatening problem. I guess I need to know which of these we're looking at or if we can even tell. I might be inclined to allow a laboratory abnormality to occur in a large proportion of

patients in whom I would use a drug like this if I knew that the risk of a clinically recognized bad outcome was extraordinarily low, but I'm not sure we have that with the suppression test.

Are you asking about detectable suppression on the test or are you asking about risks of bad outcomes?

DR. MURPHY: We're asking about the test. If you look at the next part of this, it might make it a little -- we're trying not to prejudge what you're going to say so that's why we divided it out.

If you're doing sequential testing and you're telling them we want the results of the older age group before we go into the next age group, that means that a priori you should have some criteria at which you're going to say don't go into the lower age group. So if we are going to continue to do this, what is the committee's thought again for the test itself, not for the clinical outcome, at which you should say you should no longer go into the younger age group? But it sounds like the committee was beginning to say they didn't even think that we needed to do this sequentially.

Again, if you do it sequentially and you have criteria for just the test that -- I'll just pick a number here -- 50 percent -- when you got to the 5- and 6-year-old, that 50 percent of the children suppressed, then

should you, therefore, go into the next age group? That doesn't mean you won't go. It just means we don't want you doing that trial until we know the results of what the suppression is in the older ones. You may want to put in a safety parameter. You may want to consent them differently. There's just a different process. So that's what we were saying.

Right now we're telling them that they have to do it sequentially. Do you agree that that's correct? And if you do do it sequentially, then what would be your criteria for saying before you just go on to the next lower age group, you need to have more safety parameters in place or reconsenting or whatever? That's really the question in its totality.

DR. FINK: Is this in the context of preclinical, i.e., before the drug is released for marketing?

DR. MURPHY: Yes. Again, that's why I was emphasizing this is in the drug development process.

It could be out there for some other indication, but it's being tested for kids for the indication under study. So it's not been approved for that for children yet.

DR. CHESNEY: Three people: Dr. Epps, then Dr. Stratakis, and Dr. Fost.

DR. EPPS: I would recommend sequential testing continue. As someone who sees pediatric dermatology patients, there are certain seasons of the year when my entire practice could be atopic dermatitis. Those of us who treat these kids prescribe topical steroids and other immune modulators all day every day. There are some medications under which certain ages I don't use, and certainly just like clobetasol or whatever aren't recommended below certain age groups and some of the immune modulators aren't recommended below age 2 because of side effects, I think if you march down, you pick up certain problems that can certainly be amplified in younger age groups. Some of these smaller kids can't tell you I feel bad, I'm dizzy, I'm whatever. They're so busy itching and having other issues.

But I would continue sequential testing. I tend to err on the side -- may be more conservative for safety but I think it's worth knowing. I know it would be a little bit more burdensome to industry as far as testing is concerned, but I wouldn't want to just throw it open and then everybody under the age of 5 has horrible problems when you could pick that up earlier.

DR. CHESNEY: Dr. Stratakis, Dr. Fost, and Dr. Wilfond.

DR. STRATAKIS: First of all, I would like to

ask myself a clarification of the question. When you mean sequentially, what are the age groups that you are thinking of testing sequentially? So are you dividing the groups in post-pubertal, pubertal, pre-pubertal, toddlers, and infants, or what exactly are the age groups that you're thinking of? Then I would like to make a clarification and a comment on that.

DR. COOK: Well, in the studies that we did where you saw the differential, they were divided 9 to 12 and 6 years and then 2 to 5 and then infants. However, in some studies we came to the conclusion that there probably isn't a lot of difference in patients 12 on up to 18. So they're usually grouped together, and then the younger children, and then the infants.

I will say that those studies that you saw were supposed to all have been sequential and it didn't quite happen that way. In one respect, I think it was probably good that it didn't happen that way or we would not have had any data on the infants and the younger children. Actually in one study, no infants suppressed. I don't know why, but some of the older children did. So I think sometimes assumptions can't be made.

DR. STRATAKIS: So I'm in favor of concurrent testing because the 0 to 2 adrenocortical development of zona fasciculata, which is the organ of interest here --

this is the zona that produces cortisol. It is during this first 24 months of life that zona fasciculata forms, and during this time, the fetal zone involutes. We have no data as to what the proper ACTH response of the fetal zone and then the young, newly formed zona fasciculata cells ACTH responses are. We really don't know that. I would favor concurrent testing with ACTH cautiously for these patients. I also would favor an extreme control of administration of these compounds in this particular age group.

Now, after the age of 2, until about puberty or until the onset of puberty, the only changes that take place in the adrenal is the development of the androgen production by zona reticularis. I suspect that this may have something to do to ACTH responses, in particular with androgen production, but I don't know whether it has any effect on cortisol production. I think that that can be done concurrently or sequentially, but it only makes sense to study these other groups and subdivide them in only two age groups. So from 2 to pre-puberty, 8 or 9, and then from 8 or 9 and up would be peri-pubertal and post-pubertal.

DR. CHESNEY: Thank you.

Dr. Fost, then Dr. Wilfond, then Dr. Ebert.

DR. FOST: I'm just trying to understand the

current practice. The description says if there is no evidence of suppression, you proceed sequentially to younger children until all these groups have been studied. If there is evidence of suppression in adults, do you stop there and just assume that the children also will suppress, or do you continue to test anyway?

DR. COOK: Usually there is some defined criterion. With most studies, at that time it was if you found 10 percent suppression. Usually in our safety studies, we suggest to the sponsor that if you find significant safety issues in adults, we can extrapolate downward, but we don't extrapolate upward. So if they want to get the indication in children, for example, then they need to study the lowest age group until they come to a safety problem.

DR. FOST: So if they do first studies in adults and they find substantial suppression, by whatever your criterion is -- let's say 50 percent or something -- do you then assume that you have at least that amount of trouble in children, or do you require them to --

DR. COOK: That's what we have assumed in the past.

DR. FOST: So you only go down when there are negative results or not worrisome results.

DR. COOK: Or not worrisome results. Unless

they want to start a little lower, if they're starting with a pediatric age group, say, 12 to 18.

DR. CHESNEY: Dr. Wilfond.

DR. WILFOND: Norm's question actually has made me want to ask a second question in addition to the first one I was going to ask.

So the new question is it seems to me that even if you did see some evidence of a safety issue, if there was a clinical reason why the drug might still have use and importance in children, you might still want to consider studying it. Is that correct or not correct from your perspective?

DR. WILKIN: Well, once again, I think this is an inference that we thought we were willing to make. If it turns out we have 25 adults and 23 of them suppressed, then the question is what will we learn from studying smaller patients. I think one could safely assume that they're likely to suppress as much as the adults because again, the Cortrosyn test is, we've already heard, described as the bronze standard. Then I think Dr. Ten Have could speak to the smallish kinds of numbers that we're seeing in our series. We're really not talking about point estimates that are very useful in labeling with the enormous confidence intervals. I think what we're really getting out of numbers like 25 subjects is, is there any

chance of adrenal suppression? Is it plausible? Is it very likely? I mean, it's sort of rough semi-quantitative sorts of things when we're down at this numerical level. I don't know. You may want to --

DR. TEN HAVE: Yes, a quick comment on that. In light of the small numbers in each of those separate studies, sort of a pseudo meta-analysis across studies to see if you have any sort of consistency with such wide confidence intervals, consistency in my mind is the best you can get in terms of evidence in favor of a trend. It sounds like you don't have consistency across the different studies. A couple show downward trends and a couple show high immunosuppression rates for the older age groups. So I think it's a mixed bag.

DR. CHESNEY: Dr. Wilfond, I don't think you were finished. Then we have Drs. Ebert, Fink, and Fost.

DR. WILFOND: Well, actually your answer is helpful as I begin my second question. First, I have a comment. I could imagine a situation where we were talking about the use of systemic steroids for a period of 6 or 8 weeks where we were highly confident that it would cause adrenal suppression, but depending upon why we're using it, we might still think that a study was worthwhile in children because we were interested in assessing the efficacy as well as the safety.

Which brings me to the main point I want to get to in favor of possibly concurrent testing, which is it appears that the greatest risks of adrenal suppression is when it's undiagnosed, undocumented, and something happens. Therefore, I think the risks of this are probably much higher in the clinical setting than in a research setting if there was an important scientific question to be asked because those risks could be minimized. So it seems to me that what I would want to know about whether we do concurrent is whether there was a belief that there was an important scientific question to be asked by enrolling children in that study. If it was, I think it might make sense to do that.

DR. CHESNEY: Dr. Ebert?

DR. EBERT: Regarding that, I think I favor the concurrent testing mainly because I haven't really heard a lot of compelling information that the younger children who did see suppression really had any adverse events if they were followed up over a longer period of time.

The other thing I'd just be interested hearing some comments from the endocrinologists is whether we should place a little bit greater emphasis on those who did show suppression and who showed sustained suppression as opposed to just a one-time suppression and then they regained their adrenal reactivity. The numbers that you

talked about were so small because of differences of opinion in who was really suppressed versus who wasn't, I think that's a fairly fertile area for continued study.

DR. CHESNEY: Dr. Fink and then Dr. Fost.

DR. FINK: I guess I'm relatively neutral about concurrent or sequential testing. But I guess what I would ask the agency, I believe you have four options. You cannot approve the drug. You can label it as having no indication below a given age. You can label it as not recommended, or you can label it as contraindicated. It would appear, if we're going to use HPA axis suppression, then you may want to establish percentages for each of those. I have no idea what those percentages should be, but I do think it is different to label a drug as no indication, not recommended, or contraindicated, and if you can establish those break points, it would seem to be the appropriate approach.

DR. CHESNEY: Dr. Fost.

DR. FOST: I have two comments.

I'm not following the rationale for concurrent testing. That is, if adults suppress, the assumption is that children will suppress also. It seems to me a reasonable assumption. Therefore, we can spare a lot of children from having suppression studies because many of these new products are going to suppress in adults, and if

they do, there's no need to test children. If they don't, then you need to go, but why not reduce the number of children? So I'm not following what the virtue of concurrent testing is, what it adds.

Second, to go to the second half of your question of what percent of suppression would be worrisome, 1 percent, 5 percent, 50 percent, that seems to me inextricably connected with the question we asked this morning of how severe is the outcome. If the outcome was death, if 1 in 1,000 children died or 1 in 100 from topical corticosteroids, then it would be extremely important to know about it, but if there are no deaths and if there's no really serious adverse events, then you'd use a much higher cutoff, a much higher threshold because it's a less worrisome problem.

I realize we don't know the answer to that, but I guess, if anything, it just highlights the importance of trying to get some handle on it, recognizing it's difficult to study. But you're being asked to make this decision in a vacuum without knowing whether you're dealing with a very severe adverse event or relatively trivial or nonexistent. I just don't know.

DR. SANTANA: Can I comment on that?

DR. CHESNEY: Dr. Santana.

DR. SANTANA: Since I was a proponent for

concurrent testing, my answer would be that maybe the assumption is incorrect. Maybe the assumption that what you're seeing in adults readily translates to the particularly younger age groups is incorrect. And I got a sense from some of the data that was presented this morning, albeit the numbers are very small and we take them with a grain of salt, is that there may be differences. Some of the younger children were not being suppressed, and I didn't quite understand whether that was a numbers phenomenon or a testing phenomenon. But the assumption that they're the same I'm not convinced of. Therefore, that would be an argument to suggest that they should be concurrently tested.

The second argument is what was being discussed on the other side of the table, that is, that I think maturationally they're different and so the outcome of the bad results of the test potentially could predict what that bad adverse event would be, whether it be that the younger children, because they're suppressed, will be at greater risk of developing worsening problems. I don't know that either, but the suggestion that there are maturational effects in the gland would suggest that there may be some differences that we need to explore. So for those two reasons, I would advocate that we do need to do concurrent testing.

DR. FOST: But the hypothesis would have to be then that there would be a situation in which there's a topical steroid that causes significant suppression in adults but doesn't cause any suppression in children and would therefore be labeled, be really careful in adults, but use it at will in infants and children.

DR. SANTANA: No.

DR. FOST: We're hypothesizing, one, that there would be a product that would cause no worrisome suppression in children, even though it does in adults.

DR. SANTANA: The argument is there is no good data and the absence of data is just as bad as bad data.

DR. FOST: Right, but the only reason to test the children in the presence of suppression in adults is because of the possibility that you may get a different outcome, and the only different outcome there could be is no suppression. So the reason for testing in children is to avoid a situation in which we'd have a product -- the scenario that you're worried about is that we would have a product that should be used in children but should not be used in adults or should be used with great caution in adults but it can be used without any caution in children. That seems to be implausible.

DR. CHESNEY: Dr. Gorman, then Dr. Stratakis, and then Dr. Fink.

DR. GORMAN: I think as a pediatrician, we often focus on the drugs that children have more trouble with than adults, but there's another group of drugs that children have much less trouble with or are handled very differently. I think of acetaminophen. If I give somebody who's over 18 a fairly large dose, I can be pretty confident that I'm going to cause them liver failure. And yet when you look at children under 6 who have taken huge doses acutely, there doesn't seem to be much toxicity at all. Gentamicin, which we use in adults, we have to use 4 to 17 times as much in children, depending on their age. I think there is an argument that children may handle this differently, and I'd echo Dr. Santana's argument that what we don't know we don't know, and I would test to find that out.

Does it put some children at risk? Yes, it does. But it puts a few children at risk, to echo Dr. Wilfond's argument, rather than putting many children at risk after it gets out. If you put a topical steroid on the market, it will be used in children. It just will be. Somebody will use it because whatever else they've tried hasn't worked or some parent will use it. So I think we should know what the risk is. Whether it gets tested concurrently or in a dose-ranging study or sequentially I don't think is the issue. I think the issue is it does

need to be studied because if you would have told me before today's meeting that lotions get better absorbed than ointments, I would have told you I was skeptical. But now I have data that shows me that my prejudice was incorrect.

DR. CHESNEY: Dr. Stratakis.

DR. STRATAKIS: The implication of what we said earlier, that there's a developmental difference in adrenocortical responses is not that we would allow something that would be dangerous for adults to be given to a child, although that might happen in some medications. But as I said earlier, I would have other concerns about what the effects of this would be on the adrenal cortex, in other words, that in this particular group of patients, like the infants, for example, the ACTH test may not be the best way of assessing what the damage is, if there is damage. That's why I said from the very beginning that there's a need for other markers to look at in certain groups. I think we will only find that out by doing concurrent testing and seeing what's going on in the various groups.

DR. CHESNEY: Dr. Fink.

DR. FINK: I think in terms of answering Dr. Fost's question, to some degree it also relates to the package labeling, that if 20 percent of adults showed suppression and you said that was acceptable but it was 50

percent of children and 90 percent of infants, you then might want a package label that says this drug is absolutely contraindicated in infants. And that's important information to me as a practicing physician because contraindicated is different than not recommended, and I think establishing a threshold there could be important.

DR. MURPHY: Joan, let me see if I can summarize what's been said. It sounds like the committee wants children to be studied, that we don't know what we don't know, and that the more data we get, the more confused we're getting here. I'm going to try to construct what -- I'm trying to take it out of what's been said. There might still be a reason to do some of it sequentially, maybe the much older down to 2 or whatever, and then if you saw a very high rate or a high rate, whatever one wishes to define -- if you don't do it sequentially and you go into a study and you're enrolling hundreds, you may not get the kind of follow-up and testing. While if you knew you had an issue in this older age group, you are going to take the assertion, I think, that it's going to occur, until proven otherwise, in the lower age group. Therefore, you might actually want to modify that study so you have more intense follow-up, more intense sampling, other testing that you might want to do

in the lower age group.

Does that tend to synthesize the majority of what I've been hearing around the table, or not?

DR. SANTANA: I would argue that if that's your study design, it's going to be flawed because your different populations are going to be observed differently and with different intent. So if you don't define up front how all populations, independent of age are evaluated or monitored or followed and have the same testing, then you will wind up, for example, detecting that it's 50 percent in the older age groups, 90 percent in the younger age group, but you detected 90 percent in the younger age group because your testing was much different. It was more intense. It was quantitatively and qualitatively different.

So I think you've got to be careful with that. If you start saying we're going to do the study this way -- and then we always do that in clinical research. We start a study one way and we modify it as we learn as we go through. That's the beauty of it. But I think you have to be careful because if you start saying that if you make an observation in the older age group and now you're going to treat the younger age group differently in terms of the observations that you do, you may be detecting different things. And I'm not sure that would be helpful.

DR. MURPHY: I'm not saying you change the criteria for the diagnosis of adrenal axis suppression. I'm not saying that. I'm saying you use the same criteria. And you can do this prospectively so that if you reach a certain point, you then have additional data that you would collect, and particularly I think you would want to -- actually you would have liked to have had it for all, but you may enhance the follow-up for testing to make sure that the patients revert back.

DR. CHESNEY: Dianne, can I ask you, what other drug populations is this kind of sequential testing used in? For example, we would never use it for otitis media. We would never use it for meningitis. We would never use it for a whole lot of other drugs. We would almost first test them in children. So why is this different? Why was it even initially designed differently to be sequential from old to young? And what other drugs --

DR. MURPHY: Well, just two comments. One, the diseases you named are mostly pediatric diseases, so you study them in children. So you designed them mostly based on the pediatric population.

I think the issue here is that it's a safety design issue. We do know -- and I'm trying to think off the top of my head what other products this would be, but we do know that we have products in which a couple of

things happen. Actually it's happened so much that we were in the situation we're in now with products not getting studied at all in kids. You have a safety signal and the division may have decided not to study the product at all, not just not sequentially but not at all, which we know the problems with that. You don't even need to raise your hand. We know. It's out there. It's going to be used in kids. Okay?

Or there is a safety issue. And this is actually something we do have to do at times where because the population that got studied was not as robust -- it's a serious, life-threatening disease or limited options -- you need to get the product out there. There may be other parameters you heard for follow-up or additional studies -- you are not going to go into that pediatric population until you have additional data that you can then design a better trial for children because you had such limited information when you began. So it tends to be more on the safety side that this tends to happen.

I don't know if anybody from FDA wants to enhance.

DR. CHESNEY: I could argue that atopic eczema was a pediatric disease too. In this setting, it seems to be a separate issue.

But what are other examples of drugs that are

used where you go down sequentially from the older groups?

DR. MURPHY: I was trying to think of them.

DR. SANTANA: Wasn't that done in some of the HIV trials?

DR. MURPHY: I was going to say HIV. That was the area that really actually changed a lot of pediatric testing because that's what they were doing. Products weren't getting studied in kids.

DR. FINK: It's true for 98 percent of all asthma drugs. They are always studied in the adult population above 18 before they move into pediatric trials.

DR. SANTANA: We were talking about the designation of the different pediatric age groups and moving from the older to the next younger age group.

DR. FINK: Right, and that's what happened to the asthma --

DR. SANTANA: HIV was the model that kind of presented this.

DR. MURPHY: But I do want to make an amendment to the HIV statement. Once we started studying products for HIV in the pediatric population, actually the pediatric population became the predominant database in some applications. So it just has happened. And there are certain products where they may study them first in adults before they decide whether they want -- because, remember,

sometimes these are completely new molecular entities, and people really don't know that much about them. Particularly when you get into the very young kids, back to some of the older reasons, they can't articulate some of the things that you wish to assess. So they want to have a better understanding, if they can obtain that, before they move into the younger population.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I just want to amplify Dr. Chesney's comment, which is these are pediatric diseases. Well, excuse me. Some of them are. Atopic dermatitis and eczema are pediatric diseases, and it's only because you survived long enough to get into adulthood that they then become adult diseases. But they start in our age population, and I think they should be studied in our age population. Psoriasis I will give to the adult dermatologists. But these diseases are our diseases.

I would think that pharmaceutical companies might consider wanting to try their agents on the uninitiated patient, in other words, so the signal to noise ratio for both the therapeutic effect, as well as the potential risks of therapy, would be the cleanest as opposed to people who have been previously pretreated with other therapeutic options.

DR. CHESNEY: Dr. Schneider and then Dr. Fink.

DR. SCHNEIDER: Well, clearly the drugs will have to be studied in the population that they're intended for. So they'll have to be studied in pediatrics.

The question is whether to do sequential testing or not. Part of the answer, as I see it, is what is the risk to any patient during this test. This is a very circumscribed period. It's 2 weeks, 3 weeks, 4 weeks. Presumably they're being monitored. And even if there is HPA axis suppression, hopefully they'll be monitored until their not suppressed, or they'll be followed appropriately. So if there is zero risk to these kids -- if -- then concurrent testing is probably okay. I mean, you're going to have to do it anyway, so it would be okay.

But let's say there isn't zero risk. From the data I heard this morning, there are always one or two people who remain suppressed and they're either lost to follow-up or Lord knows what happened to them, and we don't know. Furthermore, very little kids are very much more vulnerable to the effects of a subtle problem. I feel lousy. I'm sort of dragging my feet and so on and so forth. And they can't really complain the way older kids can. So they are more vulnerable.

So now you have an ethical problem because you have a disease for which there are already 11 different fluorinated steroids, and the efficacy seems to be the

same. And along comes a 12th fluorinated steroid, and unless it's in -- I don't know -- peanut oil or something where there may be some claim that it's less systemically available, it's the umpteenth drug. So now you have a child with an illness which is serious but not life-threatening for which there are other drugs that will be presumably equally efficacious that are already on the market who is now going to participate in a clinical trial of a new molecular entity. Will there be an ethical problem there? In my opinion there is if there is an ongoing risk.

DR. CHESNEY: Dr. Fink, then Dr. Fost.

DR. FINK: It would appear to me that the critical question here is can you rely on atopic dermatitis in adults as having the same underlying pathophysiology as it does in children and younger, in infants, because if the pathophysiology is similar enough to be predictive, then I would maintain that the Helsinki Agreement would mandate sequential testing. If the pathophysiology of the disease is different, then you could justify concurrent testing, but if the pathophysiology, as it is in asthma, is deemed to be the same, it would be considered unethical to do pediatric trials before you've completed the adult trials.

DR. CHESNEY: Dr. Fost.

DR. FOST: If the subtle clinical effects that

Dr. Schneider refers to were being studied as part of the evaluation process, then that would be a strong argument for concurrent testing, but since the only thing that's going to be monitored is the simple laboratory value, I mean, you're right. It may be that these laboratory values have other effects besides death or serious adverse events, but since no one is studying them, I don't know what it is.

I am persuaded by Dr. Fink's suggestion, though, that the incidence of suppression might be much higher as you go down and might lead to a difference between warning, education versus prohibition, if you had a markedly different incidence of suppression.

DR. CHESNEY: Dr. Wilkin.

DR. WILKIN: If I could just comment on some inferences that we have been willing to make. First of all, corticosteroids are somewhat unique in the indication. Most indications are for signs, symptoms, specific syndromes, diseases. It has a self-referential indication. Corticosteroids are indicated for corticosteroid-responsive dermatoses. I mean, this is paleo-regulatory. I don't know how ancient this really is.

(Laughter.)

DR. WILKIN: But I think it gets back to the question we heard. Can we assume that atopic dermatitis in adults is the same as it is in children? I'm not sure we

actually have to decide that to take efficacy data from adults which could tells us about corticosteroid responsiveness, if you will, and then also combine that with data from children.

What we've been willing to do with the corticosteroids in atopic dermatitis is efficacy can be demonstrated in adults and we're willing to extrapolate efficacy downward. But in general, we have wanted to extrapolate safety, if we're going to do that, upwards. So if it's very safe in the youngest children with large body surface area involvement, then we have been more willing to extrapolate to adults.

I mention this because there are limited resources, and it does affect ultimately the price of drugs. I think if you think about how the word "elegance" is used in organic chemistry, the organic chemists talk about an elegant synthesis as one where you have the fewest number of starting sorts of things, the fewest number of steps, and you get the highest yield. Mathematicians use the term "elegance." They talk about an elegant proof, which is the fewest logical steps that really make the case.

I think we could argue for regulatory elegance. I mean, it's not a way to minimize burden for industry per se. It's really trying to find the data set that is both

necessary and sufficient. And that's what the spirit of our question is. What is really necessary and what is sufficient for us to label these products?

DR. CHESNEY: Dr. Wilfond.

DR. WILFOND: Yes. I appreciate your comment. One of my thoughts about that is it would certainly never be enough just to include children because you won't learn anything unless the data is then reported for that particular subgroup. Certainly I've seen in many asthma studies where they will include people from ages of 15 and above or 12 and above and not report a particular pediatric subgroup. So even though children have been included, the readers of the journals never actually learn anything special about the children. So I think one of the things that will be critical, if children were included, is that we would have the data reported back for that population specifically.

DR. COOK: We do usually ask for subgroup analysis for a specific age group.

DR. WILFOND: Great.

DR. CHESNEY: Dr. Epps.

DR. EPPS: Though I do favor more sequential testing, if you were to get a certain percentage of adults that had a side effect, it would be hard to convince my IRB that it should be tested in children. So that's a

consideration too as far as testing is concerned.

I would also have a hard time recruiting if I said, well, we've tested this in adults and we've had a lot of complications, but we want to test your child. So that needs to be taken into consideration.

DR. CHESNEY: Dr. Glode.

DR. GLODE: Just a comment from the world of vaccines and related to the necessary and sufficient issue. In general, for vaccine development, it did proceed sequentially. I guess one could have argued the ethics of giving an H. flu B vaccine to adults who had very minimal risk of disease from that organism because of their natural immunity. But it was a safety issue because it was vaccines that were going to be used universally and recommended for millions of children every year.

So, I mean, necessary and sufficient. 57 children less than 2 cannot be used in the same sentence with necessary or sufficient for a product that might be used in -- I have no idea. Somebody has to tell me how many millions of prescriptions are marketed every year for these drugs. But if the prevalence of the disease is as represented this morning, then that's a lot of people using it. So I sure wouldn't have thought 57 2-year-olds was anywhere near enough to be talking about using that drug in that population. I favor sequential.

DR. CHESNEY: Maybe a way to summarize this, it sounds like nobody is against sequential, and I think many of us feel strongly that it should be tested in children unless there's a very, very real reason when you get to some point not to continue.

But I'm also very persuaded by Dr. Fink's comment and Dr. Gorman's that unless some study is done in children and it can be explicitly stated that this is contraindicated, it will be used uniformly, and then we're right back as if we had done nothing. So I think most of us would say sequential was okay, but at some point we want to be sure that it's looked at in children so that some statement about whether it's contraindicated or not could be made.

I don't know if I'm expressing that well. If somebody else would like to summarize it better.

DR. FOST: If you think they all should be tested in children regardless, then what's the point of sequential?

DR. CHESNEY: Well, no. Dr. Murphy I thought made a good argument that if you have danger signs in the adults or the older children, you might test it differently in the younger children, not that the test would be different, but that your consent might be different. I think that's what I heard you say.

DR. MURPHY: Or you could prospectively design a trial so that at a certain critical definition that you would have a different type of follow-up, you would do more intensive type of follow-up and maybe for testing to make sure that they revert. That was, again, focusing more on the safety part of it because that's really what we're trying to get at here since the division is willing to extrapolate the efficacy.

DR. CHESNEY: Dr. Glode and Dr. Danford.

DR. GLODE: I need an ethicist here to comment on whether we have a moral obligation. The example that comes to my mind is the fluoroquinolones at least initially contraindicated in children, not based on giving it to children a subset and proving it is extremely harmful. Right? I mean, based on animal data. And then people said, but they're such good drugs. Can't we study them very carefully, et cetera? So that happened.

But I would have a problem saying now let's find a subset of children because we think this is dangerous in children, but we want to establish it so we can get the contraindication instead of the "has not been studied." Isn't that an ethical problem or not?

DR. CHESNEY: Well, we'll find out from the ethicist, but for me -- what do I know about ethics? But for me, the test itself is not dangerous. In other words,

the 2 to 4 weeks of testing. I don't see that as being dangerous. I see the continued used, when we don't know what the bottom line is, and the use totally untested is much more dangerous to me than exposing a small number under very controlled circumstances with everybody well informed and so on.

DR. TEN HAVE: Excuse me. Are we going to be able to answer that question with the types of studies that were currently done, the short, follow-up studies to look at long-term use to answer your question? Is that question going to be answered?

DR. CHESNEY: With what I just proposed or with what's going on currently?

DR. TEN HAVE: What's being done currently with the types of clinical trials that are currently being done in adults.

DR. FOST: You're asking whether there may be long-term toxicities that we'll never know about.

DR. TEN HAVE: Yes, and the question you asked. I think everybody is concerned about long-term use and less concerned about the short-term use that the current studies are addressing.

DR. CHESNEY: What I was addressing was simply the short-term, 2- to 4-week. If that shows 90 percent of children ages 2 to 4 years are suppressed, then I am

anxious about recommending that for use whether it's just acute or whether it's a chronic issue. Does that answer?

The ethicist, please.

DR. FOST: Well, I think your point you said well, Joan, that it would be problematic to do that if what you were asking the parents to expose their children to was something that was life-threatening or could cause serious disability or severe pain or something. But what we're talking about is 2 weeks of something with a few blood samples. I don't think we're asking parents to volunteer their kids for something that's so onerous. It almost meets minimal risk criteria. It would be problematic if that were not the case.

DR. CHESNEY: Dr. Wilkin.

DR. WILKIN: I heard the word "contraindication" used on several occasions, and 201.57(c) of the Code of Federal Regulations actually describes what goes in different sections of labeling. Things that might be a potential risk and perhaps from animal data, that would be more of a precaution. A contraindication is something that would be expected for most people. It's been seen in humans. In general, our labeling does conform to those kinds of standards. I do understand you can find labeling for specific products that may not completely be consistent with that, but at least that's the way we're

supposed to go with it.

Having said that, what we've usually done with the adrenal suppression data set is trim the indication. In the indication section, we have said indicated for ages, and then whatever age at which we didn't see much suppression, that age and above. So that's generally how we've operated with this. Then in the precautions section and the pediatric use section, that's where we've laid out the data for the children and the adults or whichever age groups.

DR. CHESNEY: Dr. Schneider.

DR. SCHNEIDER: I will just make a comment that whether one does sequential testing or concurrent testing, in my opinion with the data that I saw this morning, these controlled studies need to have tighter control. There were patients who were lost to follow-up. There were people with adrenal suppression and we don't know the answer to what happened to them. So I don't think this is as simple an issue as you're going to study 15 kids or 50 kids or whatever for 2 weeks and at the end of 2 weeks, we'll know what happened to all 50 of them. At the end of 6 weeks, we'll know what happened to all 50 of them. In the real world, this obviously isn't happening.

Although ultimately the drug should be studied in this population, I'm concerned that ethically I think

it's mandatory to get the information on adults and in older children first before going on to these studies and also fixing the protocol if you can.

DR. CHESNEY: Dr. Murphy, have we answered question 2?

DR. MURPHY: As best as I think we can.

(Laughter.)

DR. CHESNEY: Thank you.

DR. MURPHY: Now, before we go to the third question, I want to just reiterate a little bit what has been said throughout the day. What we are asking you here -- we're going to go through a couple of facts, restate the facts and a premise, and then ask you to help us with the risk management program -- is in essence, in the state of knowledge that presently exists in which we have a known laboratory test which we know has potential severe adverse outcomes if one has adrenal axis suppression and one has a stress and one doesn't get treated and one has maintained that suppression -- we have those facts, but we also have the fact that we don't know how this is playing out clinically, and I think we tried to make that clear. From our adverse event reporting, we've seen a couple of cases where there's been clear results of overuse and misuse and suppression. But we really don't have, for the millions of prescriptions that are out there and have been issued and

are being used, a clear idea of what the clinical outcome is of the use of these products with this ongoing suppression because we do know that the products are not always used as directed and we do know that most of the kids, though we didn't have the long-term follow-up that we'd like, appeared to revert to normal responses, as far as their adrenal is concerned. So we're in this state of knowledge which is we really don't know the clinical state of how many children are having bad outcomes because of the suppression.

In that state that we are in, we're asking you, should we do anything else? The options are do nothing. Wait until we get additional studies, information, data. We have a better handle on it. Or implement some sort of program. So that's really what this third question is about.

Let's go through the facts. The facts are that there are only a few post-marketing cases of adrenal suppression in patients using topical corticosteroids. That's what you heard this morning. The AERS reporting system and what we've been able to glean from other literature.

Fact two. Data from clinical studies has consistently demonstrated that a percentage of pediatric patients using topical corticosteroids under the maximal

labeled use conditions will experience adrenal suppression. This suppression is most likely transient in nature -- and you understand the limitations of this statement -- and related to extent of exposure.

Fact three. Patients with a post-ACTH stimulation cortisol level of less than 18 micrograms per deciliter by cosyntropin stimulation testing require corticosteroid replacement at stress doses if they experience trauma, sepsis, or are challenged with any other cause of physiologic stress.

The premise is it may not be recognized that the clinical course of patients who have undergone trauma, sepsis, or major surgery is complicated by adrenal suppression for underlying topical corticosteroid use and hence this adverse event may go unrecognized and under-reported.

Given the above information, does the subcommittee think this represents a clinically significant or relevant concern for pediatric patients exposed to topical corticosteroids? If yes, should any additional risk management action be taken? Please discuss which risk management approaches below you think would be appropriate and why if you answer yes.

And we've listed -- I'm not going to read them all off. How many is it? 10? Yes, 10 different actions

that are part of a risk management program. We unfortunately have them on two different slides. But it begins with do nothing more but get additional studies and then to such things as the FDA is very good at, putting in boxed warnings, limiting it to certain age groups, which we've done, recommendations against use in certain age groups, which is slightly different, and then into these areas of actual contraindicating, then into the things that are really the risk management program issues. So it's do nothing, get more studies, do what the FDA usually does in labeling, do something more to our labeling, or include also additional risk management programs, as you've heard about this morning, if I could sort of lump them for you.

DR. CHESNEY: Dr. Santana.

DR. SANTANA: Dianne, can I ask you a question of clarification? Are these 10 points a graded system that the agency uses kind of generically, or are they just all out there?

DR. MURPHY: Well, we tried to do that. Like at the bottom, you've got education programs for providers. That would not be considered as more intrusive than the medication guide. So it isn't completely in priority of activity.

DR. CHESNEY: Dr. Epps, Dr. Ebert, and Dr. Glode.

DR. EPPS: As far as suppression is concerned, it may be under-reported and unrecognized. So therefore that's where additional studies would come into play. The agency will be happy to know that parents do read inserts in packages and everything given out by the pharmacies, and they will say, I'm not comfortable with this medication. I'm not comfortable with this. So, therefore, before putting that there, I would study it so that they don't become unnecessarily alarmed by the use of topical steroids because in most cases it's well tolerated. It's used sparingly. That's our mantra, sparing use of a topical steroid.

I think education programs for those in the ER and anesthesiologists and people who are doing procedures is reasonable, although emphasizing that we don't have exact numbers and we don't know exactly the extent and certainly additional studies are ongoing.

But as far as boxed warnings and packaging and giving out with every description, I probably wouldn't do that at this time.

DR. FOST: Because you're worried about alarming people?

DR. EPPS: Yes. We use topical steroids all the time every day, and certainly -- knock wood -- I don't know that I've had anybody with suppression. Maybe they're

out there or maybe that's part of the lack of recognition, but I'm certainly more comfortable with that as opposed to oral steroids. I don't use that very often at all, under certain circumstances. So if you're using just a small amount and they get better and you have proper follow-up, a lot of those problems that we were having described don't necessarily occur, and people with severe atopic dermatitis -- there are always those outliers who need more medication, who need stronger medication or have extensive body surface area, but you follow them. You follow them very carefully and you wean them down and you use the medication so they don't crash. Honestly, they probably do have some suppression, but they don't necessarily manifest the fever and feeling poorly and the hypotension or whatever. But they need to be followed. You don't send them out with refills for a year. Some of the side effects we've been hearing about, someone used it for 10 months in the diaper area. Was someone not following them? I mean, I wouldn't give someone refills that they could fill, you know, clobetasol 8 times in 2 months. That's not going to happen. Sometimes that's insurance motivated too. If someone is calling you back for refills, you say, well, if you've already used up your refills, you need to come in and we need to look at it and talk about it because either it's not being used properly or it's not helping. So I

think there are some management issues. But I don't think we need necessarily to alarm people or parents or physicians even about a problem that we really can't quantify.

DR. CHESNEY: Dr. Ebert.

DR. EBERT: Just a question for clarification. Are these strategies strategies that would be applied to the class of compounds or products as a whole, or would we be identifying certain high risk products within the group and targeting those specifically?

DR. WILKIN: I think it's unlikely that we would be thinking of these with the hydrocortisone that's over the counter. It's really intended for the upper end products where we see signals of suppression. That was the intent.

DR. CHESNEY: Dr. Fost and then Dr. Wilfond. Oh, I'm sorry. Dr. Glode is first.

DR. GLODE: Thanks. Just under the category of additional studies, it's really a question for the dermatologists here, the issue of clarifying the population. I would like to see studies done -- but maybe this is impossible especially with the sequential model -- in steroid-naive patients or at least be very certain about when the last time it was used and have some criteria that has not seen steroids for 2 months or 3 months or something

prior to entry into the study.

But my question for the dermatologists is the chronic intermittent use issue. So presuming you are referred the patients with the more recalcitrant atopic dermatitis that you're treating, on average how many times in a year might you use topical steroids on a given child with significant atopic dermatitis? Three or four times or once? Is there chronic intermittent use? Would it be frequent?

DR. RAIMER: There is chronic intermittent use. I think most of us try not to use anything that's mid-strength or stronger longer than 2 to 3 weeks at a time, and then you'd like to give them a rest period. But often with very chronic severe disease, you do that multiple times during the year. In other children you don't. You do it once or twice. It depends on the severity of the disease and the chronicity of the disease. But it's frequent that we give them multiple courses during the year.

DR. GLODE: So I think that's an additional study, the chronic intermittent population studied to see what their axis looks like.

DR. CHESNEY: Dr. Fost and then Dr. Wilfond.

DR. FOST: Well, a couple of things to summarize my view on this list. Good ethics starts with

good facts, and this is a classic in trying to base policy on inadequate information, namely the clinical relevance of this laboratory measurement. So any policy you come up with is going to be suspect because it's just not data-based. I don't consider the laboratory evidence sufficient. So the first point, additional studies, to me is the most important thing. Get the NIH interested in this or somebody who can do those studies.

Second, all the things on the list that have to do with education seems to be desirable. I agree with Dr. Epps, we don't want to have bad education or alarming education or misrepresented education. But all these things about boxed labels and patient package inserts, physician education, physician label stuff and so on all seems to me desirable, namely to mainly put this red flag out there if used to excess, if used for more than X number of weeks or without your doctor's advice. There are potential life-threatening dangers. It seems to me all that would be to the good to discourage inappropriate use of it.

Third, on the indication and contraindication use, it seems to me desirable to do what you can to have these more potent classes used as a last resort, that is, to have the indication say this is indicated when milder topical steroids fail. Now, I heard there is some argument

against that, that the sooner you clear it up, the better, and there may be a less good clinical outcome if you try to march up the ladder of potency. I haven't heard quite enough about that to be sure. So if there's a strong argument for starting with the bomb, then that would undermine what I just said.

But if that's not clear -- I've heard different comments from different experts around the table about whether there's overuse of the potent steroids, whether they're really being overly prescribed for children who might do very well with less potent. So I'm not sure what the facts are there, but if the facts are that that's true, then it seems to me the recommendation should be you don't use a nuclear weapon when a fly swatter will do.

I think that sums up my comments.

DR. CHESNEY: Dr. Wilfond.

DR. WILFOND: I just want to reiterate two of the points that Norm just made. But with regard to the additional studies, I think again it's not just additional studies prior to approval, but really what Norm was talking about earlier today, the idea of the Kaiser study of lots of people to see what the clinical outcome is. I think that's the sort of study that's needed. It's not typically what a particular sponsor would do in a new drug application. So it really would require some other way of

getting that study done, but I think that's really critical.

With regard to the issue of indication, I agree it does depend upon when it's necessary, but I want to return to a point that I made before. It's my understanding that part of the issue of considering something an indication is that if it's an indication, then there's the opportunity for direct to physician marketing of that indication by the sponsor. I think that's where I would have to the greatest concern about inappropriate use because I've certainly seen in my own practice of pulmonology pediatricians doing things in response to what's available such as Obenix that makes no clinical sense, but all the pediatricians are doing it because it's marketed. There there are no issues of side effects, but I would worry about it if the drug we were talking about was likely to have side effects.

DR. CHESNEY: Dr. Fink.

DR. FINK: I think I would agree with the agency and say yes to this. In terms of education, there is part of me that says this justifies a boxed warning about HPA axis suppression because I think anything less than a boxed warning won't really get physician attention. I wouldn't go beyond saying HPA axis suppression, but if you feel HPA axis suppression is a major side effect, then

the data that was presented here today would pretty clearly, I think, justify a boxed warning about it.

But I think the devil is also in the details. I think there should be a patient package insert, but a patient package insert that says, use the least amount, use it for the least period of time, and be sure to inform your physician that you're using this medication on your child or yourself in a condition of stress or if an accident occurs, or if they're very sick, is different than a patient package insert that might say, it causes adrenal suppression. I'm not sure a patient package insert would even have to mention adrenal suppression. It could just talk about proper use of the drug and making sure you inform your physician that you're using this drug. Some of it is sort of overlapping, and the real issue is how it's implemented.

DR. CHESNEY: Dr. Stratakis.

DR. STRATAKIS: I think it is very important that in the letter provided to the healthcare providers that some sort of a disclaimer that we are, in fact, doing additional studies to see what that value of 18 micrograms per deciliter in response to the Cortrosyn test means. That is very important. I wanted to bring back something that Dr. Fink had said earlier this morning, that we don't want to try to prevent a problem by creating another

problem, which is giving these patients extraordinary amounts of glucocorticoids to treat a laboratory value. 18 micrograms per deciliter at this point is a laboratory value.

Then to extend this fear a little bit further, we don't really know what stress doses of glucocorticoids are. If you look in the literature and try to find out what is being used for stress doses for glucocorticoids, that's quite arbitrary. I know this is outside the scope of this presentation, but I'm just emphasizing the need for that disclaimer that, yes, there is a risk for suppression based on that 18 micrograms per deciliter value, but additional studies are ongoing to define what exactly that means.

DR. CHESNEY: Dr. Epps.

DR. EPPS: Thank you.

Well, certainly I think education or knowledge can be very powerful. I'm not an intensivist, but the diagnosis you don't think about is the one you miss. If you have a kid who's not getting better and somebody is using potent steroids and doesn't think about it and they're suppressed, maybe that's an issue.

Certainly in dermatology and pediatric dermatology, we have people we work with such as the preacher who gives advice about medication and the aunt who

gives a medication and grandma and the health food store, they've got some kind of remedy for it. There are lots of things that people put on skin to treat eczema and atopic dermatitis from other people's recommendations. So usually -- certainly myself and some of my colleagues -- we always do a thorough medication evaluation. What are your home remedies? What do you get from the health food store? What do you get from your doctor? What do you get from your friend? Because usually people aren't using just what you give them. They're using other things too.

DR. CHESNEY: Dr. Schneider.

DR. SCHNEIDER: It seems to me that we do have a lot of information. In fact, I've learned a lot today listening to all of these data and these results. We do know that these drugs get systemically absorbed. We know that they not only can suppress the HPA axis, but they can cause Cushing's syndrome in a small number of patients and hypoglycemia and so on and so forth. And we know that perhaps as many as 20, 30 percent of people who take these drugs have evidence of a systemic effect manifest biochemically, but still a systemic effect after just a few weeks of therapy.

We also know a lot about the natural history of this. We know that, for example, if this practice continues to 6 weeks and 8 weeks and 10 weeks, there will

be more systemic effects, and the patients will be more at risk.

So the trick is to change the level of warning without really changing practice that much. In other words, if a patient really needs the medication, by all means give it to the patient, but the physician should understand that this is not a 100 percent risk-free practice and that this is not just some bizarre laboratory problem, but that diligence is required.

Really oftentimes, at least in general medical practice and endocrine practice with patients on systemic steroids where there's a recognized risk, that diligence is enough. It doesn't mean that we're spraying everybody with tons of steroids. Even if we treat them presumptively during stress with a couple of hundred milligrams of hydrocortisone given for a day or two, I don't know of any terrible adverse effect of doing that, of being overly cautious.

In my opinion, the labels that I have seen that I read through do not adequately warn about this. I don't think that they give a serious enough impression about this problem. You read about 1 or 2 percent of the material is absorbed through intact rat skin and maybe 1 percent through intact human skin and so on and so forth. We have no idea how much is absorbed across diseased human skin.

There's this constantly recurring phrase about prompt recovery, which I really can't buy, given the data that we've seen. So I think that the label needs some work.

In addition, some of the suggested laboratory tests in the label I think are just outmoded and wouldn't be used. For example, using a 24-hour urine cortisol to screen for this. That's not what the test was even developed for, let alone this. You can have a normal 24-hour urine cortisol and be really suppressed. So that really should be taken out of the label.

The basal levels of cortisol one can argue about, and perhaps it's all right if it's over 13 or 14 in the morning spontaneously and maybe not all right if it's under 3 or something like that. But basically I think that part of the label also needs to be addressed.

But I think that the major tone of the label is not serious enough in addressing this problem in my opinion.

DR. CHESNEY: I was going to take the chair's prerogative and weigh in myself unless Tom makes me ask others first.

I've also learned a great deal today. I never take a topical therapy history. It's so you got steroids. Now let's worry about why you're so sick with RSV or why you happen to have meningitis. So what I've learned is to

take a history of topical steroid use: how long have you been using it, how long has your aunt been giving it to you to use even though I didn't give it to you to use? It didn't occur to me until we addressed this issue that I should be thinking stress steroids, which doesn't mean I'm going to give them probably ever without consulting my endocrinologist, but I will consult the endocrinologist now and say this child has been on them for 10 months and now has West Nile fever. What about that? What do I do about that?

I think bringing it to the attention of parents that -- and I agree we don't know. We don't know the significance of this. We do know that inappropriate use has led to some complications, but making it apparent to them.

But then the last point is that whatever we do with the label in the box, that's not where it's at. Most of us never read those. The patients never read those, or not very often and don't know how to interpret because they're rats and dogs and birds and stuff. And I'm not putting anything down. It's just that I think that some of the other alternatives that were presented to us today by Dr. Trontell should be pursued. It has to be something that is brought immediately or soon to everybody's attention, including the parents. And I don't think it has

to be alarmist. I think it just has to say we've gained new information because we now study drugs in children, and this is just something to be aware of.

So I think Dr. Fink was next.

DR. FINK: In terms of additional studies, one that might help lend some clarity to this would be to actually look at an ICU study of drawing serum cortisol levels on admission and looking at history of prior topical steroid use with the premise that if someone is in this ICU, has already gotten there and is obviously pretty stressed, if they have low levels of serum cortisol, they probably need to be treated with stressed doses. But how often that occurs would also come out of that data because the one thing that bothers me a little bit is in the intensive care unit, nearly every study of super-systemic steroid doses, whether it's for treating sepsis or treating ARDS, has failed to show clinical benefit, and I sure don't want to encourage intensivists to just start using more steroids on random patients. But I think a well-designed study to look at serum cortisol levels in the stress situation, particularly in those patients who have a history of topical steroid use, might be very illustrative.

DR. CHESNEY: Other comments? Would you also like ideas for studies, or do you have more than enough of those?

DR. MURPHY: We always like ideas for studies. We got a couple good suggestions here. I'm still hearing a balanced opinion that giving information out to the patients is not the way to go, that maybe we need to first give information out to the healthcare providers. I'm still not clear on the message here as to whether we need to do --

DR. FOST: I thought the only disagreement was what information to give to patients. It's not whether. I mean, not give overly alarming, not mention cortisol levels. I mean, the practical stuff: don't use this more than X number of weeks without your doctor's prescription.

DR. MURPHY: But a lot of that is already in the label. Right? So I think what we're saying is what Dr. Schneider said, that some of this is already in the label. So are you suggesting --

DR. FOST: I'm talking about patient handouts.

DR. MURPHY: That's what I'm trying to get at. There are different mechanisms that we have to go through, as you heard.

DR. FOST: I think almost everyone agreed that a patient handout that gives them practical information, number one, about misuse and, number two, if your child is sick or --

DR. MURPHY: Because I didn't hear that.

That's what I want to make sure --

DR. FOST: We're all nodding our heads.

DR. MURPHY: -- that the committee wants a patient handout.

DR. FOST: Yes.

DR. MURPHY: Okay, because I thought you said the patients do read them but then you didn't want to worry them. But now I'm hearing we do want to give it to them and we want to just make sure that it's not alarming, it simply states some facts, and make sure they know to tell people about their topical steroid use.

DR. CHESNEY: Just to bring it to your attention or this may not have been -- I think the label in the box they just don't read. So unless the provider explicitly states it -- and many of us as providers didn't really think or weren't paying enough attention to this issue. So I think the providers need to hear it separately from the label and the patients need to hear it separately from the provider.

DR. MURPHY: And the other thing I want to make sure of is that what you're saying is you are favoring a patient package insert, not a medication guide. One is mandatory, the other isn't. Most of them now, as Dr. Trontell said, tend to follow this very helpful question and answer approach. Maybe we need more discussion on that

whether it's to be a PPI or a medication guide. Again, you heard what the usual use of the medication guides is for. So just to clarify which way the committee is suggesting.

DR. CHESNEY: I note Dr. Gorman wants to speak.

That has been the puzzle for me because the Lindane medication guide you gave us is very clear, and I haven't seen some of that information anywhere else. I mean, putting the cream under your nails. I never saw that before. That's extremely good information. And I've written articles about scabies, which doesn't say much for my articles I guess.

(Laughter.)

DR. CHESNEY: It was very thorough. I thought that was really excellent.

On the other hand, is this alarmist if we do that? The other part of me has said, well, maybe we should just put it in the box.

Dr. Gorman.

DR. GORMAN: I think the focus of what I would hope would be a patient package piece of information and not the mandated, got to be given out, is that just because it just goes on your skin doesn't mean it doesn't have effects on the rest of your body because I think that would apply for a lot of dermatological products besides just steroids. It would then focus on the fact that this has

systemic effects -- excuse me -- has potential systemic effects. You might make it as a class. You could put it in creams and ointments and maybe not be so fearful.

Steroids in their various forms and formulations are probably the most widely used drugs certainly that we use or certainly the most often chronically used drugs between asthma and atopic dermatitis and certain other viral infectious diseases where they help the symptoms if not the disease process.

They're certainly the drug that pediatricians get sued successfully the most on. If you're going to sue a pediatrician for malpractice, they're going to lose on steroids rather than on any other drug.

So these are drugs that I think the community out there knows about.

I'd like to amplify on Dr. Epps. There's a fair amount of steroid phobia out there already. I would hate to see that magnified and then prevent people from using what is generally an effective medicine, and while its safety may be in some doubt, it's very effective for the diseases we use it for.

DR. CHESNEY: Dr. Andrews.

DR. ANDREWS: Well, I think education is always a good thing, and education of patients, parents, and physicians, including physicians who will be treating

patients and perhaps not asking about history of topical steroid use. It's a good thing.

I worry a lot about making policy without data, and we don't have clinical data to support this surrogate endpoint. So I worry about precedent if we moved in the direction of a mandatory medication guide when the other medication guides that are out there are for very well-documented, serious risks.

I also think about what are some other hypothetical risks in other patient populations and in pediatric populations that we're not warning about, and would there be some unintended consequences and scaring of people against very important medications to actions that may be more harmful.

So I would go in the direction of some kind of patient education, not a mandatory medication guide.

DR. CHESNEY: Dr. Fink.

DR. FINK: I think we have to be a little careful because it worries me a little bit as a pulmonologist who deals with asthma. If an inhaled corticosteroid at the clinically appropriate dose caused adrenal suppression in 20 to 40 percent of patients with chronic use, it would never get approved for marketing. I'm not sure what the risk of HPA axis suppression is, but in many other areas or arenas it is accepted as a

significant risk of something and 20 to 40 percent occurrence would be considered unacceptable for a new drug.

DR. FOST: Doesn't that have to do with the chronicity of use as compared with these patients?

DR. FINK: Well, it's used chronically but it would still be considered unacceptable if you got that side effect.

DR. FOST: There's a difference between HPA suppression for a few weeks several times out of the year as compared with an asthma patient who is on it all the time.

DR. FINK: Yes, except many of these steroids do get used quite chronically in the moderately severe to severe atopics.

DR. SCHNEIDER: Could I ask a question? It wouldn't be approved for use given the fact that there are other agents that don't -- if you didn't have the other, of course, it wouldn't be. But if you didn't have the other agents, it might be approved for use, as would be systemic steroids where you'd have 100 percent suppression.

Also just a comment. I don't see this exactly as a surrogate basically. This is part of the pathophysiology of a sequence of events that will lead to X down the road. And it probably won't if the drug is used appropriately. Even if it sort of, kind of does, if

there's appropriate consciousness-raising among the physicians and other healthcare providers, then steps can be taken. But there must be a way to educate the public, starting with the physicians, without stopping the appropriate use of these drugs.

DR. CHESNEY: Dr. Fink and then Dr. Glode.

DR. FINK: I guess a question maybe for the endocrinologists. Coming again from pediatric pulmonary, it's known that inhaled corticosteroids at clinical doses that are acceptable and do not cause HPA axis suppression over long periods of time do contribute to calcium loss and some osteoporosis. They do contribute to cataracts. Is there any reason to suspect that prolonged use, even if intermittent, of topical steroids wouldn't be related to some of these same issues that we have studied or investigated?

DR. SCHNEIDER: No. I think that basically a steroid is a steroid. It's action is fairly well defined by its receptor affinity and which receptor it occupies. I think that the dose response for bone effects and growth and loss of calcium is shifted to the left actually, surprisingly, of that of HPA axis. So I think there's no reason to believe.

DR. FINK: Which would make then the finding of HPA axis suppression indicative of other potential side

effects with intermittent chronic use.

DR. SCHNEIDER: Absolutely. It just indicates to me that the material is getting absorbed and it's acting.

DR. FINK: Therefore, the risk is higher. To me that becomes then a significant --

DR. SCHNEIDER: It's mitigated only by the fact that it's used -- or the hope that it's used intermittently and appropriately.

DR. FINK: I think that is very different than how I think 99 percent of physicians view topical steroids. If you said do they cause osteoporosis with chronic use or risk of cataracts, people would say no.

DR. SCHNEIDER: Nobody has studied it. We just don't have the data. But if it gets absorbed and if it works as it does -- one steroid is like another steroid; one glucocorticoid is like another glucocorticoid.

DR. CHESNEY: Dr. Glode.

DR. GLODE: Again, following up on that issue then in the want of sort of consistency from everybody's standpoint, for oral corticosteroids then is there a boxed warning and is there a medication guide, et cetera, or not? I mean, it would be sort of inconsistent to do it for a topical if you didn't do it for oral. I just don't know.

DR. SCHNEIDER: I don't recall. The difference

is with the appropriate use of an oral corticosteroid, there is the expectation that it's going to have predictable systemic effects. These drugs are developed and in fact marketed -- by these drugs, I mean any locally active, the inhaled ones or whatever -- on the basis of having a specific local effect, at the same time minimizing systemic effects. The warning is needed not because they're more dangerous but because people are just unaware of these effects. I think the warning is needed.

DR. CHESNEY: Dr. Raimer.

DR. RAIMER: I was just going to point out that we're throwing around these 30 to 40 percent figures, and that's for class II steroids, which are not recommended for kids under 12 anyway. When we look back at prednicarbate, basically none of the kids on that were suppressed, and fluticasone was only 2 to 3 percent. So the ones that are actually approved for use in children, it's very low. So we might want to look at what we're labeling. We might want to label the stronger steroids differently than we do the weaker steroids.

DR. CHESNEY: Dr. Wilkin.

DR. WILKIN: I think Dr. Schneider has made the point on several occasions, and I'd just like probably a highly reductive reiteration. So one of the key messages to our group is that the topical delivery is the part that

isn't getting through to clinicians, anesthesiologists, internists, folks in emergency rooms, perhaps even pediatricians and dermatologists that topically applied products can have systemic effects. That seems to be a theme that would go beyond corticosteroids that we need to think about for some of our other products as well.

DR. CHESNEY: Dr. Murphy, are we finished with question 3, or another step?

DR. MURPHY: I'm probably going to be sorry I asked this, but I'll go ahead because tomorrow you're going to be talking about long-term studies. And it's been brought up a number of times today, additional studies. As you will hear, long-term studies are extraordinarily difficult. They get very confounded, et cetera. I would like to hear a little more about how you think we're going to address this issue clinically besides in the conduct of the drug development process, what we've already discussed. How are we going to delineate any potential other longer-term outcomes in the population that is using this recurrently multiple times over their lifetime? If anyone has any thoughts on that. It's a very difficult area.

DR. CHESNEY: Dr. Andrews, then Dr. Fost.

DR. ANDREWS: Well, it seems like we need more information on steroids in general since they're widely used in kids, and we don't have a good handle on the dose-

response issue going from topical to oral around a number of endpoints, including cataract and bone effects.

One possible opportunity is to use the upcoming National Children's Study which will be following 100,000 children from before birth to age 21. If there's sufficient use in 100,000 children, one could learn quite a lot.

DR. CHESNEY: Dr. Fost.

DR. FOST: Yes, just repeating I think what Ben said earlier, that I don't see pharmaceutical companies as being able to carry out these studies as a condition of approval. It seems to me these are for NIH and the Children's Study and other agencies or entities that do epidemiologic research.

I think there are many possibilities, many different studies that could be done that would not be all that difficult or expensive to pull off. I mean, rather than the ICU model that Bob suggests, which strikes me as troublesome because of all the confounding of ICU patients, if 20 percent of kids who are on these, just go to a large healthcare system and look at elective surgery or look at just hernias, and look at complication rates, post-op hospitalization rates. It seems to me there's a simpler way of looking at risk of exposure to trauma and stress in kids on steroids versus not.

DR. EPPS: I don't know whether there's an NHANES study going on right now. I think there have been at least two. But if some dermatologic questions were included regarding atopic dermatitis, that might be really helpful.

DR. CHESNEY: Dr. Stratakis.

DR. STRATAKIS: In long-term studies, one should also look again at what's happening to adrenocortical function as the child grows into adulthood. So questions like, for example, what happens to adrenarche, which occurs between the ages of 5 and 7, in these kids that are repeated users of local steroids, what happens to them with puberty, what happens to reproductive function. Are these kids that are exposed to chronic local steroids or inhaled steroids or whatever at risk for perhaps an increased risk of polycystic ovarian syndrome when they become adolescents? I'm just throwing out one question. I can't think of a direct effect, but I can think of many indirect effects. So long-term studies should look at all these variables, including the mineralocorticoid effects that I mentioned earlier.

DR. CHESNEY: I wonder if it necessarily has to be that long-term. If you have a child with moderate to severe eczema who is using four or five or six different applications in the first year of life, it seems like you

could get a fair bit of information just from studying those children over a 1-year period, and that might be within the bailiwick of the sponsor.

DR. STRATAKIS: But this would be intermediate effects. This would be between short-term and long-term. They would be referring to bone mineral density perhaps, growth rate, and things like that.

I'm also concerned about the very long-term effects.

DR. CHESNEY: No. I agree. I'm just thinking of something that might be a little more doable in the immediate future.

Dr. Fink and then Dr. Ten Have.

DR. FINK: Just a brief comment, again going back to the asthma model, which I think is fairly appropriate. One of the difficulties of doing long-term studies is people are going to bring up the fact that any chronic inflammatory disease, including one of the skin, potentially affects growth and bone mineralization. So if you have a patient who is short, the question is are they shorter because of their eczema or because of the steroids used to treat it. And that's not a trivial question. It's been confounding in asthma where untreated asthma clearly can affect growth, and I think there's no question untreated eczema when it's moderately severe also can

affect linear growth. So you may be looking at the lesser of evils rather than measuring a direct effect.

DR. TEN HAVE: Just regarding designs and gold standard designs, I think there is a precedent in the asthma world in terms of post-marketing randomized studies of safety of salmeterol. Glaxo SmithKline just finished a big 70,000 --

DR. FINK: 26,000.

DR. TEN HAVE: -- 26,000 subject study. I believe the original sample size was 70,000 and they couldn't finish it. But it ended up with sort of a controversial result.

But there is a precedent there for randomizing patients to two treatments to look at safety issues. Of course, it's a shorter-term safety issue there, but in terms of Dr. Chesney's 1-year follow-up, that is feasible from that point of view, but not necessarily longer term, though.

DR. CHESNEY: Dr. Fink.

DR. FINK: I was just going to say the SMART trial that he's referring to, which some people now are calling the stupid trial --

(Laughter.)

DR. FINK: -- was not actually a safety trial. It was a trial to try and establish that a long-acting

beta agent could be used as a primary controller for the treatment of asthma, and it turned out that the intervention group had excess deaths compared to placebo.

DR. TEN HAVE: I was actually on the DSMB. It was a safety trial. The original hypothesis was whether or not adverse event rates were the same in both groups. That was what the power was based on.

DR. MURPHY: Okay. It was very helpful. We did get some very clear instructions as to where we need some additional information.

Anne, did you have any questions for the committee?

DR. TRONTELL: No.

DR. MURPHY: Thank you all very much.

DR. CHESNEY: Thank you, Dr. Murphy, and I guess this concludes the first half of the issues that have to do with agents for eczema.

We will take a 15-minute break and reconvene at 3:25, and that's just for the committee. Is that correct? Or everybody who is here?

MR. PEREZ: Everybody who is here.

DR. CHESNEY: Everybody who is here. If we could reconvene at 3:25 please.

(Recess.)

DR. CHESNEY: I think we should reconvene, if

everybody could find their seats please.

Because this is a separate part of today's meeting, the Executive Secretary has to read the meeting statement. So we'll start with that first.

MR. PEREZ: 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 subcommittee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. 208(b)(3), Dr. Robert Fink has been granted a waiver for his membership on speaker bureaus for a sponsor and a competitor on unrelated matters. He receives fees of less than $5,001 per year from one firm and over $10,001 from the other.

Dr. Benjamin Wilfond has been granted a waiver for his consulting for a competitor on unrelated matters. His fees are less than $10,001.

Dr. Joan Chesney has been granted a waiver for her ownership of stock in a sponsor and competitor. The

stock values are between $50,001 to $100,000 and $5,001 to $25,000.

Dr. Elizabeth Andrews has been granted a waiver for her consulting for two competitors as part of her employment on unrelated matters. Fees to her employer are less than $10,001.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30 of the Parklawn Building.

In addition, Drs. Benjamin Wilfond, Victor Santana, and Sharon Raimer have been granted waivers under 21 U.S.C. 355(n)(4), an amendment of section 505 of the Food and Drug Administration Modernization Act, for ownership of stock valued between $5,001 and $25,000. Because these stock interests fall below the de minimis exemption allowed under 5 C.F.R. 2640.202(b)(2), waivers under 18 U.S.C. 208 are not required.

Further, we would like to disclose that Dr. Elizabeth Andrews has been recused from participating in today's discussions concerning Serzone and Busulfex.

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 product they may wish to comment upon.

Thank you.

DR. CHESNEY: Thank you, Tom.

Dr. Murphy has somebody she would like to introduce to the committee.

DR. MURPHY: Yes. Dr. Sara Goldkind, would you stand up please? It's with great pleasure to introduce the Office of Pediatric Therapeutics board certified internist who is our ethicist that we have brought on board in the last month. She basically, as I said, is an internist who has a clinical fellowship in ethics, has been providing consultation and policy opinions in the last couple of years. I'm not going to go through all of her background. And she has a masters degree with a focus on comparative religious ethics and religion and public policy.

Her job with the Office of Pediatric Therapeutics, as you know, is mandated by the Best Pharmaceuticals for Children Act that that office have an ethicist on board. She'll be working with us on our subpart D activities, also on the consultations inter-

center, and is our liaison with NIH and a number of the other federal activities in the area deal with ethical issues. So we're delighted to have her, and we want to make sure you at least recognize the face and knew the name.

I have one other housekeeping activity. Sorry, Joan. I forgot to tell you I need to do this. Before we move into the presentation by Dr. Iyasu and the division on the product safety update on the products that have been granted exclusivity, I needed to tell the committee that there is a product that was to be -- its due date was for this meeting. Let's put it that way. And to bring your attention to an FDA talk paper that was released this week in case you did not see that. The talk paper is that FDA issues public health advisory reports of suicidality in pediatric patients being treated with antidepressant medications for major depressive disorder. I wanted you to know that FDA -- I'm going to read from this just so you'll know why we're moving some of these products to the next meeting that will occur in February.

FDA has completed a preliminary review of reports for eight antidepressant drugs -- I'm not going to list them all -- all studied under the pediatric exclusivity provisions of FDAMA. We note to date that the data do not clearly establish an association between the

use of these drugs and increased suicidal thoughts or actions by pediatric patients. Nevertheless, it is not possible at this point to rule out an increased risk of these adverse events for any of these drugs, including Paxil, which was the subject of an FDA talk paper on June 19th, 2003.

Because of this issue, we are deferring review of any of the products in this class until February, of which I hope many of you have already been notified about the date of February 2nd, those of you on the Pediatric Advisory Subcommittee. In order to promote a public discussion of the data and pertinent regulatory actions, FDA has scheduled a meeting on February 2nd, 2004 before the Psychopharmacologic Drugs Advisory committee and the Pediatric Subcommittee of the Anti-Infective Drug Advisory Committee. So that is information to you why we may not be presenting products in this area that may have -- indicate that we should be discussing them because we will be delaying that until February.

That is all the housekeeping that I needed to do. Thank you very much.

DR. CHESNEY: Thank you, and we look forward to working with Dr. Goldkind.

Next we will hear the report of adverse event monitoring for drugs granted exclusivity under BPCA to be

presented by Dr. Solomon Iyasu and Dr. ShaAvhree Buckman. Drs. Iyasu and Buckman are both with the Division of Pediatric Drug Development. Dr. Iyasu has provided us with a written review of 1-year post pediatric exclusivity post-marketing adverse events. Today they will highlight the findings described in that report.

DR. IYASU: Good afternoon. As you recall, BPCA mandates that FDA monitor adverse event reports for a period of 1 year after exclusivity is granted. Today we will report adverse events for six drugs that have been given exclusivity. These six drugs are busulfan, losartan, tamoxifen, nefazodone, cetirizine, and quinapril. I will report on the first four drugs, and then Dr. ShaAvhree Buckman will present on the last two drugs.

I think it may be helpful to review the sources that we used to monitor adverse event reports. The data source for the adverse event reports is the AERS database, which has been earlier described. It is comprised of spontaneous and voluntary system post-marketing adverse event reports that come to FDA either from consumers, from health professionals, and also from manufacturers to a large extent.

As with all spontaneous reporting systems, it has several important limitations that should be reviewed again. Under-reporting, as earlier discussed, is a huge

issue, and also reporting biases are inherent in this system. As an example, duration of time a drug has been on the market or publicity about a certain adverse event may influence the reporting rates for certain adverse events with drugs. Often the quality of the reports is variable, and perhaps the most important limitation is the inability to calculate true exposure risk or make causal inferences between an adverse event and an exposure to a drug.

I'll also try to review some of the data sources for the frequency of medication use in pediatric patients. FDA uses various data sources.

The National Prescription Audit Plus measures prescriptions dispensed from retail pharmacies and can also provide national estimates which are projected from this database. Its chief limitation is that it does not provide estimates by patient demographics, such as age and gender. So it gives you just the total prescriptions dispensed.

The National Disease and Therapeutic Index is a continuing survey of office-based physicians and measures mentions of medications during patient visits to these office settings. While data are available by patient demographics, the small sample size can make the national data estimates very unstable. This is often problematic when use of a drug is uncommon, as is often the case in the pediatric population.

AdvancePCS is a prescription claims database from a large pharmacy benefit management company and covers about 50 million patients and processes about 300 million prescriptions annually. An important limitation is that the data cannot be projected to make national estimates. However, we do see that data does come from all 50 states. It has a reasonable approximation of the distribution or frequency of drug use, although there's no methodology really to have a national estimate.

The Premier database collects inpatient drug use from 400 acute, short-stay, non-federal hospitals. While a projection methodology is available from this database, it's only accurate selectively and needs to be interpreted with caution for newly marketed drugs. Another limitation is that there's no linkage between a drug and the diagnosis for which a particular drug may have been used. It also does not collect information on treatments administered in hospital outpatient clinics.

Let me now turn to the actual reports of adverse events for each of the drugs. The first drug is busulfan which is an antitumor drug marketed by ESP Pharma. It's approved as a conditioning regimen in combination with cyclophosphamide prior to allogenic hematopoietic progenitor cell transplantation in chronic myelogenous leukemia. In children, the effectiveness of busulfan in

the treatment of CML has not been specifically studied. An open-label, uncontrolled study evaluated the pharmacokinetics of busulfan in 24 patients as part of a conditioned regimen administered prior to hematopoietic progenitor cell transplantation for a variety of malignant hematologic and nonmalignant disease. Based on the results of this study, a suggested dosing guideline in pediatric patients is included in the label.

Now, turning to the frequency of use of this medication from the databases that we looked at, there was no outpatient busulfan use that was noted. However, inpatient pediatric use from the Premier database, was estimated to be about 10 percent of all inpatient busulfan use in 2000 and about 4.9 percent in 2002. However, these data represent a very small number of discharges.

During the 1-year post exclusivity period, there were a total of 103 adult and pediatric adverse event reports. After a manual review of all these reports, there were 9 unduplicated or unique pediatric adverse event reports that were identified. 3 of the 9 reports were pediatric deaths. None of the events, including the pediatric deaths, could be attributed to busulfan use. All reports involved also multiple drug use and complex medical conditions. Therefore, the reported events could not be attributed to busulfan use.

Just to summarize, in terms of the 3 deaths, there were clear causes that are unrelated to the drug. One was an interstitial pneumonia, a labeled event for another drug; an acute heart failure, a labeled event for a co-suspect drug which is cyclophosphamide; and an acute cardiac arrest due to aspiration. And we could not attribute any of this to busulfan use.

If there are any questions on this drug, I would open it for discussion. Otherwise, I'll move to the next drug.

DR. FOST: Dr. Iyasu, the slide that says it accounted for 10 percent of inpatient pediatric use, you mean 10 percent of its use was inpatients?

DR. IYASU: No. Of all the mentions in inpatient settings, 10 percent was in inpatients. So if you look at the numbers, it was based on very small number of discharges because it's really based from the discharges.

DR. FOST: So of all the children who got busulfan, 10 percent of them got it as an inpatient. Is that what that means?

DR. IYASU: No. Of all in patient use of that particular drug --

DR. FOST: 10 percent was in children.

DR. IYASU: -- 10 percent was in children.

DR. SANTANA: Kind of following up on that, the number of pediatric transplants hasn't gone down. If anything, they've gone up arithmetically in any time period that you looked at. So I'm having a little bit of difficulty because it reflects under-reporting if one year it was 10 percent and the other year represented half of that, whereas the number of transplants have been going up. So there's a problem with the numbers. That may be related to under-reporting, I grant you that. But that raised a red flag because we're not doing less transplants, we're doing more transplants. It could be that they're also going up faster too. That may be true.

But that was going to be my next question is. Is there any database that specifically looks at pediatric hospitals because part of the problem is the data is derived from large sets of many different hospitals, of which pediatrics is variable depending which hospital you choose.

DR. IYASU: Right. At present there is another database also which collects information from about 29 children's hospitals, and these are not probability samples of hospitals and we cannot really make national projections. They are very limited and data from that source also corroborates the finding in terms of very limited use. I don't have any data on whether there's an

increasing trend in transplant or not, so I can't comment on that unless there's someone from the division who can comment on this.

The next drug is losartan, which is an antihypertensive agent marketed by Merck. It's approved for use in the treatment of hypertension with left ventricular hypertrophy and also for the treatment of nephropathy in patients with type II diabetes and a history of hypertension. There are no specific approved pediatric indications.

The losartan label contains a boxed warning against use during pregnancy because of its potential to cause injury and death to the developing fetus. This is not restricted to this particular drug but to the class of drugs which are the ACE inhibitors and the different sartans which are in this class. Losartan has a pregnancy category C designation in the first trimester and a designation of D in the second and third trimester.

Again, looking at the use data according to the NPA, the total dispensed prescriptions seem to be increasing. The prescriptions dispensed were higher for Cozaar than for Hyzaar. Hyzaar, just to remind you, is a combination of losartan and hydrochlorothiazide. The pediatric specialty accounted for about 54,000 of the prescriptions in the year 2002. There was a total of about

16 million prescriptions for this medication in the same year, which means including adults and pediatric patients.

Pediatric use estimates during visits to office-based physicians represented approximately 1 percent of all losartan mentions in these settings. In pediatric patients, cardiomyopathy and essential hypertension were the two diagnoses most often associated with losartan use in the office settings.

Data from the AdvancePCS suggest that prescriptions for Cozaar increased slightly while they remained stable for Hyzaar. However, the percent of pediatric prescriptions were extremely small to really make any conclusions about the trends.

Looking at the adverse events, AERS contained a total of 298 adverse event reports during the 1 year post exclusivity period. A majority of these reports were from foreign sources. A manual review of these reports revealed 5 unduplicated and unique pediatric reports. 4 of the 5 were maternal exposures or in utero exposures. The remaining 1 report was due to an accidental ingestion by a 2-year-old. 2 of the 5 patients died. In one, the fetus was exposed in utero and an elective abortion was performed because of exposure during pregnancy. In the second pediatric death, an accidental ingestion and overdose of losartan was involved and the patient died.

All of the adverse events were covered in the label and therefore are expected based on the label. So there were no unlabeled events that were unexpected events observed during the 1 year post exclusivity period. But I must remind you, as I said earlier, that there's a boxed warning against use during pregnancy and therefore there's an adequate warning. Maybe it's not being heeded.

Are there any questions on this drug?

DR. GORMAN: Was the accidental ingestion that led to the death a single moiety? Was that the only agent ingested?

DR. IYASU: As far as I know, that was the only agent that was ingested and it was prescribed for an adult.

Did you have additional information? Beverly actually did the review, so she might have additional information.

DR. LINDSAY: Yes. This was a 2-year-old who ingested his grandparents' medication. So it was multiple medications, not only just losartan.

DR. IYASU: Thanks for that correction, Beverly.

Any other questions?

(No response.)

DR. IYASU: The next drug is tamoxifen. Tamoxifen is a nonsteroidal antiestrogen marketed by

AstraZeneca. In adults, it's approved for the treatment of breast cancer in women and men and it's also used to reduce the incidence of breast cancer in high-risk women.

The label contains data from a single, uncontrolled multi-center clinical trial of the treatment of girls age 2 to 10 with McCune-Albright syndrome and precocious puberty. The safety and efficacy of tamoxifen has not been studied beyond 1 year of therapy. However, an increase in the mean uterine volume was noted during the 1-year treatment, but no causal relationship could be established with the drug. In adults, it has to be noted that an increase in the incidence of adenocarcinoma and uterine sarcoma has been noted and therefore continued monitoring of McCune-Albright patients treated with tamoxifen is recommended in the label.

Now, turning to the use data, total prescriptions dispensed for tamoxifen amounted to 4.3 million in 2002. However, the pediatric specialty was responsible for only 8,000 prescriptions during the same year and for about 5,000 prescriptions during January to May of 2003.

Tamoxifen mentions during patient visits to office-based physicians represented less than 1 percent of total use. Pediatric use appears to be primarily in the adolescent subgroup of 12- to 16-year-olds. The diagnosis

associated with its use appears to be exclusively for malignant neoplasm of the brain. It doesn't mean that it was not used for the other indication. It just means that we could not adequately project the data. If was less than a certain minimum number, then you can't really make any kind of projections.

During the 1 year post exclusivity period, we received a total of 369 adverse event reports for mostly adults, but we did not find any pediatric adverse event reports in the AERS database during the year. So there is nothing to say really about this drug right now in terms of adverse events for the year. It's good news I guess that we did not get any.

DR. SANTANA: No. The other interpretation is that the majority of the brain tumor patients, pediatric patients, that are getting this drug, it's being used in the setting of multiple recurrent disease, so they're all dying from their primary disease.

DR. IYASU: That's possible too. Thank you.

The last drug I will discuss is nefazodone. Nefazodone is an antidepressant marketed by Bristol-Myers. In adults, it's approved for the treatment of MDD. There are no approved pediatric indications for use.

Nefazodone has been associated with life-threatening hepatic toxicity, and in 2001 a boxed warning

was added to the label. This is the relevant safety labeling I just wanted to mention.

Turning to drug use data, it shows that both pediatric and adult prescriptions for nefazodone declined between 1999 and 2003, largely fueled by concerns about its potential for liver toxicity. Nefazodone is one of the least prescribed antidepressants in pediatric patients. Since exclusivity was granted, nefazodone use has declined by more than half in pediatric patients and by one-third in adults. In pediatric patients, a diagnosis associated with its use were personality disorders, depressive disorder, and infantile autism.

Turning to the adverse event reports for this particular drug, we received a total of 173 reports, adult and pediatric, during the year after exclusivity was granted. Of these, 3 reports were in pediatric patients. All the pediatric events were noted as serious events. There were no pediatric deaths.

The first report is a congenital hand malformation in an infant born to a mother who was taking nefazodone along with multiple medications, some of which have the potential to cause birth defects. Nefazodone, as you know, has pregnancy category designation C. The reported event in this case could not be solely attributed to nefazodone.

The second report is a potential arrhythmia and agitation in a 3-year-old with an accidental ingestion of about 14 tablets of nefazodone. The patient's symptoms resolved after an induced emesis.

The last patient was a biopsy-proven Crohn's disease and sclerosing cholangitis in a patient who was taking nefazodone for depression and also taking multiple other medications. Her liver function tests did not begin to normalize until the fourth month following discontinuation of nefazodone. By 1 year, all liver function tests were normal. Concomitant medications with known liver toxicity included mercaptopurine and sulfasalazine. The contribution in this case of nefazodone alone to this adverse event was difficult to assess.

So there were only three reports of adverse events for this particular drug.

Are there any questions before I turn the podium over to Dr. Buckman?

(No response.)

DR. IYASU: Thank you very much. ShaAvhree Buckman, Dr. Buckman, will be presenting on the last two drugs.

DR. BUCKMAN: Good afternoon.

The next drug that we will be discussing is cetirizine, or Zyrtec. This is an anti-allergic drug which

is marketed by Pfizer. It's indicated in the treatment of allergic rhinitis, both seasonal and perennial, and chronic idiopathic urticaria. It is approved for use in adults, as well as in children down to the age of 6 months.

According to NPAPlus, the total dispensed prescriptions for cetirizine are increasing in all age groups from 9.3 million in 1998 to 25.7 million in 2002. In the pediatric specialty, about 4 million prescriptions were dispensed in 2002.

According to the NDTI database, during the first quarter of 2003, approximately one-half of the mentions for cetirizine were for pediatric patients, and approximately one-quarter of the mentions for cetirizine was with pseudoephedrine were for pediatric patients.

The adverse event reports for cetirizine during the 1 year post exclusivity period totaled 253 reports in both adults and children. 141 of those reports were from the U.S. and 112 were from international sources. There were 43 unduplicated pediatric reports. There were no pediatric deaths. 15 of the top 20 adverse events were unlabeled.

This slide summarizes 43 of the unduplicated reports in pediatric patients. It's important to note that the underlined adverse events are currently unlabeled. The most common adverse event that was seen during this 1 year

post exclusivity period was medication errors. In 8 of 9 case, there was confusion between Zantac syrup and Zyrtec syrup, and in 1 case there was confusion between Zyrtec and Zoloft. The FDA is currently discussing how to best address these issues.

There were 7 psychiatric events that included aggressive behavior, agitation, and hallucinations. There were 5 seizures, 3 episodes of somnolence, 3 allergic reactions, 3 cases of congenital anomalies, 3 episodes of liver injury which were described as either elevated transaminases or hepatitis. There were 2 cases of renal impairment with associated acute renal failure or IgA nephropathy.

In the "other" category, there were 8 additional cases, 1 case of each: accidental overdose, hearing loss, hyperglycemia, hypogammaglobulinemia, pancreatitis, supraventricular tachycardia, tachypnea of the newborn, and vertigo.

One of the other concerning adverse events that was noted was hallucinations. In a review conducted in March of 2001 by the Office of Drug Safety, there was the suggestion of a probable linkage between the use of cetirizine and the incidence of this adverse event. During the 1 year post exclusivity period for cetirizine, there were two reported cases of hallucinations. One was in a 3-

year-old male who was reportedly taking concomitant medications, and another was in an 8-year-old female who also was reportedly taking other medications. The temporal nature of when these other medications were administered was not clear in those case report forms. In both cases, however, the condition abated when cetirizine was discontinued.

Before proceeding on to the next drug, are there any questions?

(No response.)

DR. BUCKMAN: The next drug we'll discus --

DR. CHESNEY: I have a question.

DR. BUCKMAN: Yes.

DR. CHESNEY: I just wanted to be sure I understood. There was confusion with Zantac and Zyrtec syrup.

DR. BUCKMAN: Yes.

DR. CHESNEY: Are the underlying side effects clearly related to the drug you discussed or could they be related to Zantac?

DR. CHESNEY: As far as the medication errors, it was clear that those were due to patients that were dispensed the wrong medication and usually it was a pharmacy error that was noted. In the cases where there were non-underlined adverse events, those were clearly due

to Zyrtec, the medication that was administered.

DR. EPPS: Just a comment. Your number of cetirizine for 2003 actually could be higher if it weren't for some insurance company policies. Now, they're demanding, oh, you have to document 30 days' worth of loratadine or whatever before we will give you Zyrtec. So the numbers could have actually been higher.

DR. BUCKMAN: That's very true.

Any other comments or questions?

(No response.)

DR. BUCKMAN: The next drug that we will discuss is quinapril, or Accupril. This is an antihypertensive drug. It's marketed by Parke-Davis. It is indicated in the treatment of hypertension and as adjunctive therapy for heart failure in adults. There are no approved pediatric indications.

According to NPAPlus, the total dispensed prescriptions for quinapril were 10 million in 1998 and 15.7 million in 2002. Pediatric use constitutes less than 1 percent of total prescriptions dispensed.

According to NDTI, the proportion of pediatric use was less than 1 percent of the total population of quinapril mentions during visits to office-based physicians.

The adverse event reports for quinapril during

the 1 year post exclusivity period totaled 198 reports. 114 were from the United States and 84 were from international sources. There was one unduplicated pediatric report of a serious adverse event. This was described as a congenital anomaly associated with maternal use. In particular, a 1-day-old female was born with a heart malformation after maternal exposure to quinapril. Salbutamol was also reported as a concomitant medication taken by the mother.

Quinapril is extensively labeled regarding use during pregnancy and fetal exposure risks. So this was a report that was addressed in the current labeling for that drug.

Are there any questions regarding quinapril?

(No response.)

DR. BUCKMAN: In conclusion, we have provided you with information on six drugs which have obtained pediatric exclusivity. The inherent limitations of the adverse event reporting system make attribution of adverse events due to drug use particularly challenging. The FDA will continue its routine monitoring of adverse events in all populations, and we would like to thank the Office of Drug Safety, as well as the Office of Counter-Terrorism and Pediatric Drug Development for their assistance in compiling information for this report. Thank you.

DR. CHESNEY: Thank you both very much for that.

DR. SANTANA: Joan, I have a question. Has the agency noticed for these six drugs, once the sponsor has achieved exclusivity, a change in more usage pattern and is that reflective in terms of the adverse reporting patterns? Is there any way to monitor that, or do you know?

DR. MURPHY: Because the product is granted exclusivity because of studies they submitted in hopes of getting a new indication usually in which one would expect the use would go up, I'm not sure what one would make out of that except that you would expect that the use would go up.

DR. SANTANA: What I was leading to is how does one normalize the adverse event data if the denominator is changing?

DR. MURPHY: That's one of the problems. As you will hear, one of the problems with AERS is that every time there's a newspaper report or some increased publicity, then you tend to get an increased reporting from not only healthcare providers but also patients, more reporting from patients.

DR. CHESNEY: We have time allotted now for an open public hearing. Is there anybody here who would like to speak in the open hearing?

(No response.)

DR. CHESNEY: I guess not.

Let me ask Tom if there are any housekeeping issues, and we start tomorrow at 8 o'clock. Is that correct? Do you have anything else?

MR. PEREZ: Yes, that is correct.

I just wanted to clarify one thing since the next meeting has been mentioned. That will be more than a one-day meeting. We don't know what additional topics will be discussed. I just didn't want any confusion because I know we have three days allotted for that meeting. It's not just the one day. Thank you.

DR. CHESNEY: Anything else, Dr. Murphy, before we adjourn?

DR. MURPHY: I wanted to thank everybody. It's been a very helpful day. We appreciate it very much.

DR. CHESNEY: Thank you all and we'll see you again tomorrow morning at 8 o'clock.

(Whereupon, at 4:07 p.m., the committee was recessed, to reconvene at 8:00 a.m., Thursday, October 30, 2003.)