DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT SESSION WITH THE

NONPRESCRIPTION AND DERMATOLOGIC DRUGS

ADVISORY COMMITTEE

VOLUME II

Thursday, March 24, 2004

8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

P A R T I C I P A N T S

Alastair Wood, M.D., Chair, NDAC
Teresa A. Watkins, R.Ph., Executive Secretary

Committee Members:

Michael C. Alfano, DMD, Ph.D. (Industry Representative)
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Ernest B. Clyburn, M.D.
Frank F. Davidoff, M.D.
Jack E. Fincham, Ph.D.
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Michael E. Bigby, M.D.
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Thomas R. Ten Have, Ph.D.
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Michael G. Wilkerson, M.D.
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Patricia Chesney, M.D.
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Constantine Stratakis, M.D.
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FDA Participants:

Charles Ganley, M.D.
Curtis Rosebraugh, M.D., MPH
Jonathan Wilkin, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. WOOD: If everybody could take their seats and let's begin by going around the table and have everybody introduce themselves. Why don't we start with Mike.

DR. ALFANO: Good morning. I am Mike Alfano, New York University. I am the industry liaison to NDAC.

DR. FINCHAM: Good morning. I am Jack Fincham, an NDAC member, and I am a Professor of Pharmacy and Public Health at the University of Georgia.

DR. RAIMER: Good morning. I am Sharon Raimer, in Dermatology, University of Texas.

DR. TINETTI: I am Mary Tinetti, Internal Medicine, Geriatrics at Yale.

DR. RINGEL: Eileen Ringel, Dermatologist, Waterville, Maine.

DR. CLYBURN: I am Ben Clyburn, Internal Medicine, Medical University of South Carolina in Charleston.

DR. SANTANA: Good morning. I am Victor Santana. I am a pediatric hematologist/oncologist at St. Jude Children's Research Hospital in

Memphis, Tennessee.

DR. SKINNER: I am Bob Skinner from the University of Tennessee at Memphis. I am a dermatologist.

DR. PATTEN: I am Sonia Patten. I am the consumer representative on NDAC. I am an anthropologist on faculty at Macalister College in St. Paul, Minnesota.

DR. DAVIDOFF: I am Frank Davidoff. I am the Emeritus Editor of Annals of Internal Medicine. I am an internist although I started life as an endocrinologist, and I am a member NDAC.

DR. BIGBY: Michael Bigby, a dermatologist at Beth Israel Deaconess Medical Center and Harvard Medical School.

LCDR WATKINS: I am Teresa Watkins. I am the Executive Secretary with the advisors and consultant staff.

DR. NELSON: Robert Nelson, Pediatric

Critical Care Medicine at Children's Hospital, Philadelphia, and the University of Pennsylvania.

DR. SNODGRASS: Wayne Snodgrass, pediatrician, University of Texas Medical Branch.

DR. MATTISON: Don Mattison, National Institute of Child Health and Human Development.

DR. SCHMIDT: Jimmy Schmidt, Houston, Texas, dermatologist.

DR. EPPS: Roselyn Epps, Chief, Pediatric Dermatology, Children's National Medical Center, Washington, D.C.

DR. CHESNEY: Joan Chesney, Pediatric Infectious Diseases at the University of Tennessee at Memphis and Academic Programs at St. Jude Children's Research Hospital.

DR. TAYLOR: Robert Taylor, internist and clinical pharmacologist, Howard University, Washington.

DR. WILKERSON: Michael Wilkerson, University of Oklahoma, Tulsa Branch, Assistant Professor, Clinical, and dermatologist.

DR. BLASCHKE: Terry Blaschke, internist,

clinical pharmacologist, Stanford.

DR. WILKIN: Jonathan Wilkin, Director, Division of Dermatologic and Dental Drug Products, FDA.

DR. ROSEBRAUGH: Curt Rosebraugh, Deputy Director, OTC, FDA.

DR. GANLEY: Charley Ganley, Director of OTC.

DR. WOOD: I am Alastair Wood. I am an internist, Professor of Medicine, Associate Dean at Vanderbilt. There has probably never been a committee with so many people from Tennessee on it, I don't think.

Teresa, why don't you read the Conflict of Interest Statement.

Conflict of Interest Statement

LCDR WATKINS: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by the Committee

participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research 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. Section 208(b)(3), full waivers have been granted to the following participants. Please note that all interests are in firms that could potentially be affected by the committee's discussions.

Dr. Michael Wilkerson for activities on Speakers Bureaus for three firms. He receives less than $10,001 per year, per firm.

Dr. Robert Skinner for a patent licensed to a firm that could potentially be affected by the committee's discussion. He has received no royalties at this time. Also, for his Speakers Bureaus activities for two firms, he receives less than $10,001 per year, per firm.

Dr. Patricia Chesney for stock in six firms. One stock is valued at less than $5,001, one stock is valued between $5,001 to $25,000,

three stocks are valued between $25,001 and $50,000, and one stock is valued greater than $100,000.

Dr. Thomas Ten Have for stock valued between $25,001 to $50,000.

Dr. Victor Santana for stock in two firms. These stocks are worth between $5,001 and $25,000 each.

Dr. Sharon Raimer for two grants that are valued at less than $100,000 per firm, per year. Also, for stock in three firms, each stock is currently valued between $5,001 and $25,000.

Dr. Sonia Patten is an unpaid volunteer member of the Sumasil Foundation Board of Directors. The Foundation owns stock interest in two firms. One stock is currently valued between $25,001 and $50,000 and the other stock is currently valued between $5,001 and $25,000.

We would also like to disclose that Dr. Terrence Blaschke owns stock in a firm, valued from $5,001 to $25,000. A waiver under 18 U.S.C. 208(b)(3) is not required because the de minimis

exemption 2640.202(b)(2) applies.

A copy of the 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 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 note for the record.

In addition, we would also like to note that Dr. Michael Alfano is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Alfano's role on this committee is to represent industry interests in general, and not any one particular company. Dr. Alfano is Dean of the College of Dentistry, New York University.

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

any firm whose products they may wish to comment upon.

Thank you.

DR. WOOD: Thanks a lot.

Our first speaker is Charley Ganley. Charley.

Introduction

DR. GANLEY: Good morning. I would just like to start by thanking all the members for participating in this meeting. I would also like to thank the advisors and consultant staff for all the hard work they do in putting these meetings together, it is always difficult to get two different committees together, and last but not least, the staff of the Dermatologic and OTC Divisions who have put together the presentations.

[Slide.]

We are here today to discuss the safety data necessary to consider a switch of dermatologic topical corticosteroids from prescription to OTC status.

[Slide.]

The FDA presentations will cover the regulatory history of OTC hydrocortisone, the assessment of safety for current prescription

dermatologic topical corticosteroids products, an assessment of safety effects for other categories of steroid products, and testing for HPA axis suppression.

[Slide.]

Now, low potency dermatologic topical corticosteroids are currently available OTC, and the only product that you will hear in the next talk is hydrocortisone. Its purpose is for the symptomatic treatment of certain skin conditions, and there is a limitation on the duration of use.

Over the last year or so, several manufacturers have expressed an interest in switching some dermatologic topical corticosteroids from prescription to OTC, asking for similar type claims, and also for durations of use.

[Slide.]

Now, in your background package, we included a list of the various potencies of topical

steroids, and there is quite a difference in the potency of prescription dermatologic topical steroids, and potency impacts on efficacy and safety of these products.

The main issue for the discussion today is the safety in the OTC setting. The question really is where do we draw the line between safe versus unsafe products in this category for OTC use.

[Slide.]

Can all dermatologic topical steroids be used safely OTC? Well, some highly potent products used for extended periods or in large amounts may pose a significant risk for developing a serious adverse event.

At least in the OTC setting, limiting the duration of use through labeling may be effective for the majority of users. There will, however, be a minority of consumers who will use large amounts and for durations that exceed label recommendations.

I think in part of the open public session, you will hear a little bit of information

of what possible percentage of consumers that may be.

[Slide.]

So, what are the safety concerns? We have divided them up into the systemic effects and local effects, and within the systemic effects, we divide them further into HPA axis suppression, which is in this case where an exogenous steroid causes the body to stop making corticosteroid, and in stress situations, it could lead to acute adrenal crisis which would be life-threatening.

This can occur with weeks of use and the use of the OTC product may be unknown to a health provider who has to treat someone who comes into the emergency room in this situation.

The other systemic effects are essentially Cushing's syndrome, which could be osteoporosis, truncal obesity, growth suppression, and hypertension, it goes on and on, and the severity may be related to the daily dose and the duration of therapy.

The local effects during the course of the

presentations today, that will also be reviewed.

[Slide.]

Now, you may not be able to see this very well. I printed out one page, but this is one of the schematics that we are going to work with today, and what we have done is we have created a hierarchy of what we think the importance of these various potential safety issues are.

Starting at the top is HPA axis suppression. The second one is other systemic effects, and the third is local effects. You will see the way the questions are presented will also follow this course.

I don't want to go into great detail with this now, but during the course of the discussion and prior to some of the questioning maybe later this afternoon, we can go through this in a little more detail.

Right now I am going to turn it over to Michael Koenig, who is going to talk a little bit about the regulatory history of hydrocortisone.

FDA Presentations

OTC Dermatologic Topical Corticosteroids

[Slide.]

DR. KOENIG: Good morning. I am Michael

Koenig, an interdisciplinary scientist in the Division of Over-the-Counter Drug Products.

Over the next 15 minutes, I will be providing you with information about the only dermatologic topical steroids that are available over the counter, hydrocortisone and hydrocortisone acetate.

Because hydrocortisone and hydrocortisone acetate are functionally the same thing, for the rest of this presentation, I will simply refer to the two corticosteroids as hydrocortisone.

[Slide.]

This presentation is divided into three parts. First, I will describe the OTC monograph system under which these OTC corticosteroids are regulated. Second, I will review the regulatory history of hydrocortisone. Third, I will show you the current labeling of hydrocortisone products if they are in compliance with the monograph.

[Slide.]

I would like to begin by just especially for members of the Dermatologic and Ophthalmic Drugs Committee to review the way OTC drugs are regulated. All OTC drugs are regulated by one of two means, either under an NDA, or a new drug

application, or under the monograph system.

New drugs applications, or NDAs, are prepared by a drug manufacturer for a specific product, a specific drug product, and all of the review of this information and things related to the review are kept strictly confidential.

Neither of the OTC corticosteroids that I will be talking about are regulated under NDAs. Instead, they are regulated under the monograph system, and this differs because under the monograph, monographs deal with specific active ingredients rather than drug products, and I will show you how that plays out in just a minute.

In contrast to the NDAs, the information included in the monograph is a very public process. The monographs are published in the Federal

Register, and FDA actively solicits feedback from the public at every step of the process.

[Slide.]

So the OTC monographs came about with the initiation of the OTC drug review back in 1972. At that time, there were over 200,000 different drug products available OTC, and it was really impractical to think that we could review the safety and effectiveness of all 200,000 of these drug products.

So, since they were made up of about 700 active ingredients, it was determined that the active ingredients should be studied for safety and effectiveness rather than the products themselves. Again, this is a key difference between monographs and drugs marketed under an NDA.

Of the 700 active ingredients, these were classified into 26 different therapeutic categories for further review.

[Slide.]

The initial review as by an Advisory Review Panel. This was made up of outside experts,

outside FDA experts in that particular therapeutic category. There were 7 voting members, but in may respects, it was somewhat analogous to the Advisory Committee.

These panel members looked at each of the active ingredients and determined whether they were Category I or GRASE, Generally Recognized as Safe and Effective; Category II, not GRASE; or Category III, insufficient data to determine whether or not the ingredients were safe and effective for their intended use.

[Slide.]

The recommendations of the Advisory Committee were published in the Federal Register as an Advanced Notice of Proposed Rulemaking, or ANPR.

[Slide.]

FDA's first position on the ingredients in the different categories were made public in a proposed rule. This followed solicitation of comments from the public, and as I said, resulted in the publication of a proposed rule, also known as a Tentative Final Monograph, I have abbreviated

here as TFM.

[Slide.]

The last step in the monograph process is the development of a Final Rule, and that follows input of comments from the public again, as well as any new data that is relevant to generate this Final Rule or Final Monograph, which I have abbreviated FM.

[Slide.]

I would like to now speak specifically about the regulatory history of hydrocortisone.

[Slide.]

This low potency topic corticosteroid was introduced into the U.S. market as a prescription drug in 1952. Four years later, in 1956, a Citizen Petition was submitted requesting that hydrocortisone be switched from prescription to OTC.

The switch was rejected in 1957 for two reasons: first, there was a failure to demonstrate that consumers could safety self-medicate using hydrocortisone; and, second, it was felt that more

testing was needed on absorption of hydrocortisone through the skin. In other words, there was a concern about systemic effects, much as we will be talking about today.

Hydrocortisone was included with other ingredients classified as external analgesics in a review by the Topical Analgesics Panel, which met between 1973 and 1978.

[Slide.]

The findings of the panel and the preliminary regulations were published in 1979 and the Advanced Notice of Proposed Rulemaking or ANPR. Among other things, the panel did consider whether hydrocortisone had any adverse local effects, and noted that there was a noticeable lack of adverse local effects.

The striae and telangiectasia that were characteristic of more potent fluorinated corticosteroids were not generally found with hydrocortisone or hydrocortisone acetate. Dr. Cook, who will follow my presentation, will be showing you some pictures of that and discussing

this is a little bit more detail.

Pustular eruptions and crusting were reported in one case of a person who was using hydrocortisone, but was it turns out attributed to a secondary infection and the scratching of the secondary infection, and treatment with an antibiotic resolved the issue while the person continued to use hydrocortisone. So, again, a lack of local adverse effects.

[Slide.]

Also, in the ANPR, the fact that there was a lack of systemic effects was published. Several experiments look at percutaneous absorption. People used carbon-14 hydrocortisone, in one case tritiated hydrocortisone, and did not see any significant absorption through the skin.

Other measures of systemic effects were eosinophil count, there was no depression in eosinophil count in three or four studies that were presented in the ANPR. Urinary levels of 17-hydroxysteroids and 17-ketosteroids were not increased as you would expect if there were a

significant systemic effect.

Blood glucose levels were unchanged, as was the serum sodium level, and plasma cortisol did increase as expected or predicted in response to insulin stress.

[Slide.]

Insulin stress tests back in the '70s was a major test for HPA axis function. It is no longer the current standard, but one report that you will see in the ANPR, which incidentally is included in your background package, was a study by Munro and Clift, which published in 1973.

This is in Tab 5 of your background package, published in the British Journal of Dermatology. These investigators looked at 40 patients with chronic skin disease, eczema, psoriasis, who had been using corticosteroids for prolonged periods, I believe is in the title. Ninety-five percent or 38 of the 40 had been using corticosteroids for more than 10 months.

In fact, they were using a variety of corticosteroids, betamethasone, and some others.

Ten of these 40 included among the combination of corticosteroids they had been using 1 percent hydrocortisone acetate.

All 10 of those 10 subjects had a normal insulin stress response, and, in fact, 37 of the 40 enrollees in the study had a normal insulin stress response. Of the 3 that did not, 2 had occlusion over extensive areas of the body, and 2 had an exceptionally large dose of corticosteroid.

[Slide.]

Now, the panel also reported that one of the items that they had received was a review of the literature covering the period 1952 to 1973 about the serious adverse events that had occurred. The report was based on some 12,000 subjects in 90 different clinical studies, and in those 12,000 subjects, there were only 3 reports of serious adverse events.

One of these was 1960 report of temporary growth retardation in a 5 1/2-year-old male, who was having 1 percent hydrocortisone applied for 16 months. In 1962, there was a report of temporary

growth retardation in an infant, who also had 1 percent hydrocortisone applied twice daily for 6 months, and this was--that says total body--whole body and unction was what the report says in the ANPR.

In 1966, there was a rapid gain in body weight in a 3-week-old infant male, who was only using 0.25 percent hydrocortisone 3 times a day for 8 1/2 days, but over a very large coverage 2,100 mg/m2 body surface area.

So, all in all, that panel considered this a very favorable response, only 3 out of over 12,000 subjects had any serious adverse events with hydrocortisone.

[Slide.]

The panel recommendations in the ANPR were that hydrocortisone and hydrocortisone acetate should be considered GRASE over a concentration range of 0.25 to 0.5 percent. Remember GRASE is generally recognized as safe and effective.

The panel also has some recommendations for labeling, and since I will be showing you

labeling in the third part of the talk, I just wanted to let you see how this labeling developed as the monograph developed.

The panel felt that the indication should be or the use of hydrocortisone should be temporary relief of minor skin irritations, itching, and rashes due to a variety of different conditions, and we will get into that when we look at the labeling.

The panel also felt that among several warnings should be these two, which are relevant to today's discussion I think. One is that consumers should stop use if the condition worsened or lasted more than 7 days, so there was a time limit put on the use of hydrocortisone.

The other warning I wanted to mention was the one that it should not be used on children under 2 years of age. In fact, these two warnings were included on all external analgesic active ingredients, but they are directly relevant to some of some of the discussion you will be having later I think.

Finally, the panel felt that under Directions should be a direction to apply this to the affected area essentially only, not more than 3

to 4 times a day.

[Slide.]

FDA's position was made public in the Tentative Final Monograph, TFM, which published a little over 3 years later in 1983. FDA agreed that the concentration range specified by the panel was appropriate, that 0.25 to 0.5 percent hydrocortisone should be considered GRASE, safe and effective, and FDA did make some labeling modifications.

Among those was the focus of the indication on antipruritic aspects of hydrocortisone, so instead of temporary relief of skin irritations, itching, and rash, it became temporary relief of itching associated with skin irritation and rashes due to a variety of conditions, and hydrocortisone is today, that is the only indication, antipruritic.

Additionally, to the stop use condition,

FDA added the clause, "Stop use if condition worsens or last more than 7 days or if symptoms clear up and occur again within a few days."

[Slide.]

The Tentative Final Monograph was amended in 1990 in response to a Citizen Petition which requested an increase in dosage strength to a maximum of 1 percent from remember the previous 0.5 percent.

This amended TFM included an extensive data and literature review mostly centered around the use of 1 percent hydrocortisone, and ultimately considered the higher concentration of 1 percent to be GRASE for OTC use.

Additionally, there were some labeling modifications. Under Do Not Use was added, "Do not use any other hydrocortisone product when using the product you are using," and "Do not use this for the treatment of diaper rash," which is still on the labeling, and this is largely due to the occlusive nature of a diaper.

[Slide.]

What about the Final Monograph, the last step? It is pending. We are working on it. We have found that manufacturers are generally

complying with the Tentative Final Monograph and the amended TFM. I will show you that in some labeling in just a minute.

We are continuing our review of data submitted by manufacturers, as well as in the literature.

[Slide.]

In light of today's discussion, I just wanted to point out some of the literature that we have been reviewing. This table represents 5 studies that have been conducted since the ANPR published in 1979. All of these studies were in children, and all of these used the modern standard ACTH stimulation to measure HPA axis function.

ACTH, as Dr. Cook will go into a little bit more detail on this, ACTH is adrenocorticotropic hormone. This is released from the anterior pituitary and stimulates release of cortisol from the adrenal glands. That is the P

and the A, adrenal glands in the HPA axis.

So, by looking at the amount of cortisol released in response to a known amount of ACTH, or in a more practical sense, some synthetic analogue of ACTH, you can tell whether the HPA axis is functioning properly.

In all of these studies, at hydrocortisone concentrations ranging from 1 percent to a maximum of 2.5 percent, and with durations of treatment ranging from 2 weeks or 14 days up to just under 18 years, the HPA axis was found to be functioning normally in response to hydrocortisone.

[Slide.]

I would now like to look at the current labeling of hydrocortisone in this third part of the talk.

[Slide.]

Since 1999, OTC products should be conforming to the Drug Facts labeling standard. This is what the hydrocortisone labeling should look like if it's in compliance with the monograph, and there are three things I would just like to

point out to you. We have been discussing the development of the monograph through the various stages, and I wanted to show you how that looks in the labeling.

So, under Uses, you see the indication, temporarily relieves itching associated with minor skin irritations, inflammation and rashes due to a variety of conditions, and the number of conditions that may be causing the itching has increased over the years with each new monograph publication.

[Slide.]

Also, under Warnings, this is very much as it appeared in the TFM, the Tentative Final Monograph's "Stop use and ask a doctor if the symptoms persist for more than 7 days or clear up and occur again within a few days."

[Slide.]

And under Directions, "Apply to affected area not more than 3 to 4 times a day, children under 2 years of age, do not use."

[Slide.]

This is labeling that is taken off of a

currently marketed OTC product, and I just wanted to show you that again, manufacturers are very much in compliance with the monograph standards.

So, in this labeling under Uses, we see the same thing, "temporarily relieves itching of minor skin irritations, inflammation and rashes."

[Slide.]

Under Warnings, "Stop use and ask a doctor if symptoms persist for more than 7 days."

[Slide.]

Under Directions, the same two that I just mentioned.

I would like to thank you for your attention and I will be followed by Dr. Denise Cook of the Division of Dermatologic and Dental Drug Products. Denise will be talking about prescription topical corticosteroids.

Thank you.

Rx Topical Corticosteroids: HPA Axis Suppression and Cutaneous Effects

[Slide.]

DR. COOK: Good morning. Good morning to

the respective chairs of the respective advisory committees that are here, also to the advisory committee members, to my FDA colleagues, and people in the audience.

I am Denise Cook. I am a dermatologist in the Division of Dermatology and Dental Drug products.

[Slide.]

Today, I will be speaking to you on prescription topical corticosteroids, the HPA axis suppression, and cutaneous effects.

The majority of the presentation will be on the systemic effect of the HPA axis and the suppression, and the FDA's experience with. I will be presenting trial data from approved drug products, the resultant labeling changes. I will also give a postmarketing summary of adverse events as it relates to the HPA axis suppression that we have in our database.

But first I will give you a background to the talk, so that you can follow it probably a little bit later. I will talk about the

classification of topical corticosteroids, give you a synopsis of the cosyntropin stimulation test and how it is performed, and also give you an evolution of interpretation of normal HPA axis function as it has been done over the years at the FDA.

I will give you background also on class labeling for topical corticosteroids and how that developed, and the cutaneous adverse events from topical corticosteroid use.

[Slide.]

The topical corticosteroids are divided into seven classes. Although the FDA does not purport this classification, it is widely used in the dermatologic community.

Class I consists of superpotent topical corticosteroids, Class II high potency, Class III through VI are mid-potency with Class III being closer, of course, to the high potency, and Class VI being close to the low potency of Class VII.

It is usually determined by a vasoconstrictor assay where the topical corticosteroids placed on the cutaneous surface,

and blanching or vasoconstriction is determined relative to the other corticosteroid.

[Slide.]

The cosyntropin stimulation test, which is the test that I will be discussing in the bulk of the studies that you are going to hear about today, is used to assess the function of the end organ, the adrenal gland, in the hypothalamic-pituitary adrenal axis.

In the case of topical corticosteroids, it is assessing an exogenous unwanted treatment effect.

What is usually done is the cosyntropin is given at 0.125 mg or 0.25 mg depending on age and/or body weight, and it is administered intravenously at baseline and at the end of treatment.

Blood is then drawn for serum cortisol values at 30 minutes and sometimes 60 minutes post stimulation. Then, the interpretation of the results determines a normal or abnormal response.

[Slide.]

The evolution of the interpretation of the normal function of the HPA axis at the FDA has undergone many revisions. First, in 1985, a.m.

serum cortisol, then urinary corticoid concentrations were used to determine whether you had normal function of your HPA axis after treatment with topical corticosteroids.

Then, in 1996, the cosyntropin stimulation test was employed. At that time, a 30-minute post stimulation serum cortisol had to be greater than 20 mcg/dL. Also, if the pre-stimulation serum cortisol was already greater than 20 mcg/dL, then, you needed to have at least a 6 increment change from pre-stimulation to post-stimulation in order to be considered to have a normal response.

In 1999, the FDA went to a single criterion to determine normal function of your HPA axis. That was a 30-minute post-stimulation serum cortisol greater than 18 mcg/dL.

[Slide.]

In 2001, it was decided that if we were going to use cosyntropin to determine normal

function of hormonal therapy HPA axis, then, the label should be followed as it is currently written, that is, that the control plasma cortisol level should exceed 5 mcg/100 mL. The 30-minute level should show an increment of at least 7 mcg/100 mL, and the 30-minute level should exceed 18 mcg/100 mL.

Currently, in 2004, there had been a lot of work in the FDA with endocrinologists and also members in the Division of Dermatology to determine that we need to go back to a single criterion for HPA axis function and determining it from the cosyntropin test. Therefore, at the present time, we only use a 30-minute level, and that serum cortisol level should exceed 18 mcg/100 mL.

[Slide.]

Now, class labeling for prescription topical corticosteroids went into effect in 1990, and I am going to give you a little background on one of the factors that propelled this into being.

This class labeling talks about the effects on the HPA axis, effects on glucose

metabolism, development of Cushing's syndrome, effects on growth, and effects on intracranial pressure.

[Slide.]

Two studies have propelled this into being. There were two open-label trials with Temovate Ointment. In Trial 1, there were 6 adult patients with psoriasis who applied 7 grams/day to 30 percent of their body surface area for 7 days.

ACTH stimulation was performed at baseline and 2 post-treatment a.m. cortisols were taken. They found that 50 percent of the patients exhibited decreases in cortisol production.

[Slide.]

In the second trial, the objective was to determine the largest dose over a 7-day period that would not cause significant suppression of the adrenal gland.

Three doses were used - 7 grams/day, 3.5 grams/day, and 2.0 grams/day.

Suppression in this trial was determined by an A.M. plasma cortisol and urinary corticoid

concentrations.

It was interesting, it was found that none of the psoriatic patients suppressed at 7.0 grams/day or even at 3.5 grams/day, but doses as low as 2.0 grams/day caused marked suppression of cortisol secretion in patients with atopic dermatitis. We can possibly presume that this may be because they may have had a higher compromise in the epidermis.

DR. WOOD: What were the numbers in that study?

DR. COOK: I don't know the numbers. You mean like exactly what the serum cortisol levels were?

DR. WOOD: The number of patients.

DR. COOK: The number of patients, I don't have that either. This was 1985, and this is taken out of the label. But I would suspect that they were small, because in the current studies that we have, the numbers are small, they are not huge numbers.

[Slide.]

So, this led to a Temovate label in 1985 that stated in the Precautions, it is a highly potent topical corticosteroid that has been shown

to suppress the HPA axis at doses as low as 2 grams/day. As you note here, it is a Class I steroid in the superpotent category.

Under Pediatric Use, it was determined that it should not be used in children under 12 years of age, at least it is not recommended.

[Slide.]

So, now we will move on to the actual class label that was generated.

[Slide.]

In the Precautions Section, it states that 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.

[Slide.]

It goes 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.

[Slide.]

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 glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids.

[Slide.]

The class label also addressed pediatric use in the Pediatric Use Section of the label.

[Slide.]

Currently, this is what is there if there haven't been any tests done on pediatric patients, but as you shall see in the studies that I will

present, since the advent of FDAMA, we have been able to get studies in pediatric patients, so some of this has been modified in the respective labels.

Safety and effectiveness in children and infants have not been established. 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.

[Slide.]

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.

[Slide.]

Now, we are going to move on to the bulk of the presentation, which is going to be about the prescription topical corticosteroid data and its relationship with HPA axis suppression.

I am going to speak about 10 drug products. There are 8 topical corticosteroid products, 2 topical combination drug products.

[Slide.]

Just to give you those, I am going to speak about Dermatop, which is a mid-potency steroid; Cutivate Cream, another mid-potency topical corticosteroid; Diprolene AF Cream, which is a high potency steroid.

You might want to look in Tab 2, I think it is, of your background package. It has that

classification that I spoke of earlier, the high potency steroids being in Class II.

Diprosone Ointment, a high potency steroid; Diprosone Cream and Lotion, both in the mid-potency category; Clobex Lotion, a superpotent steroid; and Temovate E Cream. Both of these are clobetasol propionate.

There will be 11 studies that I am going to discuss. The ages of these patients were from 3 months to adult. These are all open-label trials, and they all use the cosyntropin stimulation test to determine the function of the HPA axis.

[Slide.]

Dermatop is a Class V steroid near the bottom part of the mid-potency topical corticosteroids. It was approved in May 1996. We are going to discuss a pediatric atopic dermatitis trial.

[Slide.]

There were 59 patients enrolled and there were 2 targeted populations. The patients were between 1 month and 2 years and also between 2 and

12 years. There were 10 patients who were less than 2 years old and 49 patients were greater than or equal to 2 years of age.

[Slide.]

They had to use the medication over greater than 20 percent of the body surface area. I mean they had to have atopic dermatitis to that amount of cutaneous surface, and use it twice daily for 21 consecutive days.

Again, we used the cosyntropin stimulation test. It was administered at baseline and at day 22. In this trial, patients who were greater than or equal to 15 kilograms received a higher dose of 0.25 mg IV, those less than 15 kg received 0.125 mg IV.

[Slide.]

The criteria in this study was the adrenal response to ACTH at 30 and 60 minutes. Here, the post-stimulation serum cortisol had to be greater than 20 mcg/dL, and if the pre-stimulation serum cortisol level was already greater than 20, then, an incremental increase of greater than 6 mcg/dL in

the serum cortisol was required.

[Slide.]

There were 3 patients according to the protocol criteria who were suppressed. Two patients, 1 an 18-month-old, had a peak response of a 5 mcg/dL change from baseline, 1 patient had a post-stimulation cortisol value actually decreased from baseline.

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 mcg/dL, although they didn't have that required incremental rise, that they should not be considered suppressed.

So, this led to the current label that reads for this drug, that "none of the 59 patients showed evidence of HPA axis suppression."

[Slide.]

The next drug is Cutivate Cream, which is also a Class V steroid, was approved in June 1999. We are going to look at another atopic dermatitis trial in pediatric patients.

[Slide.]

There were 43 evaluable patients with moderate to severe atopic dermatitis; 29 of the

patients were 3 months to 2 years of age, and 24 patients were 3 years to 5 years old.

[Slide.]

The criteria for entry into the study was that they had to have at least a 35 percent body surface area involvement, and I will tell you in all of these studies, we were looking for maximum use conditions, so you could get your worst case scenario.

They applied the medication twice a day for 3 to 4 weeks. Patients up to 2 years were limited to 120 grams/week, and patients 3 to 5 years of age were limited to 180 grams/week.

[Slide.]

Looking at body surface area improvement over time to show the response to the medication, 23 of the patients, or 50 percent, had a decrease of 50 percent by 2 weeks, and 9 had a decrease of 50 percent by 3 weeks, and 9 percent of the

patients had a 50 percent decrease by 4 weeks.

[Slide.]

The cosyntropin was administered at baseline and end of treatment, and in this study, they used age, younger age group was given a lower dose than the older age group.

[Slide.]

Here, a normal response was a serum cortisol level that exceeded 18 mcg/dL at 30 minutes post-stimulation.

[Slide.]

Two the patients out of the 43 patients experienced adrenal suppression. One was a 5-year-old who actually had 95 percent body surface area involvement, used the drug for 4 weeks, used 561 grams, and his pre-stimulation, as you see here, pre-treatment value was 33.9 after stimulation, and yet it fell to 11.8, but in follow-up he recovered at 19.8 with his serum cortisol.

The other patient was a 2-year-old who had the minimum amount of body surface area involvement

of 35 percent. His duration of treatment was for 5 weeks. He used 176.5 grams, and his end-treatment post-stimulation serum cortisol was 9.4. Unfortunately, we don't know whether he recovered or not because he was lost to follow-up and the investigator did make an honest effort to try to track this child down.

[Slide.]

But this led to labeling changes for Cutivate Cream, which stated that children as young at 3 months of age for up to 4 weeks of use could use the medication, and appropriate sections of the label were updated.

[Slide.]

Now, I am going to talk about 4 or 5 betamethasone propionate products. They were all approved in 2001, and when I say approved in 2001, I mean the pediatric part of the label was changed. Their supplement for safety was changed, because, of course, they have been on the market a lot longer than just 2001.

One is Diprolene AF Cream, which is a

Class II steroid; Diprosone Ointment, another Class II steroid; Diprosone Cream, a Class III steroid; Diprosone Lotion, which is mid-potency, but the lower end of the mid-potency, and that will be significant when you see the study results of this drug, of Diprosone Lotion.

Then, I am going to speak of the 2 combination products, Lotrisone Cream and Lotion.

[Slide.]

The criteria for a normal HPA axis response in all of these studies was that we would follow the cosyntropin label, that the failure of any one of three criteria would indicate suppression of the HPA axis, and stimulation should occur at baseline and end of treatment.

[Slide.]

So, the criteria for the 30-minute post-stimulation, the three criteria that they needed to meet to have a normal response, is that the control plasma cortisol level should exceed 5 mcg/100 mL, the 30-minute cortisol level should show an increment of at least 7 mcg/100 mL above

the basal level, and the 30-minute level should exceed 18 mcg/100 mL, and a failure of any one of those three would indicate suppression.

[Slide.]

So, with Diprolene AF Cream, there were 60 evaluable patients. They ranged in age from 1 to 12 years with atopic dermatitis. They had a mean body surface area involvement of 58 percent. They used the study drug twice a day for 2 to 3 weeks, and that depended upon whether their disease cleared or not.

If they cleared within 2 weeks, they were allowed to stop and then be tested at that point. If they needed 3 weeks, they could use if for 3 weeks. They were limited to 45 grams per week.

[Slide.]

The results of the cosyntropin stimulation showed that 19 out of 60 or 32 percent of these patients showed evidence of HPA axis suppression. I won't go through all of these, but if you just took the criterion that we look at now, which is greater than 18 mcg/dL, 58 percent of the patients

had suppression.

[Slide.]

If you look at suppression by age group, it appeared that a larger percentage of patients suppressed as the age decreased.

Looking at recovery of normal HPA axis suppression, unfortunately, all the patients were not retested. We would have liked to have all of them retested, but 4 patients were retested 2 weeks post-treatment, and 3 of the 4 recovered normal function of their HPA axis.

[Slide.]

We tried to do a statistical analysis in the development of HPA axis suppression with each drug. With Diprolene AF, there was no correlation between amount of drug used, body weight, age or sex, and the incidence of adrenal gland suppression.

The statistical relationship did exist between body surface area and risk of HPA axis suppression such that for an increase of 1 percent body surface area involved, the risk of HPA axis

suppression increased 4.4 percent with a p value of less than 0.01.

[Slide.]

This led to a label change for Diprolene AF Cream, such that it was restricted to patients 13 years and older, and appropriate information was included in other sections of the label.

[Slide.]

Diprosone Ointment. That study had 53 evaluable patients with atopic dermatitis. The age range was 6 months to 12 years. The medication again was applied twice a day for 2 to 3 weeks. The mean body surface area involved was 58 percent.

DR. WOOD: Can we just go back to that last slide? The one with the 1 percent BSA involved.

DR. COOK: Excuse me. Which one?

DR. WOOD: The last slide, the slide before that, Slide 39. That is clearly key. Is that really right? I mean does that mean that a 20 percent, that is linear throughout the thing, so going from 1 percent to 21 percent would mean 88

percent of people had HPA suppression? That doesn't seem to make much sense to me.

DR. COOK: Well, you will have to talk to our statistician.

DR. WOOD: All right. Fair enough. Go on.

DR. COOK: Let's see, I have figure out where I left off. I think I was here, at Diprosone Ointment and getting ready to tell you the patient that suppressed.

There were 28 percent of patients who showed evidence of HPA axis suppression when given the cosyntropin stimulation test, and here again, if we just looked at the criterion of less than 18, of those who weren't able to exceed 18, 53 percent of the patients had a post-stimulation plasma cortisol value that would suggest suppression.

[Slide.]

Again, if you looked at suppression by age, for this drug, again, there was a higher proportion of patients who suppressed, the younger the patients were.

[Slide.]

In the statistical analysis here in the development of HPA axis suppression, these

statisticians didn't find a statistically significant effect for drug usage, for percent of body surface area involved, for weight, or for age.

It did show that for some reason, a higher proportion of males than females developed HPA axis suppression using this drug.

[Slide.]

In testing patients for recovery, 2 of the 15 patients were retested and 100 percent recovered at 2 weeks.

[Slide.]

This led to a label change similar to Diprolene AF Cream in which an age restriction was added that patients should be 13 years of age or old, and appropriate parts of the label were updated with the clinical data.

[Slide.]

Diprosone Cream studied 43 evaluable patients with atopic dermatitis. They ranged in

age from 2 to 12 years. Here, the mean body surface area involvement was 40 percent. Again, they applied the medication twice a day for 2 to 3 weeks.

[Slide.]

In this study, 23 percent of the patients showed evidence of adrenal suppression using the Cortrosyn label with all three criteria and a failure of one.

If you look again at a post-stimulation value that was less than 18, 50 percent of patients showed evidence of adrenal suppression.

[Slide.]

In this study, you can't quite see the value here. Starting here with 14 percent of patients 9 to 12 years of age showed evidence of suppression. As you march down again, the percentages went up, but here, interestingly, which will show you the dilemma that we all are in, in determining just what is going to make someone suppressed, what are the risk factors here, none of the infants in this study showed evidence of

adrenal suppression.

[Slide.]

Again, with the statistical analysis for this particular drug, in these patients, there was no statistically significant effect for number of days treated, for weight, or for age.

However, there was a statistical significance found for mean amount of drug usee - 81 grams in those who suppressed versus 37 grams in those that did not.

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

[Slide.]

When looking at recovery of HPA axis function with Diprosone Cream, 2 out the 10 patients were retested, and 50 percent, 1 out of the 2, recovered function at 2 weeks.

[Slide.]

Here again, the label was changed to add and age restriction to 13 years or older, and

appropriate portions of the label were updated.

[Slide.]

Now, Diprosone Lotion, I will remind you again is a Class V steroid, so just like two classes above the lowest potency of topical corticosteroid.

Here, they had 15 evaluable patients with atopic dermatitis. They ranged in age from 6 to 12 years old. The mean body surface area involvement was 45 percent. They applied the medication twice a day for 2 to 3 weeks.

[Slide.]

This was a very interesting study. Eleven of the 15 patients or 73 percent of the patients showed evidence of HPA axis suppression. If we look at just getting a serum cortisol value that exceeded 18 mcg/dL, 91 percent of the patients failed to do that.

[Slide.]

Although this study was supposed to enroll infants, it was felt that with such a high degree of HPA axis suppression, the proportion of patients

6 to 12 years of age, that no patients were enrolled in the lower age group. This brought up the issue that possibly it is not only the chemical moiety that might produce HPA axis suppression, but since it is coming from the skin, it may involve the vehicle in which the chemical moiety is in.

In this instance, the lotion, it may somehow with the chemical moiety quicker from the skin into the systemic circulation, and thereby cause more HPA axis suppression. So, in other words, vehicle may play a role also in determining that systemic effect.

[Slide.]

When looking at the statistical analysis in the development of HPA axis suppression, it was a numerical analysis. The subjects exhibiting HPA axis suppression used the larger mean amount of drug. They had a slightly higher percent of BSA involvement.

They had lower mean weights at visit 1, lower mean weights at visit 4, but the difference with respect to age and days of treatment, at least

from a statistical point of view, were minuscule.

[Slide.]

Looking at recovery of HPA axis function with Diprosone Lotion, it's good to report that 67 percent of the patients who were retested recovered their HPA axis function at 2 weeks.

[Slide.]

So, the labeling change for Diprosone Lotion was that an age restriction was added to 13 years and older, and appropriate sections of the label again were updated.

[Slide.]

Just to look at the four betamethasone products together, again, you see that the three here, Cream, Ointment, and Cream, all seemed to suppress somewhat where in the same range. When you got down to the lotion, you had a much, much higher percentage of patients who experienced HPA suppression. Again, it may have to do with the vehicle, if there is an absorption enhancer in it or other factors.

[Slide.]

Lotrisone Cream is the other betamethasone product that I am going to speak about. It is a combination product of betamethasone dipropionate

with Lotrimin Cream. It is indicated for the treatment of tinea pedis and tinea cruris, so we did a study in both of those.

Both studies were in the adolescent population, 12 to 16 years. Medication was applied twice daily. The study duration for tinea pedis was 4 weeks and for tinea cruris was 2 weeks.

[Slide.]

Here, we also have some surprising results. Seventeen out of 43 or 39.5 percent of patients demonstrated adrenal suppression in the tinea pedis study, and we might not have actually expected that given that the stratum corneum of the feet is somewhat thick, but it might also be teenagers wear sox and tennis shoes all day long, and that might also cause more occlusion and absorption of the drug product.

In tinea cruris, there were 47.1 percent who demonstrated adrenal suppression, and this is

also is an area where you may have some natural occlusion, increasing absorption.

[Slide.]

So, this led to some labeling changes for Lotrisone Cream and Lotion. The Indication Section was expanded, it added an age restriction to patients 17 years and older. It also recommended that effective treatment may be obtained without the use of a corticosteroid for non-inflammatory tinea infections. Then, other appropriate sections of the label were updated with clinical information.

DR. FINCHAM: Dr. Cook, may I interrupt for a second and just ask a question about the data sets that you are reporting on?

DR. COOK: Sure.

DR. FINCHAM: Is this Phase IV data that is provided by sponsors, that then the Agency has acted on to change the label?

DR. COOK: No. Most of this was done in response to what we call "pediatric written requests," which is part of the FDA Modernization

Act. So, we could either ask them to do the studies--I mean all of this was post-approval, but I don't know if we actually call it Phase IV--we could either ask them to do the studies or they could propose the study to us, but we would have to then issue them the pediatric written request which would allow them to do the studies. That is sort of a quick summary.

[Slide.]

Now, this steroid, Clobex Lotion, was actually approved in 2003, and this actually was part of their NDA, and was not a Phase IV. At that time, we were able to ask for and get trials in pediatric patients if we needed it.

These trials, atopic dermatitis and for psoriasis, were done in both pediatric and adult patients.

[Slide.]

There were 3 studies involving Clobex Lotion, 2 adult studies, 1 in psoriasis and one in atopic dermatitis, and 1 pediatric study, ages 12 to 17 years in atopic dermatitis.

In all of the studies, there was a comparator drug, Temovate E Cream, which is also clobetasol propionate, so the same chemical moiety

in a different vehicle. As I say here, it is a Class I steroid.

[Slide.]

The construct of the HPA axis evaluation for this study went back to the 3 criteria, and that is because the actual NDA and construct of the study was done prior to our criterion of just 1, because it was approved in 2003, so the studies were done prior to that.

[Slide.]

In the adolescent study, there were 24 evaluable patients, 14 were treated with Clobex Lotion and 10 were treated with Temovate E Cream.

They all had moderate to severe atopic dermatitis. They had to have a body surface area involvement of at least 20 percent. The medication was applied twice a day for 2 weeks, and there was a 50-gram/week limit, and a lot of this at the time was driven by the fact that Temovate E Cream, that

is how it's labeled.

[Slide.]

It was found that 9 of the 14 or 64 percent of subjects treated with Clobex Lotion were suppressed versus 20 percent of subjects treated with Temovate E Cream, again suggesting that the vehicle may have something to do with the amount of drug that gets into the systemic circulation.

[Slide.]

In the statistical analysis the mean percent body surface area treated was higher for patients that had adrenal suppression, 32.8 percent versus 27.7 for the Clobex Lotion and 35 percent versus 25.3 percent for the Temovate E Cream.

[Slide.]

When retested, 1 of the 4 patients treated with Clobex Lotion remained suppressed after 2 weeks, and 1 of the patients, which was the only 1, that was suppressed with Temovate E Cream recovered.

[Slide.]

In the adult study, there were 18

evaluable patients, 9 were treated with Clobex Lotion and 9 with Temovate E. They all again had moderate to severe atopic dermatitis. The mean body surface area treated was approximately the same for both drug products. They applied it twice a day for 2 weeks, again with a 50-gram/week limit.

[Slide.]

Here, 56 percent of the patients treated with Clobex Lotion suppressed and 44 percent with the Temovate E Cream suppressed.

[Slide.]

When looking at recovery for these 2 products, 1 of the 3 patients retested failed to recover function 7 days post-treatment with the Clobex Lotion, and 2 out of 2 patients on Temovate E Cream recovered their function 7 days afterwards.

[Slide.]

Finally, in the adult study, moderate to severe plaque psoriasis , there were 20 evaluable patients, 10 in each arm. Again, the mean body surface area treated for both was approximately the same. The medication was applied twice a day here

for 4 weeks, and there was again a 50-gram/week limit.

[Slide.]

Eighty percent of the patients treated with Clobex Lotion suppressed and 30 percent with Temovate E Cream suppressed. One of the 2 subjects retested with Clobex Lotion remained suppressed after 8 days, and none of the 3 subjects on Temovate E Cream unfortunately were retested.

[Slide.]

So, the indication for Clobex Lotion, when it was approved based on these results, was that it would be restricted to patients 18 years of age or older. It could be used for two consecutive weeks not to exceed 50 grams/week.

For moderate or severe psoriasis, for localized lesions less than 10 percent body surface area involvement, that an additional 2 weeks of treatment, the lotion could be used. Appropriate other sections of the label were updated.

[Slide.]

Now, I am going to shift gears from our

trial data and look at a postmarketing summary of HPA axis suppression across all topical corticosteroids since the induction of the AERS database, which is one of our sources since 1969, and also from medical literature case reports.

[Slide.]

I will just give you a background on the Adverse Event Reporting System. It is a spontaneous, voluntary surveillance system. It is voluntary reporting by health care professionals and consumers, but it requires mandatory reporting by manufacturers.

There are approximately 3 million reports in the database. Again, the database originated in 1969. It contains human drug and therapeutic biologic reports. The exception is it doesn't have vaccines.

The quality of the reports are variable and they are often incomplete, so you have to keep that in mind. It is also subject to under-reporting, the true numerator is not known, and duplicate reporting does occur.

[Slide.]

There have been 94 cases reported spanning 3 decades, 65 adult cases and 29 pediatric cases.

The gamut of manifestations had been adrenal insufficiency, Cushing's syndrome, and growth retardation.

[Slide.]

In the 29 pediatric patients, and some of these overlap within same patients, 11 were with adrenal insufficiency, 17 with Cushing's syndrome, and there are 13 with growth retardation.

The ages ranged from 6 weeks to 15 years with the mean being 5 years. The duration of use was 22 days to 7.5 years with a mean of 20.8 months. Fifty-five percent of these patients received medication for 3 months or longer. There were varied indications, but 34 percent in the pediatric population were using topical corticosteroids for diaper rash.

Betamethasone containing, clobetasol, and mometasone products were implicated most often with 34 percent using high-potency topical

corticosteroids.

In these 29 pediatric patients who had evidence of some type of HPA axis compromise, it resulted in 14 hospitalizations and 2 deaths. The latter were from Cushing's syndrome or complications thereof.

[Slide.]

In the adult cases, there were 65, 46 with adrenal insufficiency and suppression, 32 with Cushing's syndrome.

The age range was from 19 years to 74 years, with the mean age being 47.4 years. The duration of use 7 days to 12.0 years, and the mean use was 35.6 months.

Forty-six percent of the patients received the medication for 3 months or longer. Again, there were varied indications, but 51 percent used topical steroids for psoriasis. Again, betamethasone containing and clobetasol products were implicated most often, with 61 percent using high potency topical corticosteroids.

These cases resulted in 34

hospitalizations and 2 deaths, and the deaths were attributed in part of the adrenal event.

[Slide.]

So, the postmarketing reports, just in summary, the common factors were that most of the AEs occurred in the following settings:

Prolonged use of the topical corticosteroid, use of a superpotent topical corticosteroid, use of multiple topical corticosteroid products or concomitant use with other corticosteroid formulations like inhaled or systemic, and also use of excessive amount or possible inappropriate use of the topical corticosteroid product.

[Slide.]

In summary of the data for the HPA axis suppression, HPA axis suppression does occur with the use of topical corticosteroids.

The adrenal suppression is not limited to the superpotent class of topical corticosteroids.

High BSA involvement and amount of drug used appear to be risk factors for HPA axis

suppression.

[Slide.]

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.

Long-term use of topical corticosteroids, particularly high potency ones, can lead to serious morbidity and even death.

[Slide.]

Now, we are going to move on to cutaneous safety. We will first speak about the known cutaneous adverse events, and then we will just address here briefly the question of cutaneous malignancy as it might relate to topical corticosteroids, if at all.

[Slide.]

Now, the adverse events associated with topical corticosteroid use include atrophy of the skin, telangiectasia, striae, erythema of the face, steroid rosacea, hypopigmentation, infection, and retarded wound healing.

[Slide.]

Because pictures speak a thousand words, I am going to give you a pictorial presentation of

these adverse events.

[Slide.]

This is a photo of cutaneous atrophy. It is not the best photo, but here you can appreciate a little bit of thinning of the skin and some shininess to the cutaneous surface.

[Slide.]

Here, we have telangiectasia. You can see the very fine blood vessels coursing here through this person's chin.

[Slide.]

This is a picture of striae, probably long-standing.

[Slide.]

Another picture of striae, maybe a little more of acute onset in nature.

[Slide.]

This is a picture of facial erythema.

[Slide.]

Another of facial erythema.

[Slide.]

This is a picture of steroid rosacea where someone was applying topical corticosteroids and had a flare of the disease. Certainly, here, the potency of the topical corticosteroid would have to

be weaned down, and then the rosacea, which is the underlying disease, had to be treated appropriately.

[Slide.]

This is a picture of hypopigmentation from topical corticosteroid use.

[Slide.]

Other adverse effects that can happen. Topical corticosteroids placed on certain infections, for example, tinea infections, may exacerbate them. Topical corticosteroids placed on open or surgical wounds will retard healing. Use of topical corticosteroids in the periorbital area may cause an increase in intraocular pressure.

[Slide.]

Now, as far as cutaneous malignancy, we

will look at the postmarketing reports out of the same system that I was speaking about prior, the AERS database, and there are 2 reports as of February 5, 2005, that spans all the way back to 1969.

One was a 7-month-old male with a history of mastocytoma, and he reported or someone reported cancer several months after discontinuation of clobetasol. The patient actually used fluticasone for a short while, and then used clobetasol propionate for 1 week, stopped for 1 week, and then started to reapply for another week, but developed cutaneous atrophy, and the medication was stopped, and then several months later, the report came that he developed skin cancer.

The second case is a female of unknown age who used betamethasone cream for psoriasis and then reported "what started as psoriasis became cancer".

So, from this we can say that the AERS data do not suggest a compelling safety signal for malignancy formation with the use of topical corticosteroids.

[Slide.]

So, as far as cutaneous adverse events, corticosteroid-induced adverse events can be early

or late event. It depends on the potency of the drug and the duration of use. It depends on the site of application. Occlusion at the site may increase the risk.

Corticosteroid-induced adverse events may resolve slowly or they may not resolve at all.

[Slide.]

So, in conclusion, HPA axis suppression can occur with short-term use of topical corticosteroids. HPA axis suppression can occur with even mid-potency topical steroids. It can occur as early as two weeks of continuous therapy.

[Slide.]

The suppression that occurs is usually reversible. The interrelationship between body surface area, amount of drug used, and potency of the medication is complex as it relates to the development of HPA axis suppression.

Long-term use and/or misuse of topical

corticosteroids, particularly those of high potency, can lead to serious medical complications and death.

[Slide.]

The cutaneous adverse events can be related to both duration of use and potency of topical corticosteroid use. It can occur with short-term or long-term use.

Resolution of these cutaneous adverse events is possible with some, but not all of them.

There also is no firm evidence to date to link cutaneous malignancy with the use of topical corticosteroids.

Thank you for your attention for this presentation.

Next, we will have Dr Stephen Wilson. He is in the Division of Biometrics II. He will speak on lessons learned from growth studies with orally inhaled and intranasal corticosteroids.

Lessons Learned from Growth Studies with Orally Inhaled and Intranasal Corticosteroids

DR. WILSON: Gray Gaithersburg morning to

you.

It is my pleasure to be here this morning substituting for Peter Starke. I think that I was elected for this job because I am the only one that was around when they did the class labeling advisory committee in 1998, but we have had some lessons that we have learned from that advisory committee in dealing with growth studies for orally inhaled and intranasal corticosteroids, and I would like to share some of those with you in the short amount of time that we have.

[Slide.]

Specifically, we have been charged with providing you with somewhat of a background of why we do these studies within our area for intranasal and orally-inhaled corticosteroids, and then talk about what these growth studies are.

In particular, we are going to focus on what we call longitudinal growth studies, which are fairly long-term growth studies. Then, we will talk about some of the design issues with these studies and the regulatory history that sort of

brought us to this moment in terms of the science.

I will provide with the results from some of the studies that we have seen within the Division. When I say "we," I mean the Division of Pulmonary and Allergy Drug Products.

[Slide.]

So, why do we perform growth studies? I think that looking at it from our perspective, growth is an indicator of systemic exposure and of the potential to cause systemic toxicity.

Growth suppression is a well-known side effect of systemic corticosteroid use. It has a class effect. We view it as a class effect, that all CS given in sufficiently high doses will produce growth effects. It is thought to be a direct effect on the bone, and may also act through secondary mediators and hormones.

We believe that growth is the most sensitive indicator of systemic effect within our review environment because we have seen growth effects in the absence of effects from HPA axis studies by cosyntropin stimulation.

[Slide.]

There are basically two types of studies that are presented to us by sponsors. One goes by

the name of knemometry, and the other is the longitudinal or long-term growth studies.

Sponsors have done knemometry studies. These are generally short-term studies, so it is attractive in the sense that they can be done rather quickly, and there are a number of methodological issues. They can essentially be done in only a few centers.

The consistency of results has been puzzling and a little bit problematic to us as a regulatory agency, because we don't always see the same kinds of results coming out, and we view these as primarily a research tool.

So, focusing on longitudinal growth studies, these are growth studies designed to measure growth velocity over a 1-year treatment period, so this is a long treatment period.

The patient population has to be carefully selected because this is a patient population that

needs to have the treatment, but we also need--and you will see in a minute--we also need to be able to run a concurrent control, so some on corticosteroids and others using other kinds of medications.

[Slide.]

What is the population that we look at in these growth studies? These two CDC charts are provided primarily to show you where we consider growth to be fairly linear.

For one thing, it is very difficult to get growth measurements in the youngest children, zero to 2 years old. By 2, you are able to get the stadiometry measurements, and the growth is fairly linear, until you get up to puberty, about 9 to 11 years old depending on sex.

So, this is the focus of these growth studies that are provided to us by the sponsors.

[Slide.]

So, what are these growth studies, what do they look like? Basically, it is fairly straightforward. It's serial stadiometry. There

is a baseline period of about 3 months in which we measure growth, baseline growth.

Then, there is an on-treatment period and then another follow-up of 3 months. There was a guidance that was developed following the advisory committee that I mentioned in 2001, and it is still available on the website, so you can see some of the details of what we are suggesting.

[Slide.]

So, longitudinal growth studies. As I said, they are technically difficult to perform. They require relatively large numbers of children. In fact, in the guidance that we provide, we say that ideally, they would have almost 125 children in each of the treatment groups. So, you can see they are quite a bit larger than the studies we have been looking at.

They require a long baseline and treatment period, and the measurement and compliance issues are very difficult, in other words, you have got to keep children on these studies for a long time, working with parents and providing treatment.

There are also statistical issues in terms of when the data has been provided to us. This is what I think probably sponsors have the most

problem with is we are not looking at these as superiority trials or even equivalence or non-inferiority trials. It is just too difficult to make a judgment as to what the delta or the difference that you are looking at would be.

So, we essentially are presuming that there is a growth effect from these drugs, and we are designing them to best characterize that effect, so this is a little bit different, and that means that you have to have the proper size, you have to conduct the studies appropriately, and that is what we are going to be reviewing if we are going to describe what your study has done in the label.

So, the size of the growth effect that is clinically relevant is unknown or not fully known. That is what our presumption is.

[Slide.]

So, how did we get here? Actually, there

is some OTC history here. In 1996-97, there were two longitudinal growth studies done to better characterize the systemic risks prior to consideration of taking beclomethasone dipropionate nasal spray over-the-counter.

So, in other words, the company was developing, wanted to go OTC, had these growth studies going, and when the results of these growth studies became available, it was recognized that there was a growth effect that hadn't been shown in the other kinds of tests.

Then, at that same time, the number of other companies who were doing growth studies also came in and demonstrated this same kind of effect.

So, 1998, we held a Joint Pulmonary-Allergy and Metabolic-Endocrine Advisory Committee, which ended up recommending a class labeling for all orally inhaled and intranasal corticosteroids, and we ended up also implementing that recommendation.

[Slide.]

So, what did that label end up looking

like? Well, in the General Use and Pediatric Use Subsections, we essentially said orally inhaled/intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients.

Also, in the Pediatric Use Section, we noted that growth effect may occur in the absence of laboratory evidence of hypothalamic-pituitary-adrenal axis suppression, potential for treatment "catch-up" growth has not been addressed, and basically, our advice to the physician was to titrate to the lowest effective dose for each patient and monitor growth routinely.

If reported, cases of growth suppression should be noted in the Advise Reactions Section.

So, basically, in terms of this being a class labeling, we would only note certain kinds of growth suppression if it was being reported to our systems.

[Slide.]

So, how did this original study look, the one that we were looking at for the advisory committee?

Intranasal beclomethasone basically was a randomized, double-blind, placebo-controlled, parallel group, prospective, one-year study.

The age groups of the children, they were children with allergic rhinitis being treated by intranasal corticosteroids, ages from 6 to 9.5 years. Basically, the same size study groups, and you just had a placebo against the intranasal corticosteroid, about 50 in each group.

[Slide.]

Now, the results showed that the growth rate centimeters/year on the BDP treatment group was 5.1 versus a placebo of 5.8, or a difference or a delta of minus 0.7. So, that was the extent of the depression that we saw for that one year.

Now, this was a statistically significant difference based on the prespecified analysis, and it was an unexpected result, but basically, we were comparing mean annual growth rates.

In the same study, however, these same children were tested, and there was no significant differences observed between treatment groups by

mean basal cortisol or ACTH-stimulated plasma cortisol levels.

[Slide.]

I wanted to make sure to include this slide. This is again these same patients, and looking at those charts that you saw earlier, the growth charts, these are the results of the patients based on where they fell on those charts after a year.

I can remember the endocrinologist, Sol Malozowski, was extremely interested in thinking about what it meant. Even though we were looking at mean data, in other words, there was a sense of a minus 0.7 that I showed you, we were also looking obviously, and very concerned about, how the children as individuals or groups fell within these two groups.

So, the mean data as expressed in percentage within growth rate percentiles is displayed here, so you can see something like 22 versus 4 in placebo or less than 3 percent in terms of the average growth., and that was true

throughout, so this is the mean data expressed another way.

[Slide.]

We also looked at some other intranasal drugs, and these are the data that came in later. You notice, as oftentimes happens, this was actually the largest difference that we saw was on the first one, and the intranasal drugs that came in afterwards, budesonide and fluticasone, also showed some growth depression. Mometasone, however, as you can note, did not show.

[Slide.]

The orally inhaled drugs tended to show more growth suppression, BDP, for example, minus 2 versus the 0.7 that you saw before. This slide also indicates that this is a study that was done, and you had some of those younger children, so you tended to see a lot more variability in the estimate, so the recommendations in the guidance became, you know, you had to have these older children that you could measure, because a lot of these included recumbent measurements, and those

are difficult measurements to make.

Another thing here is that there is some kind of apparent dose effect from a company that did try to test two doses. So, we had all of this data available to us in trying to make these determinations.

[Slide.]

So, the issues. These are indeed difficult studies to perform if you are thinking about doing one of these studies. They are also difficult studies to review. Now, if you are in a regulatory setting, so basically, you are taking what the company has given you as evidence, and you are making some assessment of that.

If a company has, for example, if there are a lot of subjects that have dropped out, you have to worry a lot about missing data, and you have to worry about if they haven't measured them carefully over time, in other words, there are some sort of glitches in the measurement, they then make decisions as to how they are going to analyze that data, so then as a reviewer, you have to respond to

that, so these are difficult studies.

Growth studies are not designed to evaluate obviously the reversibility of the HPA axis effects or changes greater than a year. So, although we do measure for another 3 months after the study, we do not try to see whether or not this would be long term.

A lot of these patients, a lot of these children are going to be on the drug for a lot longer than 1 year.

We have not identified a clinically relevant effect size, and that means that we all sit around a number of time, on a number of occasions, saying how could we pin down what the effect size is, so that maybe we could look at non-inferiority trial, but everybody said that basically, it is not acceptable or there is no clinically relevant effect size on that mean value.

[Slide.]

So, conclusions. We use growth studies as a stand-alone measure. We believe that they are a sensitive indicator of systemic effects, and we

think of this because sometimes the HPA axis and the growth study results are discordant, they don't agree with each other.

We take them as a surrogate for systemic exposure and potential to cause systemic toxicity. So, we are looking at children, these are people that are going to need these drugs, but we also take them with the notion that this is a sentinel, this is something that is going to tell us is this drug going to have effects more generally.

We believe that results are applicable to all age groups. Obviously, you can't study growth in 20- to 25-year-olds. We also feel that the class effect labeling, when you look at the class effect labeling, we state, as I stated earlier, all orally inhaled and intranasal corticosteroids have this effect.

As these studies come in to us from companies, we review them and we determine whether or not this is information that is going to help the physician. This is information we need to put into the label.

Sometimes we put what the company has offered, and other times we feel that we are not as sure that the results of the study are as reliable

as we would like them to be.

[Slide.]

Again, there is reference Division of Pulmonary and Allergy Drug Products.

I can't believe that I actually finished early, but I look forward to any questions you might have.

Thank you.

The next presenter is Dr. Markham Luke.

HPA Axis Suppression Studies: Conduct, Utility, and Pediatric Considerations

DR. LUKE: Good morning, Dr. Wood, members of the Committee, ladies and gentlemen in the audience.

[Slide.]

Today, I am going to speak on topical corticosteroids and testing for adrenal suppression in the context of potential Rx to OTC switch.

[Slide.]

This is a brief outline of my talk. First, I am going to speak a little bit about the various systemic effects that have been seen with topical corticosteroids and some which have not been seen.

We are also going to discuss specifically

the hypothalamic pituitary adrenal axis testing, what tests are available to look at HPA, and more specifically, we are going to focus in on cosyntropin stimulation testing, look at what our current testing recommendations, how we are trying to standardize the testing, and we are going to discuss how precise an estimate would we need for adrenal suppression potential for OTC.

[Slide.]

Now, as Dr. Cook and Dr. Wilson have stated, prescription corticosteroids have systemic effects which we evaluate during drug development.

[Slide.]

Now, I would like to separate these out into those areas where specific studies have not been required for dermatologic topical

corticosteroids. These include sodium retention on mineralocorticoid effect, glucose tolerance, growth suppression, osteoporosis, and what we do look at, which is HPA axis suppression.

With regard to sodium retention, they are receptor-specific effects and they may be less concerned with glucocorticoids. I am going to go a little bit into that.

Regarding glucose tolerance and growth suppression, data available for glucose tolerance from clinical studies, the growth suppression studies, as Dr. Wilson has discussed, is technically challenging and is difficult to perform and to review.

Further, for osteoporosis, the same could be said for that. It is difficult to have these topical corticosteroids used for the long term. The patients wax and wane with their disease, so the application of the topical corticosteroid can increase and decrease, plus the strength of the corticosteroid may vary during the conduct of a year-long study, so there is the potential for

change in dose and potency, which again leads to inconsistent and very challenging evaluation of any data that would be obtained from such a study.

Regarding HPA axis suppression, we will get into that a little bit more.

[Slide.]

This is a table of the relative potencies for various steroids with a cortisol at 1.0 and there are two references in the package that was given to the Committee regarding this. This table is excerpted from those references.

As you can see, the two examples of topical corticosteroids given in this table are triamcinolone and betamethasone. Both of those have a higher affinity or a higher relative potency regarding glucocorticoid effect but a lower mineralocorticoid effect. This can be contrasted to aldosterone which has a much higher mineralocorticoid effect as compared to glucocorticoid effect.

(Slide.)

This is a schematic diagram of the HPA

axis. We have been talking a lot about the HPA axis. Regarding specifically what it is, we have the hypothalamus. This is a schematic representation, again; the pituitary, anterior pituitary, and what their effects are on adrenals.

This is a neural, hormonal axis and is important for the human response to stress. Humans respond to stress by producing ACTH which then causes cortisol rises. F stands for cortisol here in this diagram. If there is a failure to mount such a response, it can lead to a hypotension and cardiovascular collapse.

Now, this failure to mount may not be easily clinically recognizable so attributing cause and effect may be difficult with regards to adrenal suppression in the clinical setting.

The ACTH here, in general, causes a rise in the cortisol. However, with constant exposure to exogenous corticosteroids, it has been thought that there is a down-regulation of receptors here and here which may lead to decrease-ability of the adrenals to then respond and produce cortisol.

(Slide.)

With that, we get into HPA axis testing.

(Slide.)

There are two classes of tests, basic classes; the basal testing, which is done with basal plasma levels and 24-hour urine cortisol levels. These are thought to be less useful in measuring an adrenal response to stress than dynamic testing where you try to stimulate the adrenals to cause a response and you measure the magnitude of that response.

(Slide.)

There are various dynamic tests of HPA axis function. Earlier, it was mentioned, the insulin tolerance test which is an older test. When you administer insulin, you cause a hypoglycemic event. It then results in a potent stress stimulus for the adrenal glands.

Now, these subjects, when you administer insulin, you need very close subject monitoring. It is thought that this test, as it is currently done, produces undue risk to the subject and,

therefore, the agency does not recommend this as a test for HPA axis function.

The cosyntropin, or ACTH amino acids 1 to 24, test is available in higher or lower concentrations. The higher dose is the labeled dose for cosyntropin. Lower dose studies vary and there is no standardization regarding how much of a rise in cortisol you need with lower dose and the timing of the rise is not standardized. So the lower test is still experimental at this time and if one is to use it, there should be discussion with the Agency regarding how it is used.

For higher dose testing, we will discuss that in just a moment. There is also a corticotropin-releasing hormone test, the CRH test. This also is experimental and not widely available.

(Slide.)

The higher dose cosyntropin test is the most commonly used test to evaluate for adrenal suppression. The procedure is to administer a superphysiologic dose. It is currently labeled for IV or IM use of 125 micrograms if the patient is

less than 3 years of age or 250 micrograms if the patient is 3 years or older. The serum or plasma cortisol concentrations are measured before and 30 minutes after the cosyntropin administration.

(Slide.)

The advantages of this test are that it is simple, it is fast and relatively inexpensive. It is an outpatient test and it takes approximately 30 minutes to do. There are some limitations. It is not the most sensitive test. It can be equated to being a physiologic hammer. I mean you are giving a very high dose of what is equivalent to ACTH to cause the adrenals to respond. So the sensitivity may have some concern.

(Slide.)

The criteria for a normal response in Cortrosyn, according to label and the 30-minute test is as follows: The control of basal cortisol level should be greater than 5 mcg/dL. At 30 minutes, after administering the Cortrosyn, there should be at least a 7 mcg/dL rise above basal--the incremental cortisol rise, that is--and the

30-minute level should exceed 18 mcg/dL.

However, we note that basal cortisol levels vary throughout the day and the higher the basal level, the lower the incremental cortisol rise. So, for regulatory purposes and for drug development, it is thought that normal response of peak cortisol level of greater than 18 mcg/dL 30 minutes after giving Cortrosyn should be sufficient as the test for adrenal suppression.

(Slide.)

With that, we segue to what are current testing recommendations for adrenal suppression.

[Slide.]

There was an Advisory Committee on October 29th of 2003, and there was some discussion about the HPA axis test, Joint Committee discussion. It was discussed that higher dose cosyntropin test is a sufficient determinant of HPA axis function with regard to prescription topical corticosteroids.

A greater than 18 mcg/dL or 500 nM/L post-stimulation cortisol level at 30 minutes is equivalent to that subject being not suppressed.

It was also discussed at that Advisory Committee where data was presented on reversibility, and you saw the reversibility data, we have very little of that. We need follow-up for reversibility when we do these studies.

[Slide.]

It was a pediatric meeting, so there was discussion about the pediatric cohorts. The pediatric population was divided into 4 cohorts here. Sequential testing was usually done for these studies with the older patients first, but at this Advisory Committee it was discussed that potentially concurrent testing can be done if the safety of the patients can be assured. The rationale for that is to obtain more data regarding the adrenal suppression in each of these cohorts.

[Slide.]

Additional recommendations from the Agency are as follows: the 60-minute cortisol is not recommended. The standardization for a 60-minute level is poor, and the results can vary somewhat from one, 60-minute test to another 60-minute test.

Testing less than 4 weeks apart is not recommended. Administering the ACTH or Cortrosyn start to leave an impression on the adrenals and

there may be effects on later response especially when the tests are done closer than 4 weeks apart.

There is a need to monitor the local cutaneous adverse events during the conduct of this study.

Finally, it is important to note when interpreting these studies that the percent of patient suppressed, not the mean cortisol levels is important. Mean levels may mask individual patients, so if someone were to present data on mean levels, ask them what the percent of patients suppressed was.

[Slide.]

Finally, we note Dr. Cook's presentation, the body surface area involved can vary from atopic dermatitis, at least 30 percent body surface area is needed, for psoriasis, at least 25 percent body surface area involvement for these patients, and these are maximally involved diseased patients.

It is also important to note that patients who enter the study should not be adrenal suppressed, so there should be testing for adrenal suppression prior to exposing them to corticosteroid to make sure they are not suppressed at baseline. Often these patients will have come

into a study having been on other corticosteroids for a protracted length of time because of their significant disease.

[Slide.]

The last part of this talk, we are going to discuss a little bit about what precision do we need for OTC use of corticosteroids.

[Slide.]

For topical corticosteroids drugs to be used in an OTC setting, how acceptable is HPA axis suppression, and how many subjects need to be evaluated to rule out corticosteroid-induced adrenal suppression for an OTC product if this is one of the tests that is going to be used?

[Slide.]

Here is an exercise I would like to pose

to you. If we had 30 subjects and we treated them all with topical corticosteroids for 4 weeks, and we noted those 30 subjects, zero had cosyntropin stimulation test indicative of adrenal suppression, that is, the rate was zero out of 30.

The question arises with what risk, if any, of adrenal suppression induced by topical corticosteroids might these results be compatible, is it zero risk? I would like to propose that it is not.

[Slide.]

Zero out of 30 subjects rules out, with 95 percent confidence, a greater than 10 percent chance for adrenal suppression to occur in the global population. This is a statistical concept, and there is a paper in the package that was handed out discussing the rule of 3's, and this is one way to look at this.

The sample size determines the extent we can rule out adrenal suppression in the global population with zero subjects suppressed.

[Slide.]

With that, we can go to this table on sample size effect on the upper confidence interval to just go over and give an example. Say we have

10 subjects and we had zero of those 10 subjects suppressed.

Well, that would rule out with a 95 percent confidence interval no greater than 26 percent adrenal suppression. Whereas, if we double the number and go to 20 subjects, we can increase that upper confidence interval to 14 percent.

To get to really small percentage numbers for upper adverse event occurrences, we need larger sample sizes. So, the greater the number of patients you have, the more assuredly you can be of that zero that you see for that study, if the study does give you zero.

[Slide.]

So, the question asked for the Committee: Cosyntropin stimulation studies are used to inform labeling for prescription products with regard to potential for adrenal suppression.

If the cosyntropin stimulation studies are

to be used for OTC products, how many subjects are needed for those studies, that is, what is the level of tolerance for adrenal suppression for an OTC drug product?

That is it for my portion of the talk. Thank you.

DR. WOOD: Okay, great. It is exactly 10 o'clock, so let's take a break for 10 minutes and be back ready to start again at ten past 10:00, and we will go straight to the questions for the speakers, and then pass on to the questions for the Committee at that point.

[Break.]

Questions from the Committee and
Committee Discussion

DR. WOOD: So we have heard all the presentations. Let's open the session for the Committee to question the speakers. Terry?

DR. BLASCHKE: I have a technical question, I think for Dr. Luke. In your presentation, you indicated that the cosyntropic administration could be IV or IM. I am just

wondering how many of the subjects, for example, in the studies that we were presented actually got the cosyntropin IM and do we know whether there is more variability or sensitivity, differences in sensitivity, when the cosyntropin is administrated IM versus IV.

DR. LUKE: As far as I know, there are no comparisons in the literature between IM and IV use. For pediatric studies, it is often more convenient to do an IV study rather than an IM study simply because of the pain threshold of those patients. You can insert a cannula and inject the cosyntropin and also withdraw blood from the same cannula afterwards and so there is only one stick.

When you go to do the IM, it may be due to access difficulties that one would resort to an IM. Regarding whether one should do IM or IV, I think it is important to be consistent throughout each study as to what route you choose to administer the cosyntropin. But, as far as I know, there are no studies to compare the two routes.

DR. BLASCHKE: I suspect it is not done

consistently because I suspect that it really does relate to ease of access of a vein in a small child and so forth. We know that there are a lot of compounds that, when they are administered IM, depending on where, et cetera, that the absorption and the absorption rate is quite different for IM, obviously, than IV.

It sounds like, as you say, there is no comparative data so maybe no answer to the question.

DR. WOOD: Dr. Snodgrass.

DR. SNODGRASS: Are there any standards required for the timing of the test, 8:00 a.m., for example, and knowledge about their sleep patterns for the circadian rhythm aspects?

DR. LUKE: Because of the circadian rhythm, it is thought that a standard time might be helpful but keep it close within. It is often difficult to do a study where you have all the patients done at the same time. So there is some variability allowed for it.

Just to go back, also, to the IM versus IV

concern. Of note, the lower cosyntropin stimulation test, the lower dose, there have been concerns raised about the peptide sticking to tubing, so that may be a concern raised if you are performing lower dose cosyntropin testing.

DR. WOOD: Dr. Epps.

DR. EPPS: My questions actually are for Dr. Wilson. Is that okay?

DR. WOOD: Sure. We are taking questions for all of the last speakers.

DR. EPPS: Okay. The growth charts, the CDC growth charts, were those based on the standard growth charts that are used or are they updated and different?

DR. WILSON: Those are the standard growth charts that everybody sees and are available from the government.

DR. EPPS: The reason I ask is that--I thought it was my understanding that they were standardized on a group of cohorts in Kansas in the '50s or '60s or something and that is why I wondered if they had been updated at all.

DR. WILSON: That is a good question. I don't know. I mean we kept looking for whatever the most current was. We recommend the most

current. These are trials in which we have comparators and are randomized. So we have all those kinds of things taken care of.

But you are right. We pondered a lot about the growth charts and what they really meant for individuals. As you were looking at those percentage breakdowns, that is where it becomes more important probably.

DR. EPPS: Also, my question was do the kids recover. You were taking about growth velocity which is different from overall growth potential and whether--you know, kids accelerate and decelerate and, really, the lines are kind of percentiles or averages. So that was one question I had, whether the velocity--I guess, the long term.

DR. WILSON: The long term. Again, sponsors have presented to us, and there have been a few studies done on trying to assess whether

there are some long-term effects. But those are even more difficult to do than these annual studies.

I think that the assumption has always been, and Gene, you could correct me if I am wrong, that a lot of this will be recovered. We have never looked at ultimate height. Companies, of course, are always saying this. They want to have that in their label that this isn't going to affect it.

This is Gene Sullivan from the Division.

DR. SULLIVAN: Hi. I am a pulmonologist in the Pulmonary Division. I think what you are getting at is part of the reason why the slide said we don't know the clinical significance. We can measure what happens in that year, what happens when you stop the drug, is there catch-up growth, is the full adult height affected? Those are still, we consider, unknown.

DR. EPPS: To follow up that, what about children who have asthma or are on these medications? Is their velocity different from

normal? In other words, sometimes growth is affected just by having chronic disease.

DR. WILSON: By the disease itself. But these pediatric studies, for a number of reasons including ethical considerations, are done in children with the disease. So the studies of orally inhaled corticosteroids are done in children who need the medications. So the comparison is the placebo group versus the active treatment should take that out of the picture.

DR. EPPS: Certainly, breathing comes first.

Now, my last question is, for any of these studies with inhaled and intranasal steroids, did any of them also have atopic dermatitis? They usually run together, so you might have topical steroids and intranasal and inhaled steroids all working together, and would that affect their growth, as well

DR. SULLIVAN: I can't say categorically because I don't know these studies, each one, that well, but I presume that almost all of them would

have excluded concomitant use of other corticosteroids.

DR. WOOD: Dr. Bigby.

DR. BIGBY: I have actually four questions. The first one actually is a philosophical question both for the FDA and for the people here on the panel. If one of these classes of topical corticosteroids has been shown to produce HPA axis suppression, would we not recommend it for OTC approval? That is the philosophical question.

DR. WOOD: That is the question we are going to address in the discussion on the questions, so I guess right now let's just confine our questions to the last set of speakers, so we can let them off the hook.

DR. BIGBY: The second question is has an ingredient ever gone backwards from being OTC to by prescription? What I am really asking is, if we make a mistake, can we go backwards?

[Laughter.]

DR. WOOD: I will answer for them, because

they won't. Not without a huge amount of difficulty is the answer. It is much harder to get something off the market than it is to not approve it to go on.

DR. BIGBY: Lastly, other than hydrocortisone, is there any foreign country experience with an OTC more potent topical corticosteroid?

DR. KOENIG: I am sorry, I thought about looking at that, but I did not, so I can't say.

Does anyone in the audience know?

DR. GANLEY: We have some industry folks here, they may know that answer.

DR. WOOD: Let's move on then.

Dr. Davidoff.

DR. DAVIDOFF: Yes, I would like to shift away from the HPA for a moment back to bones, but bones at the other end of the age spectrum, because as you hit around my age, there is obviously the problem of osteoporosis, and I understand that it is difficult to study osteoporosis, but that is such a huge public health and medical problem, I

wonder if there are any data on potent corticosteroid dermatologic preparation's effect on bone density in the older age group. However preliminary or partial or whatever, I would think that any hints as to that potential toxicity would be extremely important.

DR. WILKIN: Well, I think we are limited somewhat in looking at the long-term safety with topical corticosteroids, because the conditions that they treat, the dermatologic conditions wax and wane significantly.

It is not like with the pulmonary inhalers where a child may be expected to be using a product for very long periods of time. The situation for dermatologic conditions is that often things will resolve, and maybe moisturizers alone, and then when things begin to come back, it's a high potency. Then, as it gets under control, it goes to a medium potency corticosteroid, so it would be difficult in that setting to say which corticosteroid actually led to it.

So, that is the reason why I don't think

we have that in a regulatory environment, but someone could look at a more general question in an academic environment I suppose, just, you know, would the use of mid- to potent, but not specific products consistently over a long period of time, would those people be at risk.

DR. DAVIDOFF: Yes, exactly. I mean I didn't expect that you would necessarily have it as part of the regulatory process, but whether you have looked or anyone has looked into literature specifically on that question.

Mary, do you have any idea from the geriatric literature?

DR. TINETTI: I am not aware of any with the topical. Certainly with systemic, it's a major issue.

DR. GANLEY: I just want to add something here. I think in some of the presentations, that this growth suppression is really a surrogate for a possible systemic effect even when you would not have HPA axis suppression.

That is how I think the Pulmonary Division

has looked at it, is that if it causes growth suppression in kids, you could assume that in an adult, it could potentially cause this.

I did a lot of literature search, and I think other folks did, trying to, in Pub Med, attach topical corticosteroids with osteoporosis, and you just don't get a lot of hits from it. So, I don't think there is data, but our assumption is that, in this setting, that growth suppression is a surrogate for other things.

Now, the dose-response may be different, but we don't have the data to really answer that.

DR. WOOD: When we get to the questions, I guess, the question you are trying to get at is would a topical steroid go OTC if it had systemic effects, and the specific targets you have illustrated it with are ones that are easily measured. Is that fair? Okay.

DR. GANLEY: I think Dr. Luke pointed out, and Jon has just mentioned it, with the topical corticosteroids, it is much more difficult to conduct a long-term study because of the variation

in dose, the waxing and waning of the disease, and so forth.

DR. WOOD: Dr. Whitmore.

DR. WHITMORE: I think one other thing that is most disturbing is in the betamethasone dipropionate studies looking at growth suppression, the 49 individuals, none of them showed any suppression, any adrenal suppression.

I am presuming the same type of testing was done as was done in the steroid patients. So, from that presumption, you can step from there and say there probably is some effect on growth in our patients who are having HPA suppression with their topical steroids.

It is a different marker obviously, but it seems like if that is occurring in those patients with the inhalers, they are not getting HPA suppression. We are getting HPA suppression in our patients with the topical steroids. I would presume there is some bone effect, some growth effect if used long term.

Was the testing that was done, the

cosyntropin testing in those 49 patients? That was for Dr. Wilson, I am sorry.

DR. WILSON: It wasn't the same test as I understand it.

DR. WHITMORE: Oh, it was not?

DR. WILSON: No. Markham has some more details on it. Unfortunately, I was looking yesterday, trying to find out all of the data from that test for this committee, but was not able to locate the original. It's a different test.

DR. WHITMORE: So, we can't make any assumptions about that, I presume.

Dr. Cook, I have a question for you. In the pediatric testing that was done for the steroids, excluding clobetasol, you didn't have any adult testing for HPA suppression with those same steroids.

I am presuming that the only HPA suppression was that we found in our brown book here in terms of testing in adults, so it is pretty much lacking. The only reason they did that was to go back to get pediatric approval.

Is there any reason to presume that if someone is 13 years of age and has the same body surface area of involvement, they are not going to

get the same HPA suppression?

So, the companies that make the pediatric products that were doing the testing in pediatric patients, after they found HPA suppression with their products, they came back to the labeling saying 13 years of age or older. Is there any reason to presume that HPA suppression is any different in a 13 through 100-year-old individual? It just is concerning.

DR. COOK: Yes, I see your point because the other, meaning 13-year-olds who are fully developed, just as adults, and I don't think it is to say that HPA axis suppression would not occur in adults. It is just that we didn't have the exact data to be able to put that in labeling.

DR. WHITMORE: Has the FDA considered asking the companies to go back and study adults with any of these things?

DR. WHITMORE: Didn't you propose a

hierarchical sort of structure? At least that was the way I heard it, that it would be easiest to do HPA suppression in adults, so you would start with adults. If that was positive, you would stop there, right?

DR. COOK: I think for newer drugs, like Clobex, because we have all this data, you know, it started with adults, and we also could ask for children. For some of those products that I discussed there, have been on the market for many, many years, and I don't know that there is any regulation that could make the companies go back and look specifically at adults.

The reason that we were able to do that for pediatric patients is because we got a new regulation that said we need more safety information in pediatric patients.

Now, in some of the older tests that were done, like looking at a.m. serum cortisol levels when the drug products first came out, that is how they looked at HPA axis suppression back then.

That was certainly in adults and did, you

know, propagate the class labeling that said that you can get HPA axis suppression in adults, because the Temovate was done in adults and in children--well, it is done in adults, adults with atopic dermatitis and adults with psoriasis.

DR. WHITMORE: One last comment. With the inhalant steroids, they oftentimes will look at markers of bone metabolism as opposed to looking for evidence of osteoporosis. So, you can look at urinary calcium to creatinine ratios, you can look at PTH, so there are things you can look at to see if there is evidence for decreased calcium absorption or excretion, and things like that.

DR. WOOD: Dr. Ringel.

DR. RINGEL: I was struck by the difference between the cosyntropin test and the tests that were originally done on hydrocortisone to justify its approval as an over-the-counter drug. I think it was Dr. Malkinson who did radiolabeling of hydrocortisone and showed that it was not absorbed, which seems very different from the cosyntropin test.

As I was reading the preparatory material that was sent, I was struck by the fact that 95 percent specificity of the test was 57 percent

sensitive, and I guess I wanted to explore that, because I am want to make sure I really understand what this test can and can't do. I am a dermatologist, I am not an endocrinologist, and I just want to make sure I understand the test.

Correct me if I am wrong. It is a test of chronic effects of corticosteroids, so that you are looking for adrenal atrophy, you are looking for the adrenal gland not to be able to respond to ACTH stress, which means to me that this test does not mean that the steroid is not absorbed, it doesn't mean that you have excluded the fact that the pituitary may be insensitive to the cortisol, in other words, that it may just not be able to respond with its own ACTH.

And it doesn't mean that let's say you have an increase in cortisol after the ACTH test, it doesn't mean that that increase in cortisol is necessarily going to be sufficient for a particular

stress. It other words, maybe the person should have responded with an even greater cortisol increase for that level of ACTH stimulation.

I guess what I am trying to do is explore the limits of what we are really testing with cosyntropin, and making sure this is really an appropriate test and it is going to pick up people whose pituitaries are suppressed.

DR. WOOD: Don't all rush to answer that.

DR. LUKE: We do have an endocrinologist on the panel who can help us with some of those answers, I think. The test, as we have discussed, having 18 or less of post-stimulation was thought to be a sufficient indicator that that patient would be suppressed.

Now, as far as how much more of a rise would you need for other stressors, I think the 18 was thought to be sufficient for most stressors.

DR. RINGEL: Do you know what the sensitivity was?

DR. LUKE: Of the test?

DR. RINGEL: Yes.

DR. LUKE: Dr. Stratakis, do you want to address that?

DR. STRATAKIS: The cosyntropin test is a

screening test for the diagnosis of adrenocortical insufficiency. Therefore, as a screening test, it has a good specificity, a very good specificity. You can set out the specificity wherever you want, and it has a low sensitivity, of course, and that is how we use it.

With the 18 as the cutoff, it has a sensitivity of about 70 percent, a specificity of about 95 to 100 percent, so it is very good in detecting the patient who is adrenocortical insufficient. It is not very good at identifying all the patients that have adrenocortical insufficiency, it misses about 30 percent of them.

What I wanted to say is that a limiting step in the recovery of the HPA axis after adrenocortical suppression--and this has been shown in a couple of studies, that are very good studies--is the cortical trough, in other words, the pituitary cell. It is not the adrenal.

There is actually a very good paper that was published about 10 years ago about that, and it is clear that it is the cortical trough. So, when we are suppressing by endogenous steroids or exogenous steroids, the HPA axis, all we are doing is we are suppressing the cortical trough cell of

the pituitary and, to some extent, the CRH-producing neurons of the hypothalamus.

We are not doing anything to the adrenals or this has not been shown convincingly I should say. We don't really know whether we are doing anything to the adrenal cortex.

Up to recently it wasn't even known, and to this day it is not known with certainty, that the glucocorticoid receptor is expressed in normal adrenal cortex. I believe it is. In some of our experimental data, it seems that it is, but at very low levels.

The other point is that since the rate-limiting step is the cortical trough, then, the question is how long does it take to develop adrenocortical atrophy in response to suppression,

and that varies a lot from individual to individual, but on average, we consider that time to be approximately two weeks, approximately two weeks.

I was surprised to see that in some of the studies with the mid-potency steroids, you have levels, we have levels of response to the ACTH stim test down to about 9 or 10, which actually, if I look back at my patients with endogenous Cushing's, it is something that we get about 6 months of so of recovery time after a pituitary tumor-producing ACTH is excised.

So, this is quite significant general atrophy, and since the test if not very sensitive, you would consider that as the tip of the iceberg, that you are really missing a lot of patients that have developed moderate adrenocortical atrophy, and you have no way of picking up those that have moderate cortical trough cell suppression in other words.

DR. WOOD: So, what would be your estimate of the number you are missing, 30 percent, is that

what you said?

DR. STRATAKIS: The sensitivity is about 70 percent, so I would say about 30 percent.

DR. WOOD: Jack.

DR. FINCHAM: This is just an observation in the context of what we are going to be discussing this afternoon as far as how these products may be used by consumers in an OTC setting, a nonprescription setting.

I was struck by Dr. Cook's presentation of a couple of instances where we saw an effect, and I would assume that these are controlled situations where the individuals had some limits on what they could obtain and how they could obtain it, but in the 5-year-old subject that was detailed in Slide 31, 95 percent body surface area, but there was an ounce a day being used, which is an enormous amount of product.

For the 2-year-old, it was an ounce a week, and in the Diprosone study, it was an ounce a week. I was just struck. Were there controls, Dr. Cook, on oral systemic agents that perhaps would

have been used? Were there strict limits on this being only topical application?

DR. COOK: Yes, since they were patients with atopic dermatitis and they weren't supposed to be on any other medications that would affect the outcome of the study.

DR. FINCHAM: I guess the observation is that was an enormous amount of product being used even in a controlled setting, and we can only presume what might happen or might not happen in an uncontrolled over-the-counter setting, whether it be worse or better, but it just struck me as an amount that was being used.

DR. COOK: In the 5-year-old, I believe that the parent continued to use the medication even when the patient was getting better over that same amount of body surface area, and even though you would think that the integument would not have been as compromised as time went on. Somehow there was a lot of absorption, but when you look at the smaller child, didn't use quite as much, but still HPA axis suppression.

DR. WOOD: Dr. Stratakis, before we go on to the next question, I guess, none of the presenters actually told us why we care about HPA

suppression that I can remember, and maybe we should just, for the record, say something about for everybody's benefit why we care, or what are the consequences of having your HPA axis suppressed particularly in response to stress or surgery or if you end up in a road accident or whatever. Just very briefly.

DR. STRATAKIS: The reason we care is because HPA axis suppression can lead to sudden death. In fact, there was a recent study that looked at the long-term morbidity and mortality of patients with panhypopituitarism, and the single most frequent cause of death in this long-term status was, in fact, the absence of ACTH secretion by the pituitary, adrenocortical insufficiency, in other words, so sudden death.

DR. WOOD: So, showing up in an emergency room and not being recognized as having a failure of your stress response may be bad for you is the

point we are getting at here.

DR. STRATAKIS: Right. In fact, one would like to go back to the studies where I think in one of the studies, there were two deaths that were recorded as Cushing's, I mean do you know what the cause of death was, because Cushing's doesn't actually kill you.

DR. COOK: Right. No, it could have been complications thereof, it didn't really say.

DR. WOOD: Dr. Patten.

DR. PATTEN: I have a question about the HPA suppression retests. It appears to me that the longest time lapse to retest was 14 days in these studies that Dr. Cook summarize for us.

My question is this. Does this imply that if recovery has not happened by 14 days, it is unlike to ever happen, or is after 14 days, is that simply unknown territory?

DR. COOK: I would have to say that the studies are really inadequate to answer that question. First of all, we didn't have all of the patients retested like we would have liked, and

then once we got the studies, for some reason, when patients failed to respond, they weren't retested again. Those are certainly things that we are trying to address in future studies, especially now, we don't even want them retested until they have been out at least 4 weeks because of the possible influences of the results on continuously re-stimulating the adrenal gland.

Unfortunately, we don't have the answer to that.

DR. WOOD: Dr. Nelson.

DR. NELSON: I would like to make some observations on the data that Dr. Cook presented and invite comments to just see if I am getting it right.

This is just looking at what I see as 9 pediatric studies that you presented. If you look at it by class, there is a 27 percent incidence, ignoring the differences in methods of adrenal suppression.

If you scan it, in terms of potency, it looks to me like there may be an effect based on

potency, but not being a statistician and just doing it quickly, it is difficult to say, but you would assume then that the incidence of impact on growth philosophy would be higher than 27 percent given the data presented about the sensitivity of that finding.

Then, the other question is whether there is a threshold and most of these studies are all in class, sort of I guess Class II and above, so you can't ask the question whether there is a threshold effect somewhere in terms of Class I.

What I just did reflects my biases that since almost all studies that are submitted are usually for efficacy and other indications, that you can only see a safety signal if you do a meta-analysis, but I guess my question is I presume if you had done that, you would have presented that data.

I am curious, am I off the mark here, or is this an appropriate way for me, in my sort of rough non-statistician approach, of thinking about this data in the pediatric studies.

DR. WILKIN: I think the answer is yes. It was very complex, isn't that your point, that basically looking in the individual studies, the

denominators are small, and that you really ought to look across classes, and I think we take your point that we might learn something more about the class if we grouped these sorts of things together?

But there are some difficulties with that, and I think something maybe we didn't stress enough is that at any one given time over the last 20 years, we have been consistent at least for 6 months in how we think about topical corticosteroids, but we have really changed radically from the beginning, you know, paleoregulatory 20 years ago, I am not sure exactly what kind of studies were done for HPA axis suppression.

Then, when we looked, we looked at endpoints that were serum cortisol. There was no Cortrosyn stimulation. Then, subsequent to that, we looked at perhaps more stringent criteria. We looked at what is in the Cortrosyn labeling, which

gives 3 criteria, and would identify more subjects as being positive than what we are now looking at today given the benefit from the endocrinologists telling us that they only use the single criterion in their practice.

So, just how we look at it has changed radically over time. Also, over time we have been able to, now armed with PREA, the Pediatric Research Equity Act, we are now able to ask for much more data that we have gotten in the past.

So, I think one of the great difficulties is there is enormous heterogeneity in the data sets and the conduct of the studies in each of these classes.

DR. NELSON: If I could just make one comment in response, all of the pediatric studies, it looked to me the only difference in the stimulation testing was whether you picked the threshold alone versus the rate of rise, and if you drop out the rate of rise and just pick threshold, you are still going to end up around 20 percent overall incidence among all these studies.

So, since that is since 1999 or 1998, so I guess I would encourage you to look at the pediatric studies. I think there is probably

enough homogeneity that you could draw some conclusions from those studies, if you grouped them as a class or did it by potency.

DR. WILKIN: I take your point on the pediatric patient being a better sentinel population in which to look for this particular event. I think one of the things that we have learned is that while we can make some correlations and say that, in general, a higher body surface area, longer use, younger age, more severe disease, these things tend to correlate with the finding of HPA axis suppression.

In point of fact, in any one study, we may see an adult who has a very small body surface area involvement who suppresses, a child who has a much larger body surface area involved, and not suppress with this.

So, it is certainly not a mathematically precise kind of outcome.

DR. WOOD: The reason we have all these pediatric studies is sort of an experiment in commerce. I mean we happens that we got these studies because of the Pediatric Rule that people came in to you to get an indication. It's not so much that there is some specific reason to

investigate children here except for the commercial reason.

There might be reasons, as well, but that wasn't why it was done, right?

DR. WILKIN: Well, no, I mean that isn't the reason for PREA being enacted certainly, but I can say within our Division, we recognized that atopic dermatitis was primarily a pediatric disease, and so even before PREA, our Division was asking for pediatric studies.

DR. WOOD: Right, but if someone came in for an OTC indication, which is what we are looking at, they wouldn't necessarily have had to have done--let me ask it s a question--they wouldn't necessarily have had to have done a pediatric study, right?

DR. WILKIN: I would agree with that.

DR. WOOD: Dr. Chesney.

DR. CHESNEY: Thank you. I think my question is along the lines of Dr. Whitmore's earlier, and it is for Dr. Cook. In Slides 55 and 58, this is looking at Diprosone Lotion. The suppression was 80 percent for the 9- to 12-year group, and yet it was approved for 13 years and older, and I was curious, that it wasn't approved

for adults, and at that time there was no data on 13 and older, and I don't know of any reason to think that a 13-year-old is different than a 12-year-old.

So, I guess my question was why was it approved for 13 and older instead of perhaps adults, only given that there wasn't any information for the 12- to 18-year-old.

DR. COOK: All I can say is that that was the cutoff that was chosen. I mean your point is well taken. I mean it could have just said don't use this product at all because, you know, by the time you are 12, you may be near adult size, but I

guess there are some 12-year-olds who are still prepubertal or whatever. That was where the study was taken to, so that was the age cutoff there.

DR. WOOD: Dr. Taylor.

DR. TAYLOR: My question is really for Dr. Luke. In his Slide No. 4, when he talked about systemic effects, indicating that HPA axis suppression is the only one that had really been studied well, I was concerned about glucose tolerance and sodium retention although I recognize with these drugs, sodium retention is going to be minimal since they lack significant mineralocorticoid effects.

But what about in effects on glucose tolerance, is there any data to suggest that topical steroids might alter glucose tolerance in susceptible individuals, for example, in diabetics?

DR. LUKE: When these products are used under a physician's care, you would expect that those patients would have some monitoring.

DR. TAYLOR: That is my point, though.

DR. LUKE: The class labels for the

corticosteroids do include discussion about glucose tolerance and the sodium retention and mineralocorticoid effect, so when these prescription products are being used, it is thought that those are things that would fall under the rubric of a physician-patient discussion of examination.

DR. TAYLOR: So, what is the Agency's position in terms of when the physician is no longer there, what is the Agency's remedy for ensuring that this growing population of diabetics, for example, have some guidance other than just the label on the box?

DR. LUKE: I think when you go to the history of hydrocortisone, there was discussion in that monograph about mineralocorticoid effects, and it was found that there was no studies that showed that hydrocortisone had a mineralocorticoid effect.

DR. WOOD: My sense of what we are trying to do, though, is this. What we are trying to decide is what is the most sensitive test for systemic effect of these drugs, and at what level

would you put a barrier up to a demonstration of a systemic effect that would preclude OTC marketing.

So, I guess maybe we should turn the question to Dr. Stratakis. I mean what is the most reasonable, sensitive, and doable test for systemic effects of steroids administered by any route?

DR. STRATAKIS: Well, having said all the caveats of the ACTH stim test, I still think that the ACTH stim test satisfies all the criteria you just mentioned, the big response of cortisol of 30 minutes to 250 micrograms of synacthen. I mean it's still the most doable, the easiest to interpret, you can do it anytime of the day, you can do it IM, you can do it IV, and it has a sensitivity of around 70 percent with specificity of 95 percent, you can't get in any other test.

DR. WOOD: So, to address Dr. Taylor's question, would you expect to see people who had elevation in blood glucose who did not demonstrate suppression of HPA axis?

DR. STRATAKIS: That would have glucose intolerance?

DR. WOOD: Right.

DR. STRATAKIS: Especially if they are predisposed to that? Oh, yes. I think it is the

same thing that we see with growth. Growth is a very sensitive index of the systemic effect of glucocorticoids, and yet you don't see abnormal ACTH stim tests in these patients, so I agree, but at this point there is no good test to identify these individuals.

DR. TAYLOR: So, the point is that the HPA stim test is not a good surrogate for the variety of systemic effects that one is likely to see.

DR. STRATAKIS: I agree with that statement except that there is nothing else.

DR. WOOD: Charley.

DR. GANLEY: Let me just tough on that and just think about it. We would be asking the same questions if we did this test in 25 diabetics and saw no effect on glucose tolerance, would we write a label that says it has no effect on glucose tolerance.

I would be a little uncomfortable in that

the labeling for the physician is that you are treating the individual, so there may be patients that are much more sensitive than others.

Well, to carry that over into the OTC setting there may be always that patient out there, well, how do you address that. Well, you would try to address it through labeling, so anyone who is diabetic should talk to their doctor, for example, before using this product.

Then, you get into the issue, well, does that have the impact that you want, is the person going to follow that advice. So, I am not sure that having that data in front of me would make me feel better about being at OTC if it showed that it didn't have an effect, because I couldn't absolutely be sure that maybe there is someone out there, so you err on the side of caution and you label it as such.

I think we will get into that discussion a little more about some of these systemic effects of whether--and if you look at the options, one is that you just label for them, because the outcome

isn't as critical as death with a stress situation when there is HPA axis suppression.

DR. WOOD: Frank, do you want to engage in this?

DR. DAVIDOFF: Yes. I had a somewhat related question because we are hearing that the HPA axis assessment using the cosyntropin test has a sensitivity of about 70 percent, but that implies that there is a gold standard of some sort, and I was curious what gold standard it is being measured against.

But the related point I wanted to make was that the results of this test are clearly a surrogate measure, and admittedly, if you don't want to hang around until people have experienced the ultimate criterion of suppression, which is to die because of adrenal insufficiency, so you have to use the surrogate measure, but that does get to the question of what is the sort of intermediate gold standard short of death that is used on the basis of which you can say it is a sensitivity of 70 percent.

DR. STRATAKIS: The gold standard for the diagnosis of adrenocortical insufficiency has always been the insulin tolerance test, the ITT, so

hypoglycemia induced by insulin is the gold standard except that you can't do it in the clinical setting, it is unsafe today.

We have to realize that ACTH stim test is a sensitive screening test, is a good screening test, not a sensitive screening test, and it was designed to prevent exactly the adverse event that we all want to avoid, sudden death in the setting of undiagnosed adrenocortical insufficiency.

It was not designed to pick up mild glucose intolerance. It was not designed to pick up growth suppression effects, it was not designed to pick up all these other--blood pressure elevation perhaps, and so on.

So, that is what this test was designed for and that is what it is good for.

DR. WOOD: Dr. Mattison.

DR. MATTISON: To follow up on that, what do we know about age-related differences in adrenal

suppression with exogenous corticosteroids? Then, I would like to follow up with a comment after that.

DR. STRATAKIS: Well, I am a pediatrician, so I haven't reviewed the literature recently. What I can tell you as a researcher in the glucocorticoid field, is that as we grow older, we have generally a lower sensitivity of the HPA axis, of the central part of the HPA axis. We tend to have slightly high cortisol secretion, and the ACTH levels are, in turn, higher in older individuals.

Now, why do we say we have a lower sensitivity? Because you actually need, as a result of what I just said, of this epidemiologic data, you seem to need higher ACTH levels to maintain normal or slightly higher cortisol levels.

The other thing that we need to realize is-- which I like the question about the pediatric studies being a good index of perhaps what is going on--is that as we grow older, the HPA axis, the central part of the HPA axis is very sensitive to almost everything we have.

So, if you have a mild autoimmune disease, for example, if you suffer from chronic fatigue, you present at this meeting at 6 o'clock in the

morning, or if you travel a lot, your HPA axis suffers from all that, and that has an effect on the sensitivity of the cortical trough, we know that.

So, how to interpret the ACTH stim test in older adults will be different from how to interpret the HPA stim test in kids, where all these other factors are simply not present.

DR. CLYBURN: I just more had a comment going to the New England Journal article in here talking about critical care, and following up with Dr. Ringel's comment and questions earlier about sensitivity and severity of illness, they actually talk about if an increase of less than 9 mcg/dL in Cortrosyn stim is, in two references, associated with a higher risk of death, so I mean it does matter which population and the severity of illness that we are dealing with.

The other question is for the FDA. I

think I know the answer, but we saw the data with Lotrisone, if clotrimazole and betamethasone are over-the-counter, there is nothing to preclude the combination being sold from what I understand. Is that the case?

DR. WILKIN: I would think that were it over-the-counter, it would still need to have the same duration of treatment for the primary indication, which would be tinea pedis, and that that might be a different duration than what we are talking about today, which is limited at 7 days, I believe, with the monograph. So, I think there might be a distinction.

DR. WOOD: Dr. Mattison, I forgot to go back to you for your comment, sorry.

DR. MATTISON: I wanted to follow up on Dr. Nelson's and Dr. Wilkin's comments about how I understand the data that has been presented, and I am a little bit frustrated because my sense of the data leaves me with a lot of uncertainty about the dose or structure-response relationships, and relationships with therapeutic efficacy, that is to

say, the structure or dose required to produce a therapeutic effect and the adverse events that might be produced.

So, if I could just share my sort of thinking about this to see whether I have got it right or wrong. You indicated that as we go from the less to the stronger potent compounds, there appears to be greater efficacy, but roughly proportional or something like that safety hazard, and that in addition, as either dose or surface area or duration of treatment increases, efficacy increases, but concomitantly, safety concerns increase, as well, but there are a range of other factors that are poorly understood including what is in the medium that is used to put the drug on the skin and age-related effects and others.

So, I am sort of hard pressed to come to some kind of a concrete description of this safety-efficacy balance that we are trying to achieve in other than just sort of general terms.

Am I missing something, or is that kind of the state of what we understand or what is

understood?

DR. WILKIN: I guess I would make one point, which is that I think the way you describe this, you would present the moiety as having a potency, but it is actually the product that has the potency which can be determined in substantial part by the vehicle.

The vehicle may have a penetration enhancer. Not all of the active ingredient may actually be in solution, only that which is in solution participates in the concentration gradient which drives it across the barrier, which is the stratum corneum, so we don't really think of it in terms of the moiety. We think about it as the product itself.

But the other things that you said, I think are quite true. These are sort of rough guidelines on what might actually get more systemic exposure, greater body surface area, under-occlusion, all of these sorts of things.

I think that maybe we didn't make the point that, you know, one can look at what we

provide in the professional labeling for the prescription product and maybe interpret it in too precise a manner, because I don't really think that is what the ultimate intent is.

I don't think the denominators are large enough and that we really know all of the degrees of freedom in the suppression model, all the different aspects, that we have really solid labeling that says at 35 percent body surface area, in a child who weighs X amount, who applies this amount of cream, we are never going to have that.

We see people that are actually out of order, when you think you have got the order of the factors, some people suppress when you would expect, and others suppress when you don't.

So, we have taken this as a very rough way of looking, and then how we use it, I think one of our most recent labels was the--was it Clobex Lotion? I think in there, I think it gives the notion of what we do.

We said the product was approved I believe for 18 years of age and above, but we don't say

under Contraindication that it is contraindicated. I think we have in there, in the Indication Section, it is not recommended, but that gives I think the physician the kind of information, if they really read through the Indication Section, the notion that it is much better in the 18 and over, and the younger the child, the more one really needs to think about this, but at the end of the day, this is never going to be mathematically precise. I think that is one of our great difficulties.

DR. WOOD: Jon, I am always impressed by how subtly you think we interpret these labels. I don't think any of us ever understand that kind of subtlety.

Let me take Dr. Skinner next.

DR. SKINNER: I just had a question about labeling. I was struck in Dr. Ganley's lecture about low potency, Slide 4, use of OTC hydrocortisone, and he had used limits into 1 week. Later on when they actually showed the labeling warning, "Stop use if condition worsens or lasts

greater than 7 days."

Certainly, atopics from 3 months to whatever, 12 years of age, hydrocortisone 1 percent ointment and cream are rubbed on 2 and 3 times a day for years at a time, so it seems a little different than what the labeling actually says.

In fact, if you are managing atopics and they do well in hydrocortisone 1 percent ointment, it is great, you know, come back in 3 months or whatever, in fact, even on 2.5 percent ointment. So, I was surprised to see the label says 7 days.

DR. WOOD: Well, that was my point to Jon.

Dr. Alfano.

DR. ALFANO: Growth suppression mediated by malnutrition is coupled with sort of a spectrum of other functional deficits - the immune function, the salivary gland development, sexual maturation, and the like, some of which are permanent. In other words, when you restore nutrients, the deficits stay.

In corticosteroid-mediated growth suppression, are any of those other factors

identified?

DR. WOOD: Dr. Stratakis.

DR. STRATAKIS: Are you asking whether the growth suppression is permanent or are you asking whether there is additional effects on these patients that have--

DR. ALFANO: I am asking related effects. In other words, there is critical periods in development, if the animal isn't growing properly at that time, there are functional deficits which persist into adulthood.

DR. STRATAKIS: In the studies that have been done, no, to my knowledge, there is nothing that seems to be associated with growth suppression.

Let me just say one thing about the permanence or not. I can tell you from endogenous Cushing's syndrome, from patients that have either adrenal tumors or pituitary tumors in childhood, there is a long-term effect on growth. These patients seem to end up about 1 to 1.5 times deviation shorter than controls that are age and

gender matched.

So, there is a permanent effect on growth in patients that have been exposed to consistently high cortisol levels from adrenal or pituitary tumors.

DR. WOOD: Dr. Whitmore.

DR. WHITMORE: May I just ask, if you were to look at a large population of patients, what dose of prednisone would result in a 20 percent incidence of HPA suppression, oral prednisone?

DR. STRATAKIS: Well, the equivalent, in a 70-kilo adult, with replacement dose of hydrocortisone that I consider proper replacement is about 20, 25 milligrams of hydrocortisone a day, and the equivalent for that in prednisone would be 7.5 milligrams.

So, I would say that any prednisone that is given consistently every day, that is higher than 10 or 15 milligrams a day, would result in suppression.

DR. WHITMORE: So, kind of what we are saying here, with 30 percent of patients showing

HPA suppression, that is like having somebody on prednisone at a higher dose than 7.5 or so for an adult.

I mean my point here is the fact that is like having somebody on oral prednisone every day with this evidence for HPA suppression, is this worse than 5 milligrams of prednisone every day? I mean it looks like it.

DR. WOOD: You have to be careful. I mean clinical pharmacologists, the amount you get into the systemic circulation may differ if you give it orally and some of it is metabolized pre-systemically, and so on.

DR. WHITMORE: We are still looking at the end result, though.

DR. WOOD: I know, so it won't just be concentration, it won't just be dose dependent, because you may get a higher concentration in the blood, but you are right in terms of effect.

DR. STRATAKIS: To add to that, remember what I said earlier, that a limiting level to suppression is the cortical trough. So, the

cortical trough is not regulated in a steady way. It is regulated in a pulsatile manner, and it receives input from many sources.

So, the amount of glucocorticoids that the cortical trough sees is just one of the sources where the cell receives input from to determine ACTH production. So, it is not one and one.

DR. WHITMORE: One of the issues in safety with the steroids the way we use them, we use them bid, so we get a.m. and p.m. dosing, which you never do with oral prednisone unless there is a reason to produce more suppression, so that is one thing.

Only one of the steroids, I think just Elocon has the FDA approval of once daily dosing, and for the most part, the other topical steroids have not been tested 1 qd versus bid.

So, if the pharmaceuticals are interested in looking at possibly lesser suppression, applying a.m. 1 dose versus bid, would be something to think about if they are doing HPA suppression studies anyway, just to look at that, and even the thought

of qod dosing with superpotent steroids in terms of affecting HPA suppression.

Just one more comment and that is about carcinogenesis. We received a notice from the FDA that Lachydrin was changing their label in terms of use on sun- exposed areas because of concerns about using it on sun-exposed areas, and I think that probably relates to carcinogenesis, but the other concern about topical steroids going over-the-counter is looking at carcinogenesis.

So application of topical steroids producing immune suppression or contact hypersensitivity suppression, and also the thought of suppression of "rejection" of tumor antigens and things like that.

The idea of having this go over-the-counter with not really knowing if topical steroid application on a regular basis to the face might increase the risk of skin cancer, and we are almost indicating that now with the Lachydrin warning.

I am not quite sure how to take the

Lachydrin warning, but with the question about Protopic and Elidel and Lachydrin, I think you also have to start addressing the idea of corticosteroids and increased risk of skin cancer with corticosteroid use on a chronic basis and UV-induced skin cancers.

DR. WOOD: Dr. Ringel.

DR. RINGEL: I have two questions. The first is kind of this simple-minded idea that I have, which is so simple-minded that it must be wrong, but I was wondering if Dr. Stratakis could tell me why.

Why can't you take 100 people, half of whom are on steroids and half of whom are on placebo, measure their ACTH before and then during the treatment, and if it looks like there is less ACTH in the treated versus the placebo, then, you know that they are being suppressed and that's the end of it. Why doesn't that work?

DR. STRATAKIS: Well, that's a simple question. The ACTH is secreted in a pulsatile fashion, so you can't do ACTH measurements, single

ACTH measurements, and see whether a patient is suppressed or not.

What you have to do, if you want to do that, would be to really do either 12-hour sampling or 24-hour sampling every 20 minutes. Then, there are statistical ways of analyzing these 12-hour/24-hour data that will look at how the cortical trough has behaved, but that is a complicated study and quite expensive.

DR. RINGEL: Thank you, I appreciate it. I knew it was too easy to be true.

Just one other quick question. Are we interested here in only chronic HPA suppression, or are we also clinically interested in acute HPA suppression?

In other words, if somebody has been on steroids for a week and then gets in a traffic accident, are they going to--I mean my impression is that people would not, in the ICU, then give them supplementary corticosteroids.

Is acute HPA suppression really not that important, do you need to have the adrenal atrophy

for us to be concerned about it?

DR. WOOD: I think we have had the answer, but go ahead and tell us again.

DR. STRATAKIS: I think what we are asking here is whether, in a stress situation, a patient will have adequate cortisol secretion. That is all we are asking. We said that, on average, it takes about 14 days or so to atrophy the adrenal, but that also is quite variable between individuals, so I don't know--

DR. WOOD: But the hypothalamic pituitary--

DR. STRATAKIS: Oh, absolutely.

DR. WOOD: That is the key point that needs to be put across, so I mean there is two different dynamic things going on. One is the suppression of the pituitary and hypothalamus, and then there is the consequence of that, which is the adrenal atrophy, and one occurs first.

DR. STRATAKIS: But what leads to that--so there is sort of a gap here--what leads to that is not the absence of ACTH, what leads to that is the

absence of glucocorticoids.

So, really, the question is whether these patients will have adequate cortisol secretion in a stress situation, because there are many other factors that regulate cortisol secretion, it is not just ACTH. There is a problem there, but that is what they have to deal with.

DR. RINGEL: If you have been taking corticosteroids, will your ACTH respond appropriately to stress, or increase appropriately?

DR. STRATAKIS: Most likely not.

DR. WOOD: Jimmy.

DR. SCHMIDT: I am glad to follow you, Dr. Ringel, from Maine, because there was the funniest cartoon last Sunday in Doonesbury where the minister was calling to check on the snow plow and he got the exact times, and then, he said, "How is the weather in Calcutta?" He said, "I don't have any windows here."

The reason I bring this up is I think globalization is a real important thing, and I want to just comment on something that Dr. Bigby asked

about, about what is going on in other countries.

In preparation for this trip, I excerpted an article from the Lancet about a Chinese woman who developed Cushing's from taking a vitamin pill that had prednisone in it. I just want to read the last paragraph of this. There is a reference in a British medical journal by Shuster about over-the-counter sale of topical corticosteroids, which I apologize, but I didn't excerpt it to bring.

But essentially what it says is guidelines for over-the-counter steroid availability vary between countries. Iatrogenic Cushing's syndrome from topical steroids is well known, and major debates on the pros and cons of over-the-counter topical steroids have been carried out in developed countries.

Although systemic steroids should be unavailable without a doctor's prescription, such restriction is difficult to achieve in developing countries.

In a study from Brazil, clients were able

to buy 65 percent of prescription-only systemic steroids that they require for the treatment of arthritis.

Then, it just goes on. It says that this particular patient epitomizes the nefarious effects of unregulated over-the-counter steroids.

Then, I want to make one more comment. I am sort of a paleodermatologist, having been in practice for a while, and the way it was recommended, we used to, and this is my bible for topical steroids, it is Topical Skin Therapeutics by Polano is the way we used to do this was patients who were treated with large amounts of topical steroids may be monitored in the following way:

Estimation of the 9:00 a.m. serum cortisol every 14 days, as long as the level is 6 mcg/mL or more, 100 mL, the treatment may be continued. If the level is lower than that, then, your test must be performed for the synacthen test.

As long as this test shows a normal response, continuation of the treatment is safe; if

abnormal, the topical steroid treatment should be stopped, and then they talk about backing them up with some prednisone.

So, I throw that out for the group.

DR. WOOD: Okay. Mary.

DR. TINETTI: I wanted a clarification from the FDA, if you will, how you decided on the cutoff for a positive test for the cosyntropin, because I want to differ a little bit with Dr. Stratakis. Usually, with a screening test, we maximize sensitivity.

We don't mind if there is a few false positives and usually one would not sort of pick for something as serious as this, where it's a surrogate for all the systemic effects, wouldn't pick a cutoff that gave you a 70 percent sensitivity, therefore, lose 30 percent at the expense of a 95 percent.

I am sort of curious, with that in mind, why you made the switch to really an 18 versus the 20, because one way to deal with this problem would be to have a more stringent cutoff for a positive

test, and that would sort of deal with some of the concerns we have here, particularly as we are saying already, it is a surrogate for a lot of other outcomes that we are particularly interested in.

I just sort of wondered what the reasoning was.

DR. WOOD: You mean a less stringent, so that you would catch the--

DR. TINETTI: Less stringent, so that you would want a higher result of the test, and why they made the switch from 20 to 18, for instance.

DR. STRATAKIS: This was taken in the context of the whole test. I mean you have a minimum body surface area of application which is fairly large, I mean 35 percent, 30 percent, greater that 30 percent body surface area.

You are exposing those patients to fairly large amounts of topical corticosteroid.

DR. WOOD: I don't think that is what she is asking. Go ahead, Mary.

DR. TINETTI: What I am asking is that we

heard from Dr. Stratakis that the present measure, I presume that is based on 18, is only 70 percent sensitive, so therefore we miss 30 percent of the people.

One way to deal with that is to require a test to have at least, for instance, to 20 milligrams, so I am not talking about how much surface area, et cetera, I am just talking about how you define a positive or a negative response to the cosyntropin.

DR. STRATAKIS: This has been looked at. We will increase a little bit the number of false positives, but that is again not in the setting of topical corticosteroids, this in endocrine literature.

So, what has to happen here is that essentially, a cutoff from the endocrine literature on how you pick up patient with adrenocortical insufficiency has been applied in that setting, and it may not be the appropriate cutoff.

DR. WOOD: It is important to emphasize, endocrinologists, we use it clinically for a

different purpose from what is it is being used for here.

DR. STRATAKIS: Absolutely.

DR. WOOD: You have always got the other option of extending it to other tests if you are still unsure or if you think the diagnostic situation is unclear. Mary's point I think is that that is not the situation you are in with a regulatory--

DR. STRATAKIS: The proper idea of testing the test here would be to apply the gold standard that we use in endocrinology, for example, in central adrenocortical insufficiency, studies have compared the ACTH stim test with the ITT, the insulin tolerance test in the setting of central adrenocortical insufficiency, but, to my knowledge, this has not been done in long-term application of corticosteroids, local corticosteroids, again, do the ITT, do the ACTH stim test, and then compare the two.

DR. WOOD: But I guess one response to Mary's question would be that would tend to force

you further down this chart that we have I guess.

DR. TINETTI: Right. It would seem logical that if we want to maximize safety, the other alternative would be to, in the absence of that information, would be to require a higher response. That would be another simple response barring all that other information, because I think we all agree that we are maximizing safety.

DR. WOOD: Frank.

DR. DAVIDOFF: I wanted to get back to Dr. Whitmore's question about the dose equivalence, because I think it is important to recognize that in glucocorticoid therapeutics, it isn't just the dose, it's the timing of the dose, and that the kind of long sustained input of steroid into the systemic circulation that is more likely to happen with putting it on your skin, is going to mimic Cushing's syndrome abnormality in the sense of cortisol being around when there should be a trough in the blood level, so that even a smaller dose is likely to be more suppressive because of the long sustained activity.

DR. WOOD: Dr. Wilkerson.

DR. WILKERSON: Just some observations. Either we are standing on the head of the giant or

this is a tempest in a teapot, and unfortunately, I don't feel like we have the database to really understand this.

Just some observations. When we have hormonal patches of one sort or another which literally have micrograms of product that exert significant hormonal influences on the body of similar sterol-based molecule.

So it is no surprise that our topical steroids are doing this, we have all had a trivialization I think of topical therapy over the years by tradition or whatever that we have not considered these things to be significant, but the data that we have seen presented today I think certainly begs the question that maybe we really are standing on the head of the giant and we don't even realize the events that occur around us, we don't recognize because of lack of the prepared mind to recognize these events.

I think if we all go back to our practices and start looking for these things, I bet we start seeing more instances of effects and particularly the things that we are concerned about as far as osteoporosis and hypertension and glucose intolerance.

I mean there are times that we literally, as dermatologists, coat our patients with topical steroids with the knowledge and with that yes, we know that we are exerting a systemic effect there, but I don't think that knowledge extends many times out into general practitioners, and it certainly doesn't extend to the public as a whole in terms of their misuse of these products.

I think we need a lot more information personally about the pharmacology and the pharmacodynamics of these products before we go any further with this issue.

DR. WOOD: And I suspect, just to extend what you are saying, most emergency room doctors or anesthesiologists don't take a history of topical steroid use before they--

DR. WILKERSON: Nobody. I have had the unfortunate or fortunate experience of having seen a patient within the last 6 months who was using a very small amount of clobetasol-containing product that had been given to her by another physician, and the only reason I dug into this, she had significant cutaneous atrophy in the areas of application, but she had also noticed extension to other areas of the body.

We did the appropriate screening test, and she was using less than 50 grams a month of product and receiving significant suppression, so it is out there, it happens, and I think it probably happens with a variety of preparations, not just that preparation, but I think we just don't know the pharmacodynamics, we don't know the pharmacogenetics or genomics of this either at all.

I mean what is the difference in metabolism of different people or particular steroids. We sort of make an assumption that they are the same, and I don't see any reason why they would be, and that may explain part of the

differences that we see in these studies.

It may be nothing more than rates of hydrolysis and metabolism, and certainly that makes some people not affected, it makes other people probably severely affected by some of these potential side effects.

DR. WOOD: Dr. Santana.

DR. SANTANA: I want to get back to this issue of age-related differences in the test results and what this data means.

Can you clarify for me, when you addressed the question earlier, I think the discussion went to the side of the adults, but I didn't hear a discussion whether age-related differences in this testing and whether this value of 18 applies across all pediatric age groups, that is, are we under- or overdiagnosing based on this test?

I think that is going to be critical because if these products become over-the-counter, they are going to be used in a large pediatric population, because that is what they are indicated for pharmacologically, for atopic dermatitis.

Can you clarify that for me, is that test really applicable across all age groups in terms of the value of 18?

DR. STRATAKIS: Yes, it is.

DR. WOOD: Any other questions? Yes, Wayne.

DR. SNODGRASS: I have two questions. One is does the FDA have any plans to request or require studies that demonstrate a dose threshold for ACTH suppression for topical products?

Secondly, what is the error rate, if it's known, or any estimate of it, of the general population for misuse of OTC topical products?

DR. GANLEY: I will address the latter question and Jon can address the first question. We don't have a lot of data per se, but I think one of the presentations during the open session provides some survey data and also purchase data, and it will give you a sense mainly based on purchasing of how many people would use these chronically, so then that I think would address your question.

DR. WOOD: In the absence of any other questions, I think what we will do is we will take a break--I am sorry, Charley.

DR. GANLEY: We have one more question. Jon had to finish the first question.

DR. WOOD: I beg your pardon.

DR. WILKIN: I think the question was will FDA be looking for a way to find out what the threshold dose of a topical product might be. Again, because of all the degrees of freedom in the model, I just think it's incredibly difficult to say that, you know, 22 grams used in a child of a certain age, I just think really that it doesn't allow that kind of--

DR. SNODGRASS: What I was getting at, that is a different study design. In other words, you really could find a dose-response. If you had more than one dose, you could find a dose-response for the effect you are looking at, and you could set your a priori criteria 1 in 100 or whatever to be suppressed, and that would give much more information than we currently have product by

product.

DR. WOOD: Although it would be difficult to conceive of an over-the-counter product being over the counter in which even a high end showed suppression, it would seem to me. I mean the complexity of that label would be pretty tough, I think.

DR. SNODGRASS: Well, I think if you did it, you know, it depends on what dose you have got. If you have got a test right now that is 30 percent insensitive, once you get beyond, look at the table we have got here, and beyond 100 in yours arms, I think you might begin to find some numbers there.

I realize it would be much more expensive, more complex, and all that, to do that type of studies.

DR. WILKIN: Well, actually, the way the study is conducted, I realize there is this sensitivity issue, and I think Dr. Tinetti's comment that if we altered the criterion, we could tinker with the sensitivity, but also think about the context in which we are doing these studies. We

are looking at the extreme upper end of body surface area involvement although Dr. Wilkerson mentioned that from time to time, dermatologists will give patients topicals to cover most of the body, I am not sure that that is the usual rule.

I think it might be unlikely in an OTC setting if the container size is small. So, the testing circumstance is really geared towards maximum, really provocative, looking to see if, under these extreme conditions, that HPA axis suppression can occur.

DR. WOOD: Dr. Mattison, did you want to say something? No? Okay. Charley.

DR. GANLEY: I just want a clarification on this sensitivity issue. Maybe I misheard you, that your sense was for something that would be clinically significant leading to possible death, the test is fairly good. It is not a 30 percent sensitivity or we don't know that.

If you have someone that is suppressed, this test is actually pretty good to pick it up in terms of putting them in a situation that if they

were stressed.

DR. STRATAKIS: Well, that is the specificity. It will pick up all the patients that have severe adrenocortical insufficiency.

DR. GANLEY: Right, and that is the population that we are interested in is the person who is going to come into an emergency room, who is in a stress situation, who could die from it. It is actually pretty good to pick those folks up.

DR. STRATAKIS: Well, if you want to comment on that, but I mean basically, with the criterion of 18, we have a fairly low rate of false positives and acceptable rate of false negatives.

DR. TINETTI: Right. The way it says now is that if you do have a positive test, you are pretty darn sure you are going to be in trouble, but if you have a negative test, i.e., you pass this test, you still have a 30 percent chance of having difficulty. That was the point that I was trying to make.

DR. STRATAKIS: Actually, you can read studies that say as good as 85 percent, and you can

see studies that say as low as 68 percent I think.

DR. TINETTI: So, it's a little bit eye in the beholder of how many people you are willing to miss not to overestimate, so for something like mortality, you probably want to have a sensitivity of as close to 100 percent as possible, realizing you will have a lot of false positives.

DR. STRATAKIS: Because of your specificity.

DR. TINETTI: The cutoff now minimizes false negatives, but maximizes false positives.

DR. WOOD: Terry.

DR. BLASCHKE: I just wanted to make note of the fact that when we are talking about safety issues, we are not just talking about adrenal insufficiency, we are actually talking also the fact that this is picking up excess corticoid in the body, and all of the comments that have been made already about the possible effects on glucose metabolism, on bones, growth, et cetera, are also not to be overlooked as important consequences of absorption of the more potent corticosteroids.

DR. WOOD: Immunosuppression, as well.

In the absence of any other questions, let's take a break now for lunch and plan to be

back here at 12:30.

For the audience before they all rush out, we will start immediately with the public comment session. You have all got your numbers, so we will be starting with No. 1 obviously and moving on from there.

Thanks a lot.

[Whereupon, at 11:30 a.m., the proceedings were recessed, to be resumed at 12:30 p.m.]

A F T E R N O O N P R O C E E DI N G S

[1:00 p.m.]

Open Public Hearing

DR. WOOD: We are going to do the public comment period. All the people who have requested time in the public comment period have got a number, and I will call you up by number.

You have 10 minutes to present and we will strictly enforce the 10-minute rule. At the end of the 10 minutes, the microphone will go dead and only your lips will be moving.

Let's get started with No. 1.

MR. ROTH: I am Jerry Roth. I am president and owner of Hill Dermaceuticals. I was present at the last Advisory Committee meeting on pediatric corticosteroids for pediatrics. I recognize some of the panel members from the last one, so I hope I don't bore you here because I am presenting this information.

I remember Dr. Chesney said you are supposed to say if anybody paid your way here. I paid my own way, so as I said before, I am one of

the dinosaurs left in this industry.

First of all, in presenting this data, it is not our intention in any way, shape, or form to want our product Derma-Smoothe/FS to be nonprescription. It is a prescription and we intend it to stay that way, but we felt that this is giving you a little bit of data that you have not maybe heard earlier today.

[Slide.]

First of all, Derma-Smoothe/FS contains 0.01 percent fluocinolone acetonide in a peanut oil base It is considered a low to medium potency corticosteroid, and I wanted to present HPA axis suppression studies that were done in patients 2 to 12 years of age.

You have heard a lot today about vehicles and I think that this will give you once again a little bit additional evidence.

[Slide.]

This is a multi-center, open-label safety study. What you haven't heard yet is this was done in patients with greater than 50 percent body

involvement.

The dosage, it was also brought up that everything was once a day. The dosage on this was twice daily for a period of 4 weeks. The criteria was evaluation with the cosyntropin stimulation test.

Derma-Smoothe/FS was one of the first drugs that was studied for safety and efficacy, the Rules, as have been mentioned, have changed since that time, and you will see that Day 1, prior to the first treatment, and at the end of treatment we had a pre-stimulation cortisol level and then immediate followed by stimulation, and then the post-stimulation cortisol level was at 60 minutes.

At that time, the protocol or the Agency only request cosyntropin tests. It wasn't differentiated between 60 minutes and 30 minutes at that time.

[Slide.]

The population that I want you to recognize is that 18 of the patients had greater than 75 percent body involvement, and 16 had 50 to

75 body involvement. We calculated the amount of drug by what was returned, and the average drug use per day was about 9.5 plus or minus 4.7 mL/day. Now, this is important because there is something, vehicles and drug exposure.

[Slide.]

Just to remind those who aren't physicians, regarding body surface area, when you are talking about this much, 50 to 75, or 75, you are talking about the chest, front and back, legs, front and back, arms, a substantial area. Once again, I believe this is the only drug that had been tested with that level besides hydrocortisone of that amount of body surface.

[Slide.]

Before the treatment, prior to treatment, now we did averages because this is a public hearing, each of the data individually is on file with the Agency, and this was approved, so each individual case report form is on file.

Anyway, the average pre-stimulation was 11.63. At 60 minutes, it was 26.82, the doubling

which you should see.

[Slide.]

After 4 weeks of treatment, there was very little change, 11.26, and after post-stimulation, it was 25.06. Of the 34 patients, there was not one that experience any adrenal suppression.

[Slide.]

The exposure we feel is very important. Derma-Smoothe/FS is a 4-ounce container. Within this container, there is 12 mg of fluocinolone. You will see that the average patient, the 4 ounces, 118 mL, lasted 12 days. The patient was exposed to not more than 1 mg of fluocinolone per day. On the basis, which is the generally accepted percent of absorption of 1 to 2 percent, that is an infinitesimal amount that is absorbed.

What is important is this is an oil vehicle, the spreadability is great. This particular cream is 60 grams, and there are 60 mg of corticosteroid in this cream. To cover a vast majority of the body, it would require a lot more cream to do this than of this oil, so you may use

quite a bit more of the cream. I think that was brought out earlier.

So, therefore, vehicles are important and possibly does have substantial amount regarding safety data.

[Slide.]

In conclusion, after 4 weeks of daily application of Derma-Smoothe/FS , involving 50 to 90 percent of the body surface area, there was no change in the morning baseline value of the cortisol, nor did it affect the cortisol stimulation of ACTH.

You might wonder, well, if there is so little amount of steroid does it work, with this small amount on the body, after 4 weeks, 60 percent of the patients showed excellent or 75 to 100 percent improvement.

Would you like to ask me any questions especially on the amount of surface? I think, just to follow up, Dr. Wilkin has said that the tests are becoming a bit more sophisticated. We are ready to commence down to 3 months with this

product in greater than 30 percent of the body area, and we will be following, I think there was a question if you have any adrenal suppression, will you be following those patients. In that protocol, we will be. We don't expect any, but we will test until we have data.

Second of all, once again, there was also a statement that companies often just do this because they are required. That is some of the case, but in any cases it is not, and in this case, it is not. It was our request to do these.

Yes, sir.

DR. WOOD: Dr. Nelson has a question for you.

DR. NELSON: I was told it had better be a good one, hopefully, it is. You had mentioned in passing that it is generally accepted that 1 to 2 percent of corticosteroids are absorbed topically. I was just wondering what is the data and how generally accepted is that?

MR. ROTH: That is in the Textbook of Corticosteroids, I believe it is by Dr. Howard

Mayback. That is a generally accepted textbook.

DR. NELSON: For all corticosteroids?

MR. ROTH: I believe, yes, on topically applied, yes. That is why the amount that you are exposed to is quite substantial.

DR. WHITMORE: I don't know that that applies to all corticosteroids. I think hydrocortisone versus the others--

DR. WOOD: Let's hold all of our questions to all of the speakers at the end, otherwise, we will take forever to do this. Let's go through all the speakers and then we will take questions for them at the end.

MR. ROTH: I can quote out of the textbook if you would like.

DR. WOOD: Teresa has handed me a late-breaking statement that I need to read.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. 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, 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 sponsor or products.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, the 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.

Speaker No. 2.

DR. CHARLES ELLIS: Thank you very much. I am pleased to be here to speak on patterns of use of OTC topical hydrocortisone. Thank you for

allowing me this opportunity.

[Slide.]

I am Charles Ellis. I am Professor of Dermatology at the University of Michigan Medical School. I am also Chief of Dermatology at the Ann Arbor Veterans Affairs Medical Center.

[Slide.]

Here are my disclosures for my talk today.

[Slide.]

I am thrilled to be able to be here to present our research which is in press and will soon be published in the peer-reviewed Journal of the American Academy of Dermatology. Our research is entitled, "Consumers appropriately self-treat based on labeling for over-the-counter hydrocortisone."

[Slide.]

First, I am going to tell you the results of our research and then I will give you the details.

So, what has our research shown about the use of topical hydrocortisone in the United States?

The reported use is largely consistent with the OTC monograph label.

The percentage of use in accordance with the label is similar for both adults and children.

Over-the-counter hydrocortisone is used primarily for brief periods of treatment of apparently minor conditions.

[Slide.]

By way of background, you have heard that hydrocortisone has been available over the counter since 1979, and in the 1 percent concentration since 1990.

The OTC label is designed for safe use, and compliance with the label implies that there be a low risk of adverse effects, however, we found no published data on how OTC hydrocortisone is being used in the population.

[Slide.]

So, our research objective was indeed to look at real world user behavior, and we did this with a telephone survey which was performed by a company called Synovate through one of their

regular national telephone surveys. We had them ask questions about the usage of over-the-counter hydrocortisone.

This is as reported by the adult users in the family when we called them. This also included these adults' reports on the use in their children. They gave us the reason for using the hydrocortisone, the daily frequency of use, and the duration of use. We evaluated their responses for consistency with the labeling.

[Slide.]

This was one with a random digit-dialing to over 64,000 households although about 55,000 of them didn't answer the phone, so that is the problem of caller ID, I think. In the end, we achieved 2,000 adult respondents who actually completed the survey.

Of these respondents, 396 adults reported using over-the-counter hydrocortisone in the last 6 months; 168 households reported treating a child with OTC hydrocortisone in the last 6 months.

[Slide.]

So, our analysis undertook a weighting to represent the U.S. demographics in the 2002 National Health Interview Survey. Limitation of

this work is that it is based on self-reports. Of course, we couldn't go into everybody's house to see what they were actually doing, so we relied on what they told us in answer to our questions.

The strengths of the study includes that it was open-ended questioning, so we didn't use terms right off the label, and the respondents didn't have the label in front of them, so this avoided biasing them to give us answers that they might think that we wanted to hear.

Also, when we came to the children, we asked about the youngest child at home who used over-the-counter hydrocortisone, the youngest one who used it, and we picked the youngest one because we felt that that person might be at most risk for adverse effects.

[Slide.]

You have seen this prototypical over-the-counter hydrocortisone label from the

monograph. It talks about the uses for temporarily relieving itching of minor skin irritations and inflammation, and rashes due to a number of conditions. It is for age 2 and over.

Frequency is maximum 3 to 4 times daily. It is for external use only, not for use in diaper rash. Avoid contact with the eyes, and the duration for up to 7 days on the labeling, and we inquired on these points in an open-ended fashion.

If you look at the overall compliance with the label, 73 percent of adults and 72 percent of the children that adults reported on, in fact, were completely consistent with the labeling. A smaller percentage, about 20 percent, were not acting in consistency with the label for 1 reason, and a much smaller percentage were not consistent for 2 or 3 reasons.

By far and away the most common situation that we found was that they couldn't give us an answer of why they were using it that was specifically listed on the label. So, we are going to look at the people who were not consistent with

the label and try to understand exactly what was going on.

[Slide.]

So, we asked, "The last time you used an over-the-counter hydrocortisone product, what were you using that product to treat?" Eighty-three percent of adults, the reports were 86 percent of children were consistent with the label, but you can see down here is this hatched bar, there were other situations that we couldn't code as being consistent. Most of these actually were indeed called Other, they were vague responses or no condition was reported, and in a few children, they used the term "cracking skin."

So, some of these in this hatched bar may, in fact be consistent with the label, but the respondent was unable to actually verbalize it in that way. "Cracking skin" could well be eczema, for example.

About 2 percent were using it for cuts and approximately the same percentage were using it for what they described as fungus, arthritis, acne, or

diaper rash.

[Slide.]

Now, we asked, "Think about your youngest child who has used over-the-counter hydrocortisone in the last 6 months. How old is that child?" In 93 percent of reported uses on the youngest child, the age of the child was 2 years or older, which is consistent with the labeling.

So, here we have the age across this way, and the cumulative percentage reporting this way, and the dash line is the non-consistent use with the label. However, 81 percent of the adults who told us about these children, 81 percent of them said they had discussed the use of hydrocortisone with a doctor in this group.

[Slide.]

So, then, we asked, "The last time you used an over-the-counter hydrocortisone product, how many days in a row did you use the hydrocortisone?" For 92 percent of adults and for 94 percent of children, they were treated for 7 or fewer days, again showing here the duration of use,

cumulative responses, and then this segment here, the smaller segment here are the people who were not consistent with the labeling. The median use was for 3 days.

[Slide.]

And we asked, "And how many times per day did you use the hydrocortisone product?" And 98 percent of adults and 97 percent of children, they used it 4 or fewer applications per day. Again, the number of applications and the cumulative reporting, up to 98 percent, roughly 97, 98 percent, and the median use was 2 applications per day.

[Slide.]

So, in conclusion, the reported use of an over-the-counter topical corticosteroid is largely consistent with the label for conditions treated and for frequency and duration of use.

Thank you.

DR. WOOD: The next speaker is also called Ellis, and it's Valentine Ellis.

MS. ELLIS: Thank you for your time. My

name is Valentine Ellis and I am here today to present the patterns of household purchase behavior in the OTC hydrocortisone category.

In way of disclosures, I am actually not related in any way to Dr. Ellis, we only met a week or two ago. I am a full-time employee with GlaxoSmithKline Consumer Healthcare, and I work as a consumer research manager there, so the majority of my work is done behind consumer behavior analysis and consumer insights.

I am formerly an employee of A.C. Nielsen. I will be talking about them a little in the methodology where I worked as home scan specialist and specifically on this research project, which is why I was asked to present it to you today by my team.

[Slide.]

The research objectives at the time we undertook this study were to understand purchase behaviors in the OTC hydrocortisone category among U.S. households. The basic underlying assumptions that we use in research on the consumer side is

that the household data is a proxy for annual household usage, and this information that I am providing today is likely an overestimation because we are reporting against 100 percent of purchases, which does not necessarily mean people use 100 percent of the product that they bring into their household.

[Slide.]

Methodologically, AC Nielsen is a supplier, a commercial supplier of research data. Most people are familiar with the AC Nielsen TV ratings, but they do have another arm which captures, maintains, and reports data for all the products that are out in the world today that we purchase and use at home.

We are using data from their household panel, which at the time of the study had 55,000 households enrolled. It is demographically and geographically balanced to the U.S. Census.

The panelists agreed to scan all of the products that they purchased with UPC bar codes regardless of where they purchase it, provided that

they use it for personal consumption.

This is a pretty accurate reporting system. These people scan via an in-home bar code scanner, which you can see this little lady here using, everything, so in a sense, they are blindly reporting their purchases, they are not paying attention to the frequency with which they scan these products, and they transmit the data back to Nielsen once a week.

They are incented for consistent reporting, so Nielsen provides them with a non-biasing points redeemable type program, because they don't want to in any way bias a product that a person would purchase or how they would necessarily use it once they get it into their home.

Most of the panelists stay within the panel, and there is actually about an 80 percent retention rate year on year.

[Slide.]

The custom analysis that we undertook was to take AC Nielsen's hydrocortisone reported category, which is over the counter. It includes

all of the brands we have listed here, all of the, you know half-percent, 1 percent ointments, creams. Most of the sizes I believe that are out in retail today would be half-ounce, 1 ounce, and 2 ounces.

[Slide.]

The time period that we looked at was 52 weeks ending October 19, 2002, and the primary measures that we looked at were buying households and buy rate in both ounces and purchase frequency.

The sample of the data was any household that had scanned a hydrocortisone product at least once during the 52-week time period, and the advantage of a custom analysis is it allows us to take the total buyer group and break it down into both households with children and households without children, children at this point being defined as any household under 18.

These are mutually exclusive buyer groups, so the value of these two groups of households will add up to the sum total of total buying households.

[Slide.]

Some of the advantages of this methodology

are that the ongoing electronic purchase of actual behavior provides us with a pretty objective and accurate measure of purchasing across the household, but at the same time, there are limitations to this data what we want to be perfectly clear about. This tells us about household level purchasing.

We can't link it from this particular data set to who in the household is using the product or necessarily how they are using it in terms of frequency, duration, or condition. We just know that this household has made so many purchases and we know that volume is actually going into these different groups of people.

[Slide.]

Our key findings were that annual household purchasing of OTC hydrocortisone products is reasonably limited. About 13 percent of total U.S. households purchase at least one product per year. Of those 13 percent of buying households, 75 percent of them purchase only once, 90 percent of them purchase 5 ounces or less per year.

We have also discovered that households with children actually buy less volume per year than households without children, despite the fact

that there are significantly more people in that household.

[Slide.]

A little detail on that, the data that we have just presented in the key findings. Again, you see that 13 percent of the households purchase OTC hydrocortisone, and that is the little red pie sliver.

When we look at the household composition of those 13 percent of households, what we see is that 34 percent of the buying households did have children, and 66 percent did not. This number is consistent with the U.S. demographic breakdown of households with and without children.

[Slide.]

We also look at the households in total, and of the buying households, 75 percent of them make only 1 purchase per year, 92 percent of them over the course of the year make 3 purchases or

less.

[Slide.]

This chart demonstrates the cumulative percentage of households going up the bar, across the volume that is actually purchased during the course of the year.

If you look at the black bar in the center, that is our total households, all of them, and what it tells us is that 90 percent of the households purchase 5 ounces or less per year of OTC hydrocortisone.

Then, the red bar, which is on top, that is our households with children under 18. It cumulates or builds a little quicker, which is why it is above the black bar, and what it tells us is that 85 percent of households with children purchase 3 ounces or less per year, and 94 percent buy 5 ounces or less per year.

[Slide.]

Looking at it from a consolidated perspective, the gold bars on the left tell you the percent of buying households the buyer group

represents, and then the blue bar on the right tells you proportionately how much volume they contribute to the total volume purchased.

What we see is households with children, while they represent 34 percent of the buyer groups, are really only contributing about 26 percent of the total volume purchases, and this is because the average buy rate in households with children is about 1.9 ounces a year, while it is 2.8 for the households that do not have children.

[Slide.]

The conclusions we reached from this data was again that annual household purchasing of OTC hydrocortisone products is limited. It is not a large--well, it is a large group of people, but it is only 13 percent of the population. They purchase infrequently with 75 percent of them purchasing only once, and for the most part, they purchase, 90 percent of them, 5 ounces or less.

We see lower purchase volumes in households with children, despite the fact that we have twice as many people in them, and then based

on the amounts of product that we see purchased, excessive use of the OTC topical corticosteroids is probably not an issue, and, in fact, would lead us to believe that people are using it much they way they have told us in Dr. Ellis' usage survey.

That is it.

DR. WOOD: Thanks very much.

Let's go back to Speaker No. 2, who has now shown up, Mr. Paranzino.

MR. PARANZINO: Thanks very much for accommodating my late arrival, I appreciate it.

My name is Michael Paranzino, I am with Psoriasis Cure Now, which is a patient advocacy group. I have no conflicts either personally or through Psoriasis Cure Now with any content involved today.

Our written statement is available on the web at psoriasiscurenow.org, and I will just make a couple points briefly.

First, thank you for holding this hearing. While not two psoriasis cases are alike, one thing that unites just about all 6.5 million Americans

with psoriasis is that we use a lot of topical steroids, one or many over the years.

As I noted in my written statement, I took a quick look at a popular list of topical steroids, and I have been prescribed at least 15 over the last two decades, and that is the way, as many of the dermatologists in this room now, you try one, then you try another, then you flip back, and then you try another, so we do know topical steroids. It is very important to us.

We believe that some of the topical steroids that are currently prescription-only can be used safely and effectively by psoriasis patients over the counter. Most psoriasis patients are actively involved in treating their skin symptoms. They are also actively interested in minimizing the medications they use, so they are very cognizant of overuse.

Now, that said, we do have some concerns, and one of them is every rule has its exceptions, and we still come across psoriasis patients who use what might be considered excessive either through

duration or extent over the body topical steroids over a period of time, and only later come to realize that there could be side effects to that. But we think that can be dealt with through better education, maybe through labeling. There is also some education that needs to be done still we believe with dermatologists, because there is a wide range of strategies that are employed by dermatologists in prescribing topical steroids. I am not speaking anecdotally, not in terms of studies, but I have talked to a lot of patients over the years, and some doctors, every time they prescribe a topical steroid, they peel off the preprinted chart, they circle the one they are giving you, and they say this is where your topical steroid falls in the mild to strong, this is where it falls. Other just write the prescription, they are busy, they move on.

Just last month, someone came to me and said they went in for what turned out to be psoriasis on the leg. A quick appointment with a dermatologist, walked away with a Temovate

prescription, and they said to me, "But it's a mild one, because it's 0.05 percent." I said, well, according to this chart I am looking at, you can't just go by the percentage, because, well, as you all know, but we are lay people, so it's a common mistake that can be made. But again that can be dealt with through better education.

I did want to address children just for a moment, because it is particularly tough for parents trying to treat children with psoriasis, and some actually try to avoid topical steroid use in children, but it is becoming more and more complex just with the FDA's actions in recent days with Protopic and Elidel, there are some children with psoriasis and some adults using those off-label for psoriasis specifically to avoid steroid use, and now they hear some warnings about potential cancers.

So, it is very tough for a parent to weigh the costs and benefits between UV light and Dovonex and steroids, Protopic, Elidel, systemics, biologics, anything that can be done in terms of

educating, if there is a scientific consensus on what a child should do, it has to reach the patients better.

Finally, I hope you would use your influence with your colleagues downtown and closer to Washington and Bethesda and encourage more research on psoriasis. The challenges that parents face and all psoriasis patients face underscores the need for additional treatments. Psoriasis has been underfunded woefully for the last 10 years at least at NIH, and NIH funding is up 99 percent after inflation in the last 10 years, psoriasis funding is down 8 percent. It is hard to go down in the environment over the last 10 years, and you folks can help change that.

So, thank you again for the hearing. It is very important to psoriasis patients, and I appreciate the time to fit me in even though I am late.

Thanks.

DR. WOOD: Thank you.

The next speaker is Dr. Sandra Read.

DR. READ: Good afternoon, Mr. Chairman, distinguished members of the Committee and colleagues. Thank you for letting me be here. My

name is Dr. Sandra Read, and I am appearing on behalf of the American Academy of Dermatology Association.

Thank you for allowing me a few minutes to share with you safety concerns on an important matter to me, to my patients, to doctors in America, as well as to the Academy, regarding changing topical corticosteroids to over-the-counter status.

In the spirit of full disclosure, I do not conduct any research for pharmaceutical companies. I am on the Speakers' Bureau for a company that manufactures a high potency steroid cream. However, I have not been in contact with this company regarding this testimony.

I have been in the practice of medicine for 30 years, more than 20 of those in the private practice of Dermatology in the District of Columbia. I serve on the clinical faculty of

Georgetown University, and I have been lecturing on Pediatric Dermatology there for more than 10 years.

I have been prescribing topical corticosteroids since my training days, and they are an integral part of my therapeutic armamentarium. Over the years, I have developed not only an appreciation of their usefulness, but also a respect, a very healthy respect for the potential abuse of these agents. I urge the Committee not to be lulled by their route of administration. These are powerful external agents that can have serious internal and external side effects.

Treating patients of all ages with topical steroids is a mainstay of many of our dermatological practices. They are potent medications and, when used properly, they offer relief to suffering patients and enables them to lead comfortable and normal lives.

Used improperly, however, these medications can cause great harm and that is why the American Academy of Dermatology is opposed to

the proposal to make these medications available OTC.

I have done a random survey of 100 of my patients' charts. Of these 100 patients, I prescribed topical steroid creams in 36. Of these prescriptions, 16 percent were super potent, 36 percent were mid-strength, and 50 percent were low potency. Some patients received more than 2 prescription for different strengths. As the last speaker pointed out, this can sometimes be very confusing to patients on how to use. However, the usefulness of these agents is reinforced by the figures of my practice. I cannot do without topical steroid creams, neither can my patients.

However, I have seen too often the results of abuse of these agents. Cutaneous adverse effects include thinning and discoloration of the skin, telangiectasias, and striae, permanent stretch marks.

These side effects can be permanent and disfiguring and last a lifetime. Pediatric patients, our youngest patients are especially

vulnerable to these adverse events. In fact, I use a picture frequently of one of pediatric patients who was treated with a topical steroid cream, on whose inappropriately was left with thin skin, with hypopigmentation, and telangiectasias. The medical students at Georgetown tell me they never forget this picture.

I have seen patients have access to these treatments and misuse them for non-steroid responsive dermatoses, such as tinea, scabies, and even skin cancers. Now, we all know that this delays diagnosis and obscures diagnosis, but it can also worsen disease, as we all know, in topical ringworm and fungus.

I have seen, and so have dermatologists in this room seen, the inappropriate use of in steroids of body folds in genital regions. In these areas, increased absorption rapidly intensifies and produces the cutaneous side effects we are talking about, and, of course, one cannot ignore the augmented potency that is delivered by these creams when applied under occlusion. Mild

creams become strong creams, strong creams become even stronger under occlusion.

This can happen, of course, by accident with patients using these creams on their own and unsupervised. Now, not only are cutaneous adverse events accelerated and magnified, but the risks of systemic absorption and all of its complications are well known to the members of this committee.

The medical literature is rich with studies providing the direct link between topical steroid creams and hypothalamic pituitary adrenal axis suppression, growth suppression in children, and the adverse effects on the skin that I have just discussed.

It is only with close monitoring of our patients who present with adverse treatments and reactions that physicians are able to prevent and monitor for these dangerous clinical diseases and side effects.

I note to you that if you remove the physician from this equation, you would be effectively removing a very important safeguard and

protection for patients, and that is our primary duty as doctors.

By changing the status of these pharmaceuticals from prescription to over-the-counter, the FDA would effectively be turning over the practice of medicine to patients. As well informed as patients can be, I do not believe that they should be self-diagnosing or self-treating symptoms with medications that can have potential for such serious side effects.

The danger of pediatric patients being treated with over-the-counter steroids should be consider by this committee seriously. As parents search for relief for their children bothered by eczema and other skin diseases and their symptoms, it would not be unheard of for them to use a topical steroid cream incorrectly, such as too often, using too much in an application, or applying it to too large of an area and/or too long.

Pediatric patients have a higher risk of systemic absorption, which can lead to their growth

suppression because of their higher ratio of surface area to body volume.

The FDA itself has expressed concern that patients do not understand the risks of hypothalamic-pituitary-adrenal axis suppression when using steroid creams. Therefore, the risk of doctors missing a diagnosis of HPA suppression in pediatric patients when the parents fail to inform them is a real risk of topical steroid use.

This Advisory Committee is being tasked with determining at what point the risk of HPA axis suppression and other adverse effects outweighs the benefit of making these treatments more available to the public.

I believe that there is no acceptable point at which those of us in the medical community should allow our patients to not only self-diagnose, but also to self-treat at any level of skin disease.

The complications that can arise, ranging from mild to severe, as I have told you, should exclude automatically the expansion of OTC status

to topical steroid creams. Our patients are not qualified to make these kinds of medical determinations, nor should we be asking them to make these determinations.

I ask you, what is the rush to change the prescription status? I ask you, what is the marginal benefit to the consumer for stronger over-the-counter creams? There is no overwhelming need and there is no clear benefit in making these treatments more accessible. The goal here should be patient safety first and foremost. That is our duty as doctors.

Given the FDA's increased focus on drug safety, I believe that changing the status of these treatments will have the opposite effect on the public sentiment than what is intended by this committee.

Patients will not be more satisfied because these treatments have been made available over-the-counter. In fact, I believe that their satisfaction will diminish, as will their trust in the medical community and in the FDA once they

become aware of the severe side effects associated with the incorrect use of these agents.

Topical corticosteroids play an important role in the treatment of patients with skin disease and have improved the lives of countless patients. Please do not make their suffering worse by allow them the opportunity to diagnose or misdiagnose and mistreat their conditions. These are being effectively treated by countless physicians each and every day.

The American Academy of Dermatology urges this advisory committee not to make these powerful medications available over-the-counter to the public.

I think you for this opportunity and your time. Have a good day.

DR. WOOD: Thank you very much.

Could we have Speaker No. 6.

DR. FONACIER: Good afternoon. I am Dr. Luz Fonacier and I represent the American College of Allergy, Asthma, and Immunology.

I do not represent any industry in this

meeting. I am the chair of the Dermatologic Allergy Committee of the American College of Allergy, Asthma, and Immunology, and the Secretary of the Food, Drug, Dermatologic, Allergy and Anaphylaxis Committee of the American Academy of Allergy, Asthma, and Immunology.

I head the section of Allergy at Winthrop University Hospital in New York, and am Associate Professor of Medicine in SUNY of Stony Brook.

Thank you for allowing us to be represented in this hearing. The allergists use steroids in every shape and form for asthma, allergic rhinitis, and atopic dermatitis. Unlike the ENT who uses the nasal steroids, the pulmonologists for inhaled, the dermatologists for topical corticosteroids, we use all of them.

Many of our patients use topical, intranasal, and inhaled corticosteroids together or separately. The concern of the American College of Allergy, Asthma, and Immunology is twofold, the cutaneous use of topical corticosteroids for eczema especially for the less than 2 years of age for

which nor many drugs are approved, and the translation of this to intranasal and inhaled corticosteroids.

For the cutaneous corticosteroids, neither systemic nor local side effects are easily recognizable. The sensitivity of the cosyntropin stimulation test, the cortisol level, which are lower than what we would want them to be. The growth velocity, osteoporosis, even adrenal insufficiency are not recognized unless specialized testing is done.

Much of the discussion this morning was on the systemic effects of topical corticosteroids, but local side effects could be disfiguring, as well. Skin atrophy, facial erythema, telangiectasia are not easily recognizable, at least not until the irreversible stage of the striae.

There is low reporting of side effects and difficulty of monitoring is a big concern. There is also increasing incidence of allergic contact dermatitis to topical corticosteroids probably due

to greater awareness, expanding market of the corticosteroids, and improved testing procedure.

There are many reasons for potential abuse or misuse of over-the-counter corticosteroids. Mid and high potency steroids are going to be more effective than low potency. In fact, it was brought up this morning that 1 percent hydrocortisone, whose label says not to use more than 7 day, is actually being used years and years for chronic atopic dermatitis even in children less than 2.

Because of decreased efficacy, there is potential for prolonged use and thus increasing absorption and side effects, more so for over-the-counter. Because the only topical corticosteroids approved for less than 2 years of age, is fluticasone, and that is more than 3 months of age, and this is a prescription, the obvious option for patients, especially those who are concerned of drug costs or don't have medical plans, is over-the-counter topical steroids.

Also, with the proposed black box warning

for pimecrolimus and tacrolimus, there is anticipated an increased shift to topical corticosteroids. If more potent ones are over-the-counter, in chronic eczema and atopic dermatitis, there may be increased off-label use, that is, more than 7 days and under occlusion.

Other important issues that we are concerned about in over-the-counter topical corticosteroids are inappropriately linked, trivialization of what over-the-counter is, that is, the perception that over-the-counter is safe, credibility of advertising, appropriate labeling, and differences in vehicle that increase absorption.

Note, that it is the Diprosone Lotion which may be alcohol based that showed more HPA axis suppression, and in the tacrolimus and pimecrolimus study, it is the study on ethanol that showed increased absorption of the drug.

The second major concern of the allergists is how this issue will translate to intranasal and inhaled corticosteroids for asthma and allergic

rhinitis patients. We would not like to see difficulty in access of the medication, unnecessary panic or concern of the use of corticosteroids in potentially life-threatening disease such as asthma, nor suboptimal treatment. But at the same time, would like to be able to monitor our patients, not only in terms of efficacy, but most importantly the safety.

Thus, as the representative of the American College of Allergy, Asthma, and Immunology, until safer steroids are available, more sensitive tests can be used, better monitoring can be done, and more studies are conducted, we would like the current prescription cutaneous, intranasal and inhaled corticosteroids to remain prescription.

Again, in behalf of the American College of Allergy and Immunology, I thank you for this opportunity.

DR. WOOD: Thank you very much.

Are there any really pressing questions from the Committee for the public forum speakers?

Yes.

DR. BIGBY: I just have one question for Valentine Ellis. How many households are there in the U.S., the total number of households?

MS. ELLIS: Right now there are about 113 million households in the total U.S.

DR. BIGBY: Thank you.

DR. WOOD: Any other questions? Yes, Jon.

DR. WILKIN: If I could ask Dr. Ellis if he discerned why patients stopped using the topical corticosteroids over-the-counter, you have that they used it for 7 day or no more than 7 days for the most part, I think it was, no more than something like 5 percent used it beyond that, but was that because they ran out of product, or it no longer seemed to work, or it actually did work? I mean did you get that piece out?

DR. ELLIS: Jonathan, that is very good question. We did not delve into that in this survey. The only answer I could say is that much of the use was for insect bites and other trivial issues, and I am sure that explains part of it,

part of the short-term use for 3 days of median usage, so that would be my interpretation, but we didn't ask that specific question, and that would be a good one to ask at a future date.

DR. WILKIN: So, it is fair to say that their, in large part, use is consistent with labeling, but not absolutely proven that it was driven by labeling?

DR. ELLIS: I don't know how I would answer that specifically. Again, we asked them questions, the type of question that I showed you, and then we later coded the responses to determine if they were consistent with the labeling, so we found that, by and large, people do follow the label, and we presume they are reading it and that is why they are following the label.

DR. WOOD: Let me just follow up on that. I am intrigued by your confidence in that. If you look at Slide 12, 10 percent of the children were under 2, and how do you square that with the label? You need to look at that slide in the context of the way you framed the question.

You said, "Think about your youngest child who has used over-the-counter hydrocortisone in the last 6 months. How old is that child?"

Well, if that child is now 2 1/2, that child was under 2 when they were using it if they were taking it 6 months ago, so if you assume it was averaged over 3 months, that brings that up to about 10 percent. That seems to me pretty high if you think that the label is being followed.

DR. ELLIS: Well, that is a qualitative statement, I take your point. You know, we think--I don't know--again that is a qualitative statement to determine whether 10 percent is too high or too low. I can tell you that of the people who were at the time that we asked the question under 2 years old, so I take your point that there is a 6-month variation in here, but in that 7 percent of children, in 81 percent of those children, the family had discussed it with a doctor, had discussed the use of hydrocortisone with a doctor, so that is somewhat reassuring to me on that point.

DR. WOOD: And more than 20 percent were under 3, so again adding 6 months, we are well over that. That is a pretty high number it seems to me, wouldn't you think?

DR. ELLIS: You are assuming now that everybody who is less than 4 is less than 2.

DR. WOOD: I am looking at your slide, and if you put in 3, the vertical line from 3 is above 20 percent, and that is not adding in the 6 month issue. That seems to me pretty high. Anyway, okay.

DR. ELLIS: When you said 10 percent, I would go with you on 10 percent. I think 20 percent is tipping it the other direction.

DR. WOOD: The slide shows under 3 is over 20 percent without making any adjustment.

DR. ELLIS: Right, but the labeling says under 2.

DR. WOOD: I understand, but I doubt that there is a huge difference between a 2-year-old and a 3-year-old that would give us that. I mean that says that almost 25 percent of the product is being

used in under 3-year-olds. That is pretty scary.

Okay. Any other questions? Charley.

DR. GANLEY: Just to follow up on your point, Alastair, I think it is important to understand that in that case, 81 percent talked to a physician or were guided by a physician. I think one of the difficulties that we have in looking at data like this is when people fall outside the labeling, well, why did they do that, and we often don't understand that.

It is very legitimate to talk to a physician, in fact, there is 3 or 4 warnings about talking to a pharmacist, physician, or someone else either before taking it or after taking, or if this happened, you should do this.

So, to suggest that because we have this data that someone is buying 3 percent or buying 7 tubes or more per year, that that is somehow bad. Well, maybe there is a physician directing them to do that.

So, I think that is what you factor into that is how does that fit into the equation here.

DR. WOOD: Okay. Dr. Mattison.

DR. MATTISON: Sort of taking a look at the data from the other end, both of your data sets

seem consistent in suggesting that 5 percent of the kids used either more than 5 ounces a year or for 7 or more days. So, from the other end of the data, that seems like a fairly large group of children that are exposed for a long period of time or to a potentially large volume or dose.

DR. WOOD: Mary.

DR. TINETTI: My question is for the two Academy people. You are operating on the assumption that the fallback is that all these families and people have access to dermatologists or allergists, and what is your stance on the 40 million people in this country who are uninsured and probably twice that are underinsured, probably will not have access to dermatologists, and how do they sort of fit into your equation of the benefits and harms for conditions such as atopic dermatitis?

DR. FONACIER: I feel that those that have mild eczema may use the 1 percent or the 0.5

percent hydrocortisone, but once you start going to moderate to severe atopic dermatitis, which is a really chronic disease, these patients should be under the care of a dermatologist or an allergist, and once the higher potency corticosteroids are put over the counter, they will access that.

DR. TINETTI: My question to you is those people who don't have the insurance to pay for dermatologists, does the Academy demand or require that dermatologists see people who aren't able to afford the care? I understand that the perfect position would be that they see a dermatologist, but for those who financially can't, what is the position of the Academy?

DR. FONACIER: Well, I represent American College of Allergy and Immunology. You are talking about the global health care issue here for people who would have the disease and have no access to care. I would think that would be a Medicaid issue of some sort. I don't know whether the American College of Allergy would have a position on that.

DR. WOOD: Dr. Santana.

DR. SANTANA: Following up on this issue that was discussed a few minutes ago, of pediatric usage and looking at numbers, I want to follow up

on that. Do any of the two consumer surveys have data that could help us investigate that the product was bought for an adult, but was used on a child, that they elected to use it on a child although the primary indication for buying it was for an adult?

MS. ELLIS: From the purchase perspective, I can tell you we don't have that in this particular data set, but it is something we could potentially follow up on and discover. The panelists, they tend to work more so on a forward going basis when they do that kind of analysis, but, yes, that is something that could ultimately be determined.

Just to be clear, just because we see 5 ounces of product going into a household with a child, doesn't necessarily mean that the child is using it. The data would indicate to us that because there is no increased consumption in a

household with a child, even though we are seeing disproportionately increased numbers of bodies in the household, we can't necessarily make the leap of faith that they are transferring product usage to a child without further analysis, a little different than what we undertook here.

DR. WOOD: Dr. Patten.

DR. PATTEN: Yes, I have a question for Valentine Ellis. This is a question about the children under 2 years of age. Do you know what percentage of all households surveyed had children under 2 years of age?

MS. ELLIS: Yes, I do know that. I have it probably in the back of the room.

DR. PATTEN: So, then we can figure out, of those at risk, shall we say, what percentage actually were treated.

DR. WOOD: No, because they are different surveys.

MS. ELLIS: I can't tell you if the child was treated. I can tell you how much product the household purchased, but I don't know from the data

set that we have who in the household the product was used on.

DR. PATTEN: So, I guess I am thinking about the other data set, the other Ellis, Dr Ellis.

DR. ELLIS: That is a very good question. I am not sure I can answer it specifically because you see we asked the adult in the family to think about the children in the family, and we asked think of the youngest child who actually used the hydrocortisone.

So, we were skewing out data purposely toward younger children, but I cannot tell you--I am sure that in the census data, there probably are these figures, but I don't know what percentage of households in the U.S. actually have a child under 2. I mean I am sure it can be looked up, but I don't know the answer.

DR. PATTEN: It would have been really good to also ask how old is the youngest child in your family, in addition to what is the youngest child that actually is treated. That way, we would

know. I mean for all we know, 100 percent of children under 2 years of age in your survey were being treated with this.

DR. ELLIS: Well, it is probably not the case, though, because we asked the person to think about the youngest child who actually was using hydrocortisone.

DR. PATTEN: Right.

DR. ELLIS: And that turned out to be, if you are interested in children under 2, it was, depending on how you averaged the data point, but least clearly, 7 percent were under 2 and were using hydrocortisone, and the family had consulted with a physician in about 80 percent of those situations.

DR. PATTEN: Right, I understand that.

DR. ELLIS: But I don't know if there were children who were 6 who were using it, and there was also a children under 2 in that family who wasn't using hydrocortisone. I mean it must be that there were such situations, but we did not ask that.

As you can imagine, with surveys, after a few questions, you are pretty tired of answering questions.

Thank you.

DR. WOOD: We have spent an hour on the public comment period. I would like to thank the public speakers for their time and their attention to our questions.

Let's move on to the discussion of the questions and the Committee discussion.

Jack.

Questions to the Committee and Committee Discussion

DR. FINCHAM: Alastair, over the break at noon, I did as much as I could to find out what the environment is elsewhere, and I could only have time to do Canada, the UK, Australia, and New Zealand as far as what products are available.

As far as I could tell, the only over-the-counter product in the class that is available is hydrocortisone. For example, in New Zealand, there is a limit on half a percent strength of hydrocortisone in a 30 gram or less

container. There is nasal fluticasone available, but it is not topical, and it is in a class, at least in New Zealand, there is 4 classes of drugs.

There is prescription, pharmacist only, pharmacy only, and general sale, and it is for pharmacy only, so it is just like it is in the United States, but none of the other more potent agents that could determine were available over-the-counter anywhere else, at least in those.

DR. WOOD: So, none of these are available in the UK or Canada either. Okay, good. Dr. Nelson.

DR. NELSON: My impression of a lot of the questions that we were asking our public speakers, which are difficult to answer, and I am trying to get a handle on this, is what is the population exposure for this product, and if that is high, and I am getting numbers that are in the million, you know, taking the number of households, you assume 2 adults per household, which I realize is probably not correct, et cetera, you get a big number, and then the answer to the 10 percent question is 10

percent of a big number is a big number, too.

So, I guess I would say I am not terribly reassured by the fact that 90 percent might be using it on label, and even if the labeling needs to be improved, frankly, I find it confusing as a physician to keep track as a non-dermatologist of all of these different concentrations and what I should or shouldn't use, because I can prescribe it to myself, which I sometimes do, and it takes me a long time to figure out what to do.

The thought of someone going up to a countertop without my training and figuring it out is a little bit beyond me absent better labeling. I guess that's an editorial comment, but I guess the 10 percent sounds to me like a big number, as well. I share your concern on that, that I heard earlier.

DR. WOOD: Mike.

DR. ALFANO: I apologize, Alastair, for not bringing this up this morning, but I actually didn't learn it until the lunch break. In the charge to the Committee, the Agency indicated that

companies are potentially proffering more potent corticosteroids to go over-the-counter. In my mind, that said this could potentially be revolutionary, I have got Class III in my mind, I don't really know.

But at the break, I learned that one of them is actually a Class VI, which is classified as mild, so that leads to the following question. In the AERS data that was presented by Dr. Cook, I understand there was a meeting in October of 2003, at which Dr. Karowski reviewed the AERS data by class, and in October of 2003, there was not a single serious adverse event leading to Class VI corticosteroid, and my question is has that changed in the year and a half since.

DR. KAROWSKI: In our update, we didn't find any of our additional cases had involved agents that were--

DR. WOOD: Could you identify yourself for the transcriptionist.

DR. KAROWSKI: I am sorry. Claudia Karowski with the Division of Drug Risk Evaluation

in the Office of Drug Safety. So, even in the adult patients, they were all with the more potent corticosteroids. There was one case with Aclovate, but that was also used in combination with another topical steroid.

DR. ALFANO: Thank you.

DR. WOOD: Frank.

DR. DAVIDOFF: I am having some extrapolation problems here. One revolves around the Dr. Ellis study, which I am having difficulty extrapolating from his data to the general population since he really only sampled 3 percent of his potential population, so I think it is a bit of a stretch to generalize his conclusions to the rest of the population.

In effect, that study doesn't help me understand the appropriateness of use of hydrocortisone more generally, but that consideration is really secondary to my other concern, which is about what indications are being considered for the high potency steroids if they were to go over-the-counter.

Hydrocortisone is clearly being used or is approved under the monograph for--or perhaps NDA, whatever--as an acute, purely symptomatic use, but

it sounds to me as though the high-potency steroids, if they were to go over-the-counter, would be labeled and approved for more chronic use for actual therapy.

Maybe I am misunderstanding the issue, but we haven't heard a lot about what the indications would be or what the labeling would be, and it seems to me to try to extrapolate from hydrocortisone with its very limited intention for us to the high-potency steroids, which are not only a different pharmacological class, but a whole different medical class, I am having great difficulty deciding how to extrapolate from one to the other.

Could somebody perhaps let us know what is being requested or what is the intention in terms of the prescribed indications and duration of therapy?

DR. GANLEY: I think there was no specific

indications other than what is already available for hydrocortisone, and that is not atypical. I don't think it's any different than when other drugs come over-the-counter. If there is a heartburn indication when the H2 blockers came over-the-counter, they pretty much got the same labeling that a monograph antacid treatment received.

So, I think if that is as holdup, you ought to put it into that context. I think the one thing that when you do look at the current labeling, where it has conditions that are chronic conditions, it almost is encouraging some people to do that, and I think that is a valid thing that we would have to look at if we were going to put more potent products on the market, because it does have the term psoriasis and things like that.

DR. DAVIDOFF: But if I may follow up on that, it sounds like, then, that what is being proposed is to go after a flea with an elephant gun. I mean to relieve an itch with a high-potency steroid, I don't understand what the request is.

DR. GANLEY: Let me just challenge you on that a little bit, and I think you are taking away from people, allowing people to make decisions. If

someone goes out and has a case of poison ivy, and with all due respect to the dermatologists, it is not easy to get an appointment with you folks. In personal experience, it's at least a 3-month wait for family members.

But if someone chooses to use a topical over-the-counter product, and they choose hydrocortisone, or if they choose a more potent, should they not be allowed to make that choice? If it doesn't work, they are not likely to purchase it again. If it does work, they will have a future reference that this worked the last time I had poison ivy. You are not allowing them to make that decision.

That is why I have a difficulty. We have all these other products out there where there is probably 6 or 8 antihistamines over-the-counter, but we don't have the same questions about those. So, I am having a very difficult time understanding

that part of the equation as to why should someone not be allowed to make that choice.

DR. DAVIDOFF: But I think, if I may, the reason is that these--possibly--is that these are very potent, potentially very toxic drugs. It is not the same as just buying hydrocortisone.

DR. GANLEY: Again, I think the issue here was the safety of it. We recognize that these more potent products present more--you know, they could lead to bigger problems. Otherwise, we would have just been putting these out there, and one of the speakers who suggested that we are rushing to a decision here, we haven't had one out on the market in the last 20 years, and I am very encouraged that we are actually--

DR. WOOD: We are rushing to a decision here, we have planes to catch.

DR. GANLEY: Yes.

DR. WOOD: I would remind you, though, Charley, that, you know, I seem to recall the antihistamine meeting, and the same cast of characters showed up to tell us we shouldn't do

that as well. Isn't that right? Okay.

Jon.

DR. WILKIN: It is a fine point, but when we are talking about more potent, I think we at FDA are talking more potent than the currently approved OTS hydrocortisone products. We are not thinking about the more potent of all the current Rx products.

DR. WOOD: Dr. Epps.

DR. EPPS: I am going to comment and then I have a question. One thing that is rather second nature to a lot of dermatologists, but not necessarily to others, is the classes of topical steroids, even within hydrocortisone can be very different. There is hydrocortisone acetate, butyrate and valerate, and they can vary from Class IV to Class VII, so some are prescription, some are not prescription, and just as several of our speakers have said, some people confuse the percentage as being their strength. Some people think hydrocortisone valerate 0.2 percent is weaker than hydrocortisone 2.5 percent, when that is not,

in fact, the case.

There is some confusion out there, and different medications are put on the incorrect areas, which would be my concern as a pediatric dermatologist who certainly defend for the little people who cannot vote and cannot speak for themselves.

As far as application, of course, the ones who are getting the diaper rashes under 2, and, of course, there are some seniors and some nursing home patients that we become concerned about as being applied on a moist area under occlusion in the diaper, and that is where your absorption occurs, that is where the side effects occur, whether it be stria or telangiectasias or absorption, but that is where the dermatitis occurs.

That is one major concern that we are having, also people under 2 cannot express to you that they feel bad, that they feel fatigued, that they are having side effects that you may be experiencing from HPA axis for an older person or

child can do that.

One question someone asked, who treats the people if you don't have a dermatologist, people in emergency rooms, doctors treat them, pediatricians, family practitioners, nurse practitioners. They are often the first line, and as a pediatric dermatologist, if things don't respond, they end up in my office.

Is there any data--I guess my question--at other meetings, they have had express script data regarding a number of steroid prescriptions and ages for particular steroids, is any of that data available? Maybe that would help some people who have questions about how many prescriptions are written, but there has been data presented previously. I don't know if any of that is handy.

DR. WOOD: While somebody is looking for that, Dr. Wilkerson.

DR. WILKERSON: A couple of points of clarification from the Agency. Are we--or Mr. Chairman--are we actually talking about, are we deciding today that 1 percent hydrocortisone is

safe?

DR. WOOD: No. At least my impression is that what we are deciding here is the questions that are listed on the table, which is focused on what one would need to do to demonstrate that a future application by a sponsor that their drug was safe to go over-the-counter.

DR. WILKERSON: But by extrapolation, if one assumes we are making an assumption in the room that 1 percent hydrocortisone is safe, has it been subjected to the same criteria that we are now being asked to determine if these are appropriate criteria.

I can almost bet you that if I cover your body with 1 percent hydrocortisone cream twice a day for the next two weeks, I bet I can suppress your HPA axis unless somebody has evidence to the contrary, my point is I have not seen that presented today in terms of what is--we are blanket approving or passing on 1 percent hydrocortisone in any quantity to be safe, and that just doesn't pass the smell test, and if that doesn't pass the smell

test, then, why do we go on to more potent topical steroids of which we don't have a metric that we even know the validation of right now. If we don't know the validation, the metric of 1 percent hydrocortisone, what is the--

DR. KOENIG: I have two large boxes of data from the meetings regarding the 1 percent hydrocortisone, and the amended TFM that came out in 1990 addressed that specifically. I don't know if I included that in the background package, I guess not, but there was extensive data and literature reviews, and it was determined to be safe and effective by FDA.

DR. WILKERSON: In what quantities and what ages and what application rates?

DR. KOENIG: Well, it's OTC, so it follows the labeling that is in the monograph. That would be children over 2, and it is restricted to people over the age of 2 years old and no more than 3 to 4 times a day.

DR. WILKERSON: By these questions, we are being asked to determine what is an acceptable

level of HPA axis suppression, which is directly related to the volume, quantity, condition of the patient in whom it is being applied to. How can we do that if we don't even have a standard for the--

DR. WOOD: Let me try and focus the question. I think the question you are asking is has there been HPA axis suppression tests for topical hydrocortisone, right?

DR. WILKERSON: Right, and in what quantities.

DR. WOOD: Let's hear if there is an answer. Do we have an answer to that in the two boxes of data?

DR. KOENIG: We have HPA axis suppression tests with 1 percent showing no evidence of suppression using the ACTH stim test, actually, cosyntropin.

DR. WILKERSON: But what quantity, what percent body surface area, what age groups, all those things?

DR. KOENIG: It varies. The ones that I showed were all in children ranging in age from I

guess 2, 2.5 year mean, median 2.5 years up to I think 14, and the body surface areas ranged in the five studies I presented from I think the smallest was about 30 percent up to over 50 percent of body surface area.

DR. WILKERSON: Okay. Well, I mean that is a start for our metric then.

DR. WOOD: So, the answer to the question is yes, there have been studies, and, no, they didn't show HPA suppression.

DR. KOENIG: They have, right.

DR. WOOD: Any other questions? Yes.

DR. RAIMER: Just a comment. If the FDA is looking at putting Class VI steroids over-the-counter, I just want to remind folks that our ability to class steroids is so crude still. I mean what we do is basically the vasoconstrictor assay, which is running the cream on the skin and then coming back and measuring how big an area of blanching you get.

That is the best we have, and that is terribly crude. We have already seen today that

something that is considered a Class V, which is still considered really fairly mild, caused HPA suppression in 73 percent of older children, not even younger children.

So, I think we have to be careful at being too confident that things that are Class VI really all that mild. We just don't have a good way to actually classify steroids, and it's according to strength at this point in time.

DR. WOOD: Dr. Skinner.

DR. SKINNER: I think in the idea of can the public diagnose and treat themselves with strong topical steroids, you have to look at Lotrisone, which was kind of promoted as is it fungus, is it dermatitis, who cares, you know, this will take care of it.

So, how well did the family practice doctors and internists do with that? I know dermatologists have seen a whole lot problems with that, African-American babies that had white diaper areas, stria, things like that, so this is doctors not being able to do it too well, so how well in

the next step can the public do?

DR. WOOD: Dr. Nelson.

DR. NELSON: I guess I just want to keep two questions distinct in my mind. One is whether there is serious adverse events when used within the label that might be considered for over-the-counter and limiting similar to hydrocortisone versus what is the risk when you increase the potency of the particular medication you use for that 10 percent who is not using it within the confines of that label.

All the data we saw this morning is presented in a way that would not be labeled for over-the-counter use. It is 2 to 3 weeks, et cetera. To some extent, that is a question that we have not been presented any data to be able to answer, because none of the studies of the more potent agents have been done on 7 days or less of treatment, so we are trying to extrapolate on top of extrapolations, which is fairly difficult.

DR. WOOD: Right. The issue here in that context is there an over-the-counter indication in

which there would be a reasonable assumption that people will not follow the label precisely. I mean maybe they will, and that is different from an Rx situation. So, that is part of the context for this discussion, I think.

Dr. Bigby.

DR. BIGBY: I would just like to make two comments and sort of expand on what Dr. Raimer said. The first one is about this sort of Stoughton vasoconstrictor assay. This test has really not been without controversy. In fact, it was the subject of an FDA panel regarding generic topical corticosteroids, and Stoughton published an article claiming that generics were not biologically equivalent to enervators based on the vasoconstrictor assay.

The fallout from that paper was that if you take the same product and test it on different people on different days, you will often get a very different assay result and as much as a two-class difference in the product. So, I think it really is an inexact thing.

If you look at the table that was provided in Tab 1, in general, ointments are more potent than creams, which are more potent than lotions,

but Aristocort Cream, which is 0.1 percent triamcinolone is listed as being a Class VI, whereas, Kenalog Lotion, same product as a lotion, which I think all of us would agree should be less potent, is classified as a Class V, and there are many, many examples of this sort of thing.

The second one was, you know, I am very familiar with Rule of 3, so if there are no adverse events in 20 patients, you put 3 over the number exposed, and that will give you the upper 95 percent confidence interval.

The other side of that is, though, if you have a very small study and you do detect a signal, it usually implies that there are, in fact, going to be a significant number of adverse events, and if you look at what was provided in Tab 9, in that what was called Group 2 was included betamethasone valerate at 0.025 percent and fluocinolone at 0.006 percent, and 1 out of the 17 of these people tested

had HPA axis suppression, so already in the lowest group that we can consider, you already have a signal that you have HPA axis suppression.

So, I mean I think that the onus really is on showing some really good proof that these things are safe, not at what level we need to detect a signal, because we have already detected a signal.

DR. WOOD: Dr. Ringel.

DR. RINGEL: Two comments. The first is that we have talked about vehicles, and one thing that is important to remember is that the monograph process, the way it was described to me today, it is the drug that will be approved, and not the vehicle, so if we approve betamethasone valerate, we don't know what kind of enhanced vehicle the generic companies will compound it in, and it feels as if we would lose control over the product that is being used by our patients.

DR. WOOD: In fairness, though, and I don't want to cut you off here, but that is not what we are approving today. I mean we are addressing issues of HPA axis suppression. Am I

right, Charley?

DR. GANLEY: It's that, but these are products that are marketed under NDAs, and they would be marketed under NDAs, so their formulations are already set, whether it is an NDA or an ANDA.

DR. WOOD: You mean they can't come in with--

DR. GANLEY: They can't go into the monograph.

DR. RINGEL: Okay.

DR. GANLEY: They would remain NDAs, they would still have the same reporting requirements as all the others. Whatever hurdles you would set today with regard to safety would apply to a company coming in with a specific product saying we want this to go OTC, whether it's a Class I or a Class 6, but this is the hurdles that you have to get over, that's it.

So, I don't want you to get locked up in all the formulation issues, because that, I don't know if it is an issue right now.

DR. WOOD: Do you want to respond to this,

John?

DR. WILKIN: If I could just comment on the vaso, two members of the panel mentioned the vasoconstrictor assay. I can say on the new drug side, and that is what we are talking about today, is that we have never used vasoconstrictor data as a surrogate for efficacy or safety, and that is really not part of that flow chart that was presented to this group.

DR. WOOD: Charley again.

DR. GANLEY: There was a question about use of prescription products, and we do have some claims information.

DR. RINGEL: I did have one other quick comment.

DR. WOOD: Go on and finish.

DR. RINGEL: I think that generalizing about the use of other corticosteroids based on hydrocortisone may be not very accurate either. I think one reason that people don't use much hydrocortisone frankly is it doesn't work very well. I think they stop it because it is not doing

anything in many cases.

I have no trouble getting my psoriatic patients to stop using hydrocortisone. I have enormous trouble getting my psoriatic patients to stop using clobetasol, because one they get their hands on it, and they realize that it's doing something, they don't want to let go. I think the better the product, the more abuse you are going to see.

DR. WOOD: Go ahead.

DR. MOENY: David Moeny from the Office of Drug Safety. I did conduct an analysis of advanced PCS claims data. This would just cover prescription products, it doesn't cover very much OTC products.

We did find that the younger the patient, the lower the potency, and the smaller the tube that is dispensed to the patient. For instance, basically, under age 16, greater than 80, 85 percent were dispensed of a low to medium potency product at 30 grams or less. Use is kind of typically where you would expect to see that in

that age group.

Does that answer the question?

DR. WOOD: It was Dr. Nelson who asked the question, right?

DR. NELSON: What are the numbers, the total numbers of prescriptions out of curiosity?

DR. MOENY: Prescription claims per year were over 4 million.

DR. WOOD: Dr. Whitmore.

DR. WHITMORE: I think what disturbs me about this is that the first consideration probably should be the ends that we are coming to, and the ends being patients being able to correctly diagnose and treat themselves.

If we could establish that that is going to be the case, then, I think you can step back and look at the other issues, but until you can establish that, I don't think you can tell pharmaceuticals that they have any grounds to stand on in terms of getting these over-the-counter.

Surely, there are patients who know exactly what they have and they are patients who

have already seen a dermatologist, been taught how to use things, who could efficiently probably get over-the-counter products like this, but you are going to have a great number of patients who have no idea what they are doing in terms of they don't know what their skin disease is. It may be a skin cancer, it may be a fungus, it may be, you know, whatever, who are going to be using these products, and until somebody can establish for us that patients can diagnose themselves, I would say that the currently prescription products should never go over-the-counter.

DR. WOOD: Are there any new points that any Committee members want to bring up, that have not been ventilated before? Okay.

In that case, let's move on, in the absence of hearing any, let's move on to the questions, and there is a preamble which I will read.

Companies are interested in the potential marketing of OTC topical corticosteroids that are more potent than the hydrocortisone products

currently on the market.

Current OTC corticosteroids labeling limits use to approximately 7 days, however, a minority of consumers may exceed the labeled duration. Safety concerns include systemic effects and local effects. Of the systemic effects, potential adrenal suppression is the most concerning followed by Cushing-like effects.

Please discuss the questions below in regards to developing a possible paradigm to evaluate the safety of topical corticosteroid products, and if I can find it again, Charley or somebody passed out the sheet, which I can't lay my hands on right now, but it is here, the flow diagram, yes, this one, the flow diagram that Charley passed out.

I guess that is sort of is the basis for the decisionmaking process.

So, let's go to the first question.

If any subject has HPA axis suppression with ACTH testing under maximal use conditions, does that preclude OTC marketing of that

dermatologic topical corticosteroid product?

Is there discussion on this? Yes.

DR. NELSON: I wouldn't mind a clarification of what the phrase "maximal use conditions" means. Is that use as anticipated under what might be an OTC label, or is that misuse as anticipated within the population who would be potentially buying this off of the counter?

DR. WOOD: Well, my view would be the latter, but I think the FDA may be reluctant to say that.

DR. WILKIN: The idea is maybe rather than maximal use, a provocative test to see if under extreme conditions, it could occur.

DR. WOOD: Go ahead.

DR. BIGBY: I would just like to remind the panel that the test being used to detect HPA axis suppression has a sensitivity of 70 percent, so, even if the number is zero, you are missing or you are potentially missing 30 percent of people who are suppressed.

DR. WOOD: So, what you would suggest for

the sensitivity?

DR. BIGBY: My whole suggestion has been stated, I mean that is the test that we have, and that is the question we are being asked, but it has a sensitivity of 70 percent.

DR. WOOD: Well, there is the Tinetti modification of the test, widely described in the last two hours. I mean we could increase the sensitivity by going up in the requirement.

I mean I don't think we want to do that here, because none of us have a sense of where that number comes, but what Mary--I don't want to put words in Mary's mouth--but I think what Mary was suggesting was that you would increase the height of the bar and that that would bring that sensitivity up substantially, and without knowing where that number is, you would be reluctant to set it, but that is probably there in data somewhere.

Wayne.

DR. SNODGRASS: This Question 1, the way I am reading it is I am being asked to comment on sort of a risk issue, a risk consideration, and the

way it is worded is if any subject has--and it goes on--I am looking for any subject out of what number tested.

DR. WOOD: That's Question 2.

DR. SNODGRASS: All right.

DR. WOOD: So, the first one is an absolute, and then the second one is out of what sample size. That is my reading of it, right? Okay.

Yes, Ben.

DR. CLYBURN: The only thing I was going to comment is that even with a relatively insensitive test, and for secondary adrenal insufficiency, I think the numbers were 57 to 60 percent, there is still significant HPA suppression in the tests that we have already seen presented today, so we do have the smoke, so to speak.

DR. WOOD: Dr. Wilkerson.

DR. WILKERSON: I went back to my point, what is this maximal, I mean are we going to apply this to 60 percent body surface area, are we going to apply it to the back of the hand? I mean that

is what is going to determine for most of these drugs whether they pass the test or not.

If I put clobetasol on the back of my hand only, I am probably not going to suppress my HPA axis, but if I put it over 30 percent of my body surface, I am probably going to.

DR. GANLEY: The question was just answered. It is following the extreme provocative test that is already required for prescriptions, where it is two weeks and covering 30 percent or more, Jon, of the body? That is the extreme.

DR. WILKERSON: Okay.

DR. WILKIN: And I should add "involved skin," in other words, not normal skin, but skin where the area has been compromised.

DR. WILKERSON: So, 30 percent involved twice a day involved area.

DR. WILKIN: Well, maximal use, if the corticosteroid is actually approved for 3 times a day or 4 times a day, it would be at the maximum frequency, maximum duration, maximum amount to be applied, and the body surface area of approximately

30 or 35 is the minimum.

DR. WILKERSON: I think that is a reasonable pattern of potential overuse for over-the-counter.

DR. WOOD: Any other comments, questions?

No. Okay. Then, let's vote on this. If any subject has HPA axis suppression, and does that preclude marketing, so I guess if the answer is Yes, that means that precludes marketing. Right? Okay.

Let's start with Jack.

DR. FINCHAM: No.

DR. RAIMER: Yes.

DR. TINETTI: No.

DR. RINGEL: Yes.

DR. WHITMORE: No.

DR. CLYBURN: No.

DR. SANTANA: Yes.

DR. SKINNER: Yes.

DR. PATTEN: Yes.

DR. TEN HAVE: Yes.

DR. DAVIDOFF: No.

DR. BIGBY: Yes.

DR. WOOD: Yes.

DR. NELSON: Yes.

DR. SNODGRASS: Yes.

DR. MATTISON: Yes.

DR. SCHMIDT: Yes.

DR. EPPS: Yes.

DR. CHESNEY: Yes.

DR. TAYLOR: Yes.

DR. WILKERSON: Yes.

DR. STRATAKIS: Yes.

DR. BLASCHKE: Yes.

DR. WOOD: Okay. Four No and the rest are Yes.

The next question addresses the issue we just discussed. It is an attempt to sort of address I guess from two directions, but not including Dr. Bigby's although I think we probably would want to add--

DR. ROSEBRAUGH: Alastair, the people that said No, it might be of interest to the Agency to know, you know, one of the ways to look at how to

draw the bar on safety was HPA axis suppression, so the people that said No, I would be interested to know how they would draw the bar then to decide what potency, what strength that they would allow over-the-counter and what sort of safety thing they want to look at.

DR. WOOD: So the people who voted No, we are interested in knowing what, if anything I guess, you would use to distinguish it, and we will start, and I am going around the room. Let's take in the order they are on this list.

Frank.

DR. DAVIDOFF: Well, as I understood the question, it was whether there is the existence of any potential to preclude its use over-the-counter.

DR. WOOD: Not any potential.

DR. DAVIDOFF: Potential, right.

DR. WOOD: No, not potential, any actual.

DR. DAVIDOFF: Potential or actual, it seems to me.

DR. WOOD: The question is actual, it is not potential.

DR. DAVIDOFF: Okay. The existence of actual could be one case out of a million. That, to me, is not an appropriate--

DR. WOOD: That is Question 2.

DR. ROSEBRAUGH: Let me clarify it. If we do sort of something similar to what they do on the prescription side, your second question is how many people do you test, but we have it number of subjects that we test, we run HPA suppression tests like we typically do on the prescription side. If any of those people suppress, does that mean that it would not be a product that could go OTC?

That is the question, and so the people that said Yes, that means that that is where they draw the bar at. So, the people that said No, I just wonder how you draw the bar.

DR. DAVIDOFF: Well, that's the next question, I haven't gotten to that. All I was trying to say is--

DR. WOOD: Frank, I think that is not the next question. I mean the next question might be answered by the Committee that they only needed to

do 10 people, for example. I am not suggesting that will be, but if that was the question and you found one, your answer was that that would not preclude its marketing.

DR. CLYBURN: I was going to say, I went the same line of thought that if any subject, so theoretically, there could be one subject who would be suppressed, and you would look at it out of a large number, and say that that was probably an acceptable rate, whereas, I could have easily gone the other way had I said even the change here, does the potential for suppression, it depends on how much potential. That was in our original packet, the original question.

DR. ROSEBRAUGH: Well, let me just try to clarify for the panel then. A sponsor brings a package in to us. They have run the test however we decide by 2, it's Question 2, however many numbers we say you need to run it, and one of them have suppressed on that test, does that mean that that drug should not go OTC. That is what the question is supposed to mean.

DR. DAVIDOFF: May I finish my answer, because I haven't had a chance? I have been cut off four times.

Even if they brought in data showing zero, and their sample was 100, we still know that there is the potential. The point that I am trying to make about why I voted was that there are any number of drugs that are on the market over-the-counter including things like acetaminophen, which can rot your liver, and does regularly in this country. That does not preclude its utility and its acceptance for use over-the-counter.

Using the same reasoning, I couldn't a priori vote that the actual occurrence of HPA suppression, on its own merits, would be enough, by itself, to preclude over-the-counter marketing.

DR. WHITMORE: I second what Dr. Davidoff said, and there are other reasons why I would not let it go over-the-counter, but not this.

DR. WOOD: Say that again.

DR. WHITMORE: I second what Dr. Davidoff

said, and if there were 1 in 100 or even zero in a 100, well, let's say a positive, there was 1 positive, because you said any positive, so if there were any positives, 1 in 50 even, that would not be my reason for not allowing this to go over-the-counter. I have other reasons, but not that.

DR. WOOD: Ben.

DR. CLYBURN: Just echoing what I said before on what Dr. Davidoff said.

DR. WOOD: Mary.

DR. TINETTI: I agree with Dr. Davidoff.

DR. WOOD: Jack.

DR. FINCHAM: I think I am the fourth and final one.

DR. WOOD: You are the fifth and final one now that we--

DR. FINCHAM: That's a great question, and I guess I answered it in the context that Dr. Davidoff talked about relative to other products that are available over-the-counter. There are geriatric patients that have GI bleeds that die

weekly because of NSAID use or aspirin use, so I think it is a risk-benefit assessment.

That is a long answer to a short question, but that is what I was looking at was in the context of everything else that's available.

DR. WOOD: Then, let's go to Question 2. The number of subjects evaluated provides for the confidence in ruling out HPA axis suppression at a desired upper limit. With a 95 confidence limit, what is the greatest rate of HPA axis suppression to be ruled out?

The question really here relates to the sample size, and I guess we could add to that, if Dr. Bigby agrees, and Mary, that part of that could also include whether there should be some increased sensitivity for the test. Is that reasonable, Mary? Okay. So, we would review this with an increased sensitivity. Okay.

Discussion?

DR. TINETTI: Are we limited to the numbers on this?

DR. WOOD: I don't see why we should be.

Dr. Nelson.

DR. NELSON: A question for the endocrinologists perhaps. Of those individuals who

would be suppressed, what is the percent risk of sudden death in those individuals? We talked about that is what we fear, but if you took 100 patients who were suppressed from whatever steroid administration, how many of them would necessarily suffer that fate?

DR. STRATAKIS: I wouldn't have the answer to this question, because when we talk about suppression here, we define it by the criterion of 18, and for the people that have died in emergency rooms and under other circumstances of stress, that were insufficient, nobody has been able to go back and regulate the sudden death with the actual stimulated peak values.

DR. WOOD: I am not sure that they are using this just for sudden death. I mean they are using this as a surrogate for other evidence of corticosteroid--

DR. STRATAKIS: Well, he is asking

specifically about that.

DR. WOOD: I understand, but my sense is--and this can be addressed to the FDA--that we are using HPA suppression as a means, a quality to measure of systemic corticosteroid excess, you know, Cushing's, glucose intolerance that Dr. Taylor talked about, and all the other things, and that is one way to get at that.

DR. STRATAKIS: That is Question No. 3.

DR. GANLEY: I guess there is a sense that of the people who come to an emergency room or are admitted to a hospital with the diagnosis of adrenal suppression or symptomatic because they are on known steroids, what percentage of them die? That is one question.

But again I think the thing is that apparently there is a lot of people out there that are on chronic steroids topically and orally that are just going along and perking along and do fine until they get into a stress situation, so what is the risk of getting into a stress situation, too? It is fraction of a fraction.

DR. WOOD: But it is not possible to answer that question.

DR. STRATAKIS: Except that perhaps the

best way to answer that question would be--and I just thought about something, and I used the example before--of patients with panhypopituitarism who, by definition, have cortisol responses to ACTH of zero.

So, these patients, if you look at the studies I mentioned before, you look at lifetime risk of death, as I mentioned before, death from adrenal cortical insufficiency was the number one cause of death in these patients.

DR. WOOD: And these are patients who carry the diagnosis with them at all times.

DR. STRATAKIS: Correct. This is lifetime risk of a patient that has a cortisol value of zero, an endogenous cortisol value of zero in response of ACTH, lifetime risk of sudden death being the highest reason for mortality in these patients.

DR. WOOD: But I mean most of these

patients have a bracelet, and so on. These are different from people who are taking--

DR. STRATAKIS: Correct. So, there are factors, I guess, that would increase mortality in our population.

DR. WOOD: Dr. Epps.

DR. EPPS: Just a comment, I guess. Hydrocortisone has been around for 50 years, we have good experience with that. That is all the atopics had for many, many years. Some of the newer ones have been around 20 years, perhaps 10 years. We don't have as much information about them on a large area, but there is a large experience with hydrocortisone.

We don't know about the newer ones, and that is really what we are talking about, the ones we really don't know.

DR. WOOD: Any other comments on this question? Yes, Dr. Bigby.

DR. BIGBY: I actually apologize for keeping going back to this. If roughly 30 percent of the patients who have this test may be giving

false negative numbers, the actual numbers of the upper adverse event rate in this table are actually 10 times what is printed here.

DR. EPPS: I agree with what he says and also that suppression is under-recognized and under-diagnosed, so that some of those cases are being missed, too, you know, the patient is not getting better, we don't really know why, on and on. I mean this would be more of an acute situation rather than probably in the outpatient situation, but that is true.

DR. GANLEY: Could I just get clarification? I am not sure what you are saying is 10 times. If you have 10 people and it's zero, 10 times 26 is not 260 percent. I don't know what the number is, but I don't know if it's 10 times.

DR. BIGBY: That is true for the very low numbers, but if you go to 100, for example, you know, it is 3 divided by 100 or 3 percent, but there may be 30 people who gave you a false negative result, so it is really 33 out of 100, not 3 out of 100.

DR. GANLEY: But you could increase your sample size by a certain amount.

DR. WOOD: One.

DR. TINETTI: It would only be one extra, so it would be 4 percent rather than 3 percent.

DR. WOOD: It would be 30 percent of 3, not 30 percent of 100. So, it would be 4, not 3, but the point is still the same.

Dr. Skinner.

DR. SKINNER: Until this morning I really had never thought about the idea of people rolling into trauma units of emergency rooms on topical steroids and dying because of that. So, we don't know what that problem is, how big it is. Now, we are talking about multiplying that problem by something if potent topical steroids go over-the-counter.

It is hard to make these decisions not knowing what that multiplier is. If it's no problem, then, multiplying it probably isn't a problem. If it's a pretty good problem, then, you know. I guess that data is never going to be

known, but I think that certainly weighs in how you think about this.

DR. WOOD: Dr. Nelson.

DR. NELSON: My concern here is and I don't fully understand how you monitor the safety of over-the-counter drugs. Certainly, the Adverse Event Reporting System--

DR. WOOD: This is not to monitor the safety, this is to determine--

DR. NELSON: I understand that, but there is a relationship between how many people you put in the initial trials versus the ultimate safety of the drug. We have taken things off the market because things have occurred at a much lower incidence than 0.3 percent in the first 1,000.

So, I am not confident that what we do for drug approvals in non-over-the-counters in fact is sufficient, and I find myself going back and forth around that issue, you know, how much do you do in the first part, then, what do you do post-marketing to monitor it, and my confidence would be assured if I thought we had a decent post-marketing system.

Otherwise, you end up increasing the pre-marketing number quite high to where you keep things off of the market.

That is where I find it a little bit difficult to put a number on a pre-marketing study.

DR. GANLEY: For these drugs, the reporting requirements are no different than prescription, so the question is, is the reporting different for OTCs versus prescription. I mean we know the prescription adverse events are not reported as well as we would like.

DR. NELSON: That answer is both are poor.

DR. GANLEY: Both are poor, but there is mandatory requirements to reporting from a company's point of view for an NDA product.

DR. WOOD: But OTC is unlikely to be better.

DR. GANLEY: I would agree with that.

DR. WOOD: Mike.

DR. ALFANO: This will be more meaningful to the people from NDAC who were here yesterday, because yesterday we were dealing with a surrogate

test also, and we killed it basically because there was no link to a specific meaningful clinical endpoint.

So, we have another surrogate test for adrenal sufficiency, the HPA suppression test today, and we are embracing it, and yet it is not linked, as we have learned, to a specific clinical endpoint. Certainly, there is a suspicion as there was yesterday that there is a linkage there, but there is no way to directly link it.

So, that concerns me a bit that for some reason, a very analogous situation is viewed differently today than it was yesterday. Then, if you look at the AERS database, and for Class VI and VII, real world experience, there is not a single serious adverse event reported in the entire database of several million reports.

So, there seems to be an inconsistency in the way at least NDAC has acted over the last two days. Admittedly, different situations, different tests, different degrees of potential negative outcomes, but in principle, we are valuing this

particular test higher than we valued yesterday's.

DR. WOOD: I am not sure I agree. I mean this is like a blood culture for yesterday's analogy. I mean this is a diagnostic test for a disease, and this is the diagnostic test for cortisol excess in the systemic circulation, used to diagnose Cushing's, used to diagnose HPA suppression in vivo. I mean that is different from sampling bugs on the hand.

This is the test that if you walked into a hospital in this country today, and somebody said I believe you have got adrenal suppression, the test that would be done to do that is--

DR. ALFANO: I understand the subtlety, Alastair, I really do. It is just that when pressed to define what that means in terms of severe outcomes, to suppress who is positive in this test, we have not been able to relate it to anything, and that is parallel to yesterday.

DR. WOOD: I think the question that was asked was sudden death to which it was difficult to give an answer. We know a lot about the morbidity

associated with HPA suppression and with Cushing's. I don't think these are the same at all, and I think it would be misleading if we left people with the impression the only bad thing that happens to you from HPA suppression is dying in the emergency room because somebody didn't give you steroids, I mean it is substantially worse than that.

DR. STRATAKIS: I agree. I think it is misleading to say that--I voted Yes to this, the first question because I think that there is a high risk of having patients dying in the emergency room because of adrenocortical insufficiency after they have used OTCs. I don't think that is the case. I think that the risk of that happening is extraordinarily low, but I am concerned about the patients that we are missing that have some degree of adrenocortical axis suppression, that have many other systemic effects that we cannot, or at this point we don't know how to measure them.

DR. ALFANO: Again, just trying to link to the real world, we saw 60 events in over 50 years of availability, at least of hydrocortisone, and I

don't know how many millions of doses were applied, so I am just trying to--

DR. WOOD: But we see very few events with digoxin, too.

DR. STRATAKIS: What were the 60 events?

DR. WOOD: All drugs have very small number of events in AERS, so digoxin, which is the largest cause of adverse events in hospitals, and warfarin, don't have a proportional number of events in AERS database even though, in hospital-based drug safety studies, they are the most frequent causes of adverse events.

So, I mean I think you have to be careful about it. The largest reporting rate occurs in the first few months of a drug's marketing.

Dr. Whitmore.

DR. WHITMORE: I need to preface this and again say that I am not for approval of these going OTC, but what I would say is that 20 or 30 percent of our patients who are using the higher potency steroids are having this HPA suppression, which we are not doing anything about, and hopefully, if we

are seeing them on a regular basis, which may be regular or less regular, we would pick up if they had any clinical symptoms of adrenal insufficiency.

But I would have to add to that this is happening all the time, and there is nothing that is being done about it, so I don't know if it makes it any different whether it over-the-counter or by prescription, still nothing is being done about it, and maybe we should be doing something different.

Again, I have to reiterate I don't think they should be OTC for a different reason.

DR. WOOD: That is Dr. Alfano's point, as well, actually.

Dr. Chesney.

DR. CHESNEY: In response to the AERS database, I think many physicians don't report known side effects, so they may be seeing striae and they may be seeing a lot of other things, but they wouldn't report them as an adverse event because it's a well-described complication.

So, I think the fact that there aren't many reports doesn't convince me. I think the

other thing that we have said over and over again, which is we have no idea of how many patients who are immunosuppressed because they have had topical steroids come in with sudden death, and nobody thinks to ask them, nobody looks for it, so I just wanted to make that point again.

DR. WOOD: Any other comments? All right. Are we ready to take this question?

Are we going to give an answer--I guess what we need is an answer, and Mary is not here, so maybe we can do it without having to come up with other numbers, but her question was do we have to stick to these numbers, and I guess the answer is no, but you want us to give a number, right? All right. So, pick a number.

DR. BLASCHKE: I will pick a number. I would pick 100.

DR. STRATAKIS: 1,000.

DR. WILKERSON: 1,000.

DR. TAYLOR: I would pick 100.

DR. CHESNEY: I haven't a clue how to answer this, I really don't, so I am going to say

10.

DR. EPPS: Greater than 1,000.

DR. SCHMIDT: 50.

DR. MATTISON: 1,000.

DR. SNODGRASS: 1,000.

DR. NELSON: 1,000 or greater.

DR. WOOD: 1,000.

DR. BIGBY: Can you come back to me?

DR. WOOD: No, now is your moment. Now is your moment.

DR. BIGBY: I would say greater than 1,000, and then the other thing I would say is that we already have a signal in the lowest class in drugs that we can consider, 1 out of 17, so I don't know why we are giving a number.

DR. CHESNEY: I agree. That is why I didn't know how to answer it.

DR. DAVIDOFF: I would say at least 1,000.

DR. TEN HAVE: 1,000.

DR. PATTEN: 1,000.

DR. SKINNER: 1,000.

DR. SANTANA: At least 1,000.

DR. CLYBURN: At least 1,000.

DR. WHITMORE: 100.

DR. RINGEL: I don't even want to have 3

out of 1,000 people running around with HPA suppression without any monitoring, so it is going to be greater than 1,000.

DR. TINETTI: Greater than 1,000.

DR. RAIMER: 1,000.

DR. FINCHAM: 1,000.

DR. WOOD: Let's go on to Question 3. Beyond HPA axis suppression, are there any other safety concerns that would not permit OTC marketing of a dermatologic topical corticosteroid?

I guess you would mean that in the context of the absence of HPA suppression in whatever the number was you decided on, correct? Okay.

So, what we are looking for here are safety concerns that would for some reason not have been picked up with HPA suppression in that screen.

Any comments? Yes, Dr. Nelson.

DR. NELSON: I think to bring up the growth velocity as a pediatrician. I think one of

my concerns would be if it is relatively unsupervised, the duration may exceed reasonable duration, and the issue of reversibility may not then occur.

I mean a lot of that would be reversible if you stopped it and doing it unsupervised just leaves that as an open-ended question, so growth velocity is of concern to me.

DR. WOOD: Any other comments?

DR. SCHMIDT: One of the things we haven't mentioned is we are seeing a lot of contact dermatitis from the topical steroids, and I don't know how much of a safety problem that is unless you have a severe contact dermatitis that gets infected. I am going to pass this article on from Contact Dermatitis, that it gives the percentages of the different contact dermatitis with topical corticosteroids, but that is something that I would consider is severe contact dermatitis from some of these things.

DR. WOOD: Any other comments? Yes.

DR. WILKERSON: I think from a pure public

health standpoint, the elderly population, bone mineral density loss, declining levels of vitamin D levels in the population, thinning skin, probably increased percutaneous absorption, that BMD is a significant public health concern with use of large amounts of topical steroids.

DR. SANTANA: This is my interpretation of safety in a very broad sense, but as I commented to a colleague recently, you know, the issue for me for OTC products is the ability of the individual to self-diagnose and make a diagnosis that is consistent with the indication for which they are using the product.

So, to me, it is a safety risk if people are not educated to use the product for which it is indicated, and they are buying it on their own unsupervised. To me, that is a safety risk.

DR. WOOD: Dr. Taylor.

DR. TAYLOR: I still would like to see some data on the diabetes issue and particularly those individuals who have brittle diabetes, insulin dependent.

DR. WOOD: Any other comments? Yes.

DR. MATTISON: I also have some concern about blood pressure control especially in the

context of hypertension in the context of increasing incidence of obesity in the United States. So, that is an issue that I would be concerned about.

DR. SCHMIDT: One other thing that has been mentioned is the use of concomitant nasal steroids or even oral steroids with this, you know, a potentiating effect.

DR. WOOD: Other comments? Okay. I guess that is all we need on that really. We don't need a vote, or do we want a yes/no vote? Okay. We want a yes/no vote.

So, the yes/no vote is what? Are there other safety concerns that would not permit OTC marketing of a dermatologic topical corticosteroid? In the absence of HPA axis suppression you mean, right? Okay.

DR. GANLEY: To find out just what were those concerns, so I am not sure--do you need a

vote, Jon? No.

DR. WOOD: No vote? Good.

Would labeling, for example, warnings for the systemic effects other than HPA axis suppression be an acceptable regulatory path in lieu of testing for the other systemic effects, for example, growth hormone suppression, osteoporosis?

Comments? Yes.

DR. MATTISON: I am concerned that we are good enough at risk communication to be able to effectively transmit complex information about growth or other non-HPA axis impacts to the diverse populations of parents that might be using these on their children.

So, I guess I would have to see the labels and understand how effective they were in testing before I would be willing to be comfortable with that approach.

DR. WOOD: And labeling has been extraordinarily unsuccessful in prescription drugs, at least in my view, so I am not at all confident we would be very successful.

DR. GANLEY: That is because you are dealing with a population, that is the population you are dealing with in a prescription--

DR. WOOD: I understand that. It is these damn doctors, right? Okay. Dr. Epps.

DR. EPPS: On many of the prescription drugs, there already is discussion of growth suppression on the insert. Some read it, some don't.

DR. WOOD: Dr. Whitmore.

DR. WHITMORE: I would say absolutely not in terms of relying on patients to detect these things that we have to have very sensitive testing to detect? Absolutely not.

DR. WOOD: Sorry, say that again.

DR. WHITMORE: I mean you can't bypass this by saying you are going to put in the patient information package your child may have growth suppression, watch for this. We have to use extremely sensitive testing to be able to pick up that. I mean how can you tell a parent that, to be watching for--or an adult--to be watching for

osteoporosis? Well, when they get their DEXA, they are told they have osteoporosis, they will know.

DR. WOOD: Beware of fractures, right?

DR. GANLEY: Can I just interject here? The thought process here I think was what do you do with the tests that you ask for, and we think about that all the time, does it help us make a regulatory decision.

So, let's just say for the sake of discussion that we could do growth suppression, which you have already heard would be very hard to do with the dermatologic condition.

So, then, you think about, well, if I did the test and it came out and showed growth suppression, does that mean I could convey that in the labeling with some accuracy, or does it mean that this is a no-go for this drug, because it did that.

Now, if it's just a label issue, well, I don't need the test to write a label, because I can say, and you heard the pulmonologists say, that there is a lack of certainty. They make an

assumption that there is growth suppression, so if you do make that assumption, is it okay to convey that?

Again, this is for the situation where people are misusing the product, not for the actual use of the product.

DR. WHITMORE: Well, essentially, what you would be doing is just making a disclaimer, that you may have growth suppression, you may have osteoporosis when you use this if you put that on the label.

DR. GANLEY: You already have that on the prescription labels. They don't check for osteoporosis, they don't check for growth suppression. You already have that. Are you applying a different standard, that's all.

DR. WHITMORE: Well, it seems like we are for the HPA suppression, but what I would say is maybe we should readdress that in terms of the prescription medications and what testing is required for approval of prescription topical steroids.

DR. EPPS: And the difference is the supervision that's involved, over-the-counter versus prescription. You are talking about doing

it unsupervised, over-the-counter.

DR. GANLEY: No, what we are doing is saying if you use this for extended periods of time, it could lead to these things. If you go to the store and buy a nonsteroidal anti-inflammatory, acetaminophen, aspirin, antihistamines, it has all these disclaimers on it already, if you do these bad things, so that is what we are asking here.

DR. EPPS: But even under customary, regular use, there are occasions when we are seeing suppression.

DR. WOOD: Let me try and resolve this. I think if we break the question down into two parts, it might help people to focus their discussion. The question, which maybe we went over 3 too quickly, is are there other things that would preclude the drug being marketed over-the-counter, other adverse events.

For those who felt there were not other

adverse events that would preclude the drug being marketed over-the-counter, then, would labeling be sufficient, would there be a way to label the drug to explain that carefully enough to people. Is that sort of a fair summary, Charley? Yes.

DR. GANLEY: I think so.

DR. WOOD: We didn't get on Teresa's list here growth suppression, right? All right. Does that help?

DR. WHITMORE: I guess as you are saying, we don't really have to answer No. 4 because we have already said, in No. 3, there are a host of different reasons why this shouldn't be approved based on side effects.

DR. WOOD: We didn't a host, we said four things. Actually, if there are more, Teresa is trying--

DR. WHITMORE: Oh, absolutely. I didn't speak up because I thought we had already been through all these, but all of the cutaneous side effects, telangiectasias--

DR. WOOD: Wait, wait. If there are

people who didn't get a fair hearing on 3, let's go back to that. Teresa has the following things down: diabetes, hypertension, osteoporosis, and growth suppression.

Are there other--let's be clear what we are saying--we are not asking for an encyclopedic list of every potential side effect of topical steroids here, we are asking for side effects that would preclude them being marketed, and as Charley said, there are lots of side effects associated with lots of drugs that are marketed over-the-counter including renal failure, hepatic failure, and so on.

So, we are asking for show stoppers essentially.

DR. WHITMORE: Can I continue?

DR. WOOD: Sure.

DR. WHITMORE: Increased ocular pressure, glaucoma, potentially cataracts. Other things would be steroid-induced acne, which I have seen before, with mid-potency topical steroids used for 6 months on the face, coming in with this

horrendous acne from eruption that takes months and months and months to get rid of.

I think each one of those potential systemic side effects that we have already talked about are very important, and we don't have enough data to even know how important they may be.

DR. WOOD: So, before Mike has a stroke here, how would a company perform a study that would exclude these things? I mean if we are specifying show-stopping issues, then, by definition, they would have to be looked for before the drug could go OTC.

I am not arguing with you, I am just getting a sense of where we put that bar. So, how would you, for instance--

DR. WHITMORE: Well, in terms of we were talking before about osteoporosis.

DR. WOOD: I was thinking of the acne. How would they exclude acne?

DR. WHITMORE: There definitely is--well, for one thing, those mid-potency steroids should never be used on the face, but they are.

DR. WOOD: So, that would see to be Charley's labeling issue, I guess. Do you see what I am saying? I am trying to make a distinction

between the ones that set a bar that would preclude marketing, which would require some kind of investigation first, and ones that are warnings that would require labeling, "Don't use it on the face."

DR. WHITMORE: Further investigation in terms of use on the eyelids, they could label it as such that it can't be used on the eyelids or, instead, they would have to do a study where they applied it to eyelids and come up with a number of induced increased intraocular pressure, and things like that.

I think these side effects are things that we, as dermatologists, look for every time a patient comes back, and if these things are not looked for, they are going to be missed. So, I would say--I am kind of back to that ends again--and saying that diagnosis and treatment, ongoing treatment, should not be done by a patient,

and so to give the pharmaceutical recommendation about testing is difficult.

DR. WOOD: Jon, do you want to say something?

DR. WILKIN: It might be helpful, especially as the different panel members are weighing in on this, it would be helpful to know what you do when you prescribe Class I and Class II, the really upper end potency products to your patients.

I mean do you have a scheduled time when they go to the ophthalmologist to look for eye pressure, for cataracts, you know, how often does one test glucose tolerance, checking blood pressures, things like that.

Just to remind everyone, we are not talking about Class I and Class II products imminently going over-the-counter. We are really thinking that Class VI would be the target zone of candidates, not necessarily ones that are sure to go over, so much, much less potent than the Class I/Class II, and if you could give us an idea of

what you routinely do for the patients maybe at the upper end, that would be helpful.

DR. WHITMORE: I would just say in terms of seeing an ophthalmologist for an eye pressure check, if they were using clobetasol on their elbows, I would not do that, so it depends totally on where you using whatever product is you are using. You take a pill, it goes in your stomach, and it's affecting your whole body, but we are talking about application of topical products that are site specific and potentially side effect site specific, too, so it is very difficult to outline a whole program of that, and that is why dermatologists train for the period of time they train.

So, to answer your question, you would have to give me a specific body area of treatment and a potency of a topical steroid for me to answer the question about how they should be monitored.

DR. WILKIN: Well, how about brittle diabetes or blood pressure control, under what circumstances do you routinely say look for glucose

intolerance in patients who are using topical corticosteroids in your practice?

DR. WHITMORE: I don't normally do that. Most patients who have diabetes are monitoring their blood sugars on a regular basis, so I think that takes care of that issue if indeed there is enough systemic absorption to affect their glucose metabolism for that answer.

I don't have a regular program, I don't have a regular protocol that I talk to them about hypertension with topical steroid use.

DR. STRATAKIS: On the list of things that we didn't add before, I just would like to add local and systemic immunosuppression and obesity, weight gain.

DR. WOOD: Other comments? Let me weigh in on this, as well, then. i have a concern I guess about just producing a laundry list of known side effects of steroids and making that--and I am not advocating for potent steroids to go over-the-counter, but as a principle, I have a concern about creating a laundry list of side

effects from a drug and saying any drug that produces these known side effects of these drugs cannot go over-the-counter.

That is not to say that I am advocating for them to go over-the-counter, but that seems to me a dangerous sort of step. I mean, for example, if the risks of glaucoma are from applying them to the eyelids, then, you don't do a study to test, applying them to the eyelids to show that you don't get glaucoma, you label them to say don't apply to the eyelids.

I want to try and make that distinction somehow, so that we don't just go down, and we are now halfway down the page, to say that we know, for example, that drugs that produce excess systemic cortisol or any systemic increase in corticosteroids are going to produce obesity.

DR. STRATAKIS: But weight gain is a real complication of any steroid.

DR. WOOD: I understand. The implication of saying that this is a show stopper means you either have to go look for it before the drug and

be marketed over-the-counter. I mean you would have to do a study, we need to get a chart out like this again and say how many people do we need to study to exclude obesity in people who are getting the drug applied.

I mean I think the Committee needs to be clear on the implications of sort of just getting our pocket Hippocrates out or whatever and listing the side effects of topical steroids and saying if any one of these occurs with any one of these drugs, it can't go over-the-counter because that's a self-fulfilling prophecy.

DR. STRATAKIS: I agree with you the Committee needs to be consistent. You can't suggest that you look for diabetes and not say the obvious, that you need to look for weight gain.

DR. WOOD: Dr. Nelson has been very patient here.

DR. NELSON: I want to comment on growth velocity. Let me just make a couple of quick distinctions. In my mind, there is a difference between what can be seen and unseen. I mean I

can't see osteoporosis. I can weigh myself in the morning and see if I am gaining weight, and have that on a label that tells me if I am gaining weight, go see a doctor or some other approach, so I am less concerned about the cutaneous.

What bothers me about growth velocity is that is also something that is unseen, and my understanding from a lot of the pediatric studies in other product areas, is you can see growth velocity in a 3-month trial. You don't need to wait for years, that as long as it's in a population that can stand up and you can get decent measurements, and I would probably, as sort of a general principle, say if there is any topical steroid that had demonstrated systemic effects on almost any measurement, I wouldn't make that over-the-counter.

But to me, if you demonstrated growth velocity changes under your maximal use conditions, I would exclude that from going over-the-counter personally.

DR. GANLEY: But I think, I don't know if

the pulmonologists have any comments on that, but I think that there is a certain inaccuracy and then to being able to accurately estimate whether there is a reduction in growth velocity or not, and so it gets back into that situation of what are the numbers that you are talking about here.

DR. NELSON: But that is why it's a randomized trial, and that's why it falls out on both sides, and it has been demonstrated in small enough trials under the Pediatric Exclusivity Rule and pediatric trials have been conducted that you have decreased growth velocity.

I think, just as a factual question, I think it is technically doable. If it isn't, I would be open to hear that argument, but I know in some other studies, it is technically doable.

DR. STRATAKIS: I just wanted to say that growth velocity measurements are inaccurate when they are measured below 6 months. I mean that is the thinking between pediatric endocrinologists anyway.

I guess the setting is different when you

have groups of patients, though, on medication, and you record a 3-month effect, so there is a difference between a trial where you are in a controlled setting, you measure growth velocity in two groups of patients, and a control group, or a control group and a group of patients, and when you assess growth velocity in an individual child, it is when you say that 6-month growth velocity measurements and lower are not accurate, we mean about the individual child.

DR. NELSON: Just to be clear, I think the trials are generally in 6, 7, and 8-year-old patients and it is controlled. I am just suggesting that a trial could be designed to do growth velocity within a short period of time, so it's feasible, and if that demonstrated, I would personally then exclude that from OTC on the principle of a systemic effect.

DR. WOOD: Terry.

DR. BLASCHKE: I think this sort of a more general comment. I think that a lot of the dermatology members of this meeting are

disadvantaged by not knowing what the NDAC people are familiar with, and that is that there needs to be an actual use simulated study to find out whether people, in fact, do understand the label, and if that were ever to come then to this committee for determination of over-the-counter, if it was discovered that 20 percent of the people were not going to dermatologists with serious conditions, but instead were using a stronger or more potent steroid, it wouldn't get approved.

I mean they could submit the data, but I don't think that the FDA would approve that. So, I think a lot of the worry that I am hearing around the table probably would be obviated if the actual use study demonstrated that, in fact, because the hydrocortisone is not very effective, as somebody stated, and more potent steroids are effective for these minor conditions, and that is, in fact, what they were being used for over-the-counter, we wouldn't have all of these concerns about these long-term side effects.

So, it really is important to understand

that there would be a study that would actually demonstrate that the label was good, that it was understood by the people purchasing it in the pharmacy, and I think it would be much easier to make a judgment about whether or not, as Jon is saying, a slightly more potent steroid might be useful over-the-counter.

DR. WOOD: Dr. Taylor.

DR. TAYLOR: I want to get back to what Dr. Wood commented on in terms of bringing some balance to our decisions. I think we want to come up with recommendations for the Agency that will be helpful. We can't just categorically say no because we have got this laundry list.

There are other ways that you can limit exposure, for example, you can have only a certain class available over-the-counter, you can have certain formulations that could be approved. You could have amounts.

I think our assumption is most of the discussions that patients would have unlimited access to as much of the product as they want. In

reality, if you look at most of the drugs that have gone over-the-counter, the package only has 4 or 5 of the tablets in there, for example. So, there are ways that you can get around some of the exposure issues rather than just saying no, you can't have it.

DR. WOOD: Dr. Wilkerson.

DR. WILKERSON: What I just want to say is I think, as dermatologists, this has been an eye-opening experience for me today to see the degree of HPA axis suppression that was presented by Dr. Cook.

When we are looking at 40 and 50 percent axis, if you queried most dermatologists, yes, we are aware obviously that this could happen, but we would probably put it in the range of less than 1 percent in our mind of a clinical risk, and I think this, to me, speaks stronger than any other issue before us today, that not only do we have an issue as far as these drugs going over-the-counter, but we have a safety signal or an issue of the prescription use of these products that is not

being addressed back to the professional body that uses these materials the most, that being dermatologists and primary physicians.

When we are seeing these levels of suppression, this is the first time I have seen this material, and I suspect most of us in the room that are dermatologists have not seen it either, and I think this is the biggest safety signal to come out of this entire meeting.

It is not so much the question of do these drugs go over-the-counter, which is pretty obviously should not right now, but what are we going to do about clinical application of these materials.

DR. WOOD: Dr. Schmidt.

DR. SCHMIDT: I think we have always known this, you know, that these strong topical steroids have done stuff even again I get my old proto textbook and it says in adults, 100 grams a week of topical steroids in Class I, III under occlusion, or 45 grams of clobetasol without occlusion may be used, but then they say, but over that you are

going to have problems.

It is just that to me, a lot of this will affect the adrenal-pituitary axis, and even given prednisone, you affect the adrenal-pituitary axis, but then it snaps back into place normally in most patients, so to me, I wonder whether we are setting the bar too high, you know, with some of these things, and I tend to agree that if these things do go over-the-counter, there is ways that you can limit.

I remember when I was a resident, I lived in a house that was almost falling over, and several of the neighbors had kids with atopic eczema, and these people were not, you know, probably like me, weren't the most sophisticated people in the world, and they would have their little tube of 5-gram triamcinolone in a little box, you know, that they used very sparingly.

So, I think we need to give the American public some credit for not just taking this stuff and rubbing it in their eyes or eating it or anything like that. I think, I don't know, I have

got some real questions that some of these things, we have always known it, but we do it anyway, but then we stop and do pulse therapy.

As far as the clinical aspect of this thing, I don't think I have ever seen glaucoma, you know, from putting steroids in people's eyes, I don't think I have ever heard of it. I mean maybe it occurs and it is reported in the literature, and I have been in practice 32 years, I have never seen anybody get fat with topical steroids.

DR. WOOD: Let me stand up.

[Laughter.]

DR. SCHMIDT: Thank you. No, mine is from the cookie.

DR. WOOD: I am sitting here too long.

DR. SCHMIDT: I just think clinically, we need to kind of mellow out.

DR. WOOD: Okay. Mellowing out, Dr. Epps.

DR. EPPS: Thank you. That being said, the truth of the matter is once it's over-the-counter, it's available for any age, in any amount, on any part of the body, and not

everyone is as sophisticated. You have got to think about the lowest common denominator. Not everybody is going to read every warning on every box. Literally, it is equivalent to you can buy it as you could buy lotion, you can buy as much as you want, put it anywhere you want, on any age person that you want to put it on.

Certainly, there is a question, and I understand his question about whether or not it is clinically significant, but those patients we are monitoring very carefully.

DR. WOOD: Let's return and let's focus the question. We are on Question 4. Would labeling for the systemic effects other than HPA axis suppression be an acceptable regulatory path in lieu of testing for the other systemic effects?

Are there any other comments on that, that we have not heard? Yes, Dr. Chesney.

DR. CHESNEY: I wanted to weigh in with Dr. Whitmore and Dr. Nelson on the issue of labeling for growth suppression. I think growth suppression has been well documented with these

drugs, and I think it is very serious, and I think labeling is not adequate to warn the public about that, because it is not something you can see, as Dr. Whitmore said, and I think as Dr. Nelson said, it is a reason that these drugs should not go over-the-counter, and I just wanted to weigh in on that.

DR. WOOD: Any other comments specifically on labeling? Dr. Bigby? No, not on labeling? Hang on, I will get to you in a second.

Any other comments on labeling? Mike.

DR. ALFANO: It's a labeling comment, and it goes back to Dr. Ellis' report where upwards of 90 percent of the current product is used on label. I think the Chair made a comment about this relative to Rx compliance with label.

I mean this is right up there, in fact, probably exceeds many Rx drugs. So, in terms of the ability of this particular label to convey something meaningful to the population, it seems to have done that, presumably similar labeling would be developed and similar in-use testing would

confirm that if something else were to come on the market, it would be equally efficacious. Nothing stops a mother from taking her prescription drug and putting it on her baby's butt.

DR. BIGBY: But the thing that is wrong with that logic is you are making the assumption that it is being used on label because of the label. It may be being used that way because it didn't work. I mean you are making the assumption that just because people used it for less than 7 days, it is because they read the label and paid attention to that, and there is no evidence of that whatsoever.

DR. ALFANO: That is only length of use.

DR. WOOD: Hang on, if I can just intercede here. That's the point Terry Blaschke was trying to make earlier on for the benefit of the panel members who have not seen this reviewed. That will be tested before a drug could go over-the-counter, so, in other words, a sponsor would have to come in with an actual use study and a label comprehension study that demonstrated that

the label was understood by them and that in a quasi-operational fashion were able to operationalize the content of the label.

I am not necessarily arguing that. Mike, sorry.

DR. ALFANO: That was going to be my point and also that study related, not just to duration of use, but what it was used on, and for the most part, it was used on the right conditions.

DR. WOOD: Dr. Ringel.

DR. RINGEL: I guess I have sort of collected comments here. One quick one is about the labeling issue, that people will use what makes them feel good, and you can test that they comprehend it and that the label is clear, but you can't test to make sure that they are really going to do what they read on the label. If they feel bad, and the cream makes them feel good, they will continue to use it, at least that is my experience in my clinical practice.

DR. WOOD: It doesn't sound like a bad thing actually, does it?

DR. RINGEL: Yes, if there are side effects. Let me go back to Dr. Wilkin's question, which was what do you do in your office practice,

dermatologists, to monitor people, and I can only tell you what I do, and you make me kind of guilty sitting here, you know, thinking about everything we have heard today and I really do, and clearly it is not enough what I do do.

If I have somebody on high-potency steroids for a long time, over a long portion of their body, I really do do a cortisol test. I know it is not a great test to do, but I do it, and every once in a while somebody is low and I try to do something about it.

When you see people, and I think that most of the dermatologists, maybe they don't think that they do this, but I really think they do this, you see somebody with diabetes and it is not going well, and you are giving them the clobetasol, I think, huh, maybe I shouldn't be giving them so much clobetasol, or somebody who is having, you know, their osteoporosis is getting worse and

worse, and I am giving them clobetasol, I go through the same thing in my mind, maybe this is not a great idea.

Then, I start to fight with people, say, well, you shouldn't use this much, and they say, well, they want to use it because nothing else works, and I am always fighting with people, I am always trying to take it away, and they are always trying to get a little bit more from me, and that is not going to happen if it's over-the-counter.

The other thing is that for me, this whole experience has been a sort of an NGE, kind of a neurosis generating event. I mean I am going to be in my office and people are going to be wanting me to give them more steroids and I am going to be say, oh, my gosh, they are going to get pituitary suppression, and I mean what it makes me think is maybe we need to rethink what we are doing by prescription, not that we need therefore to just go ahead and make it over-the-counter.

I mean Denise gave us such convincing evidence that there really can be a problem, I was

convinced. I really think that you did a great job, and I saw no evidence presented by the FDA today that this is not a problem, so how can I then go ahead and say fine, make it over the counter.

I need to see some evidence first from the FDA or someone that it is not a problem, and that's it.

DR. WOOD: Jack.

DR. FINCHAM: Well, we are all over the map, so bear with me, but I think we have got--

DR. WOOD: Labeling.

DR. FINCHAM: I know, bear with me, please, I am with you. We have a formal health care system and an informal system, and if we assume just because we prescribe a therapy, that it is only going to be used by that individual, we are really wrong, because when this gets out in the system, regardless of whether it is prescribed for somebody or not, it is used by anybody, they share it.

Jimmy, I think eloquently talked about why we need to have something available to let people

make informed decisions, and you use the labeling to try to do the best that you can to help people make informed decisions, but if it is going to be misused, it is going to be misused whether it is a prescription product or whether it's an over-the-counter product, whether there is a board-certified dermatologist involved or not, and I just think you have to give people the benefit of the doubt, give them a chance, label it appropriately, and go from there.

DR. WOOD: I have a personal comment on that, as well. Although I don't believe that labeling actually works, I certainly would not want to leave the impression that people should have to do studies to exclude all these other effects before the drug could be submitted for OTC use. It is unfortunate perhaps the way this is worded, but i would rephrase it to say should they have to exclude all these other lists that Teresa has here, and I think the answer to that is no in my view.

Dr. Nelson. Labeling?

DR. NELSON: Yes, on labeling. What we

are not being asked is how many people would need to be able to follow the label if, in fact, the label constrained the use far enough below the maximal use conditions--

DR. WOOD: That is the question that would come up for NDAC.

DR. NELSON: I understand, so all I am saying is that what we are answering in a sense is both questions, and that is part of the confusion, to what extent, if it's zero out of 1,000 in maximal use, well, if then everybody could follow the label, that becomes a very different question, and that may be part of the difficulty.

We are conflating it, and not separating those two things.

DR. WOOD: Do we want to vote on this? Okay.

Let's start with Jack. Would labeling be an acceptable regulatory pathway, so Yes would mean it would be acceptable.

DR. FINCHAM: Yes.

DR. RAIMER: I am going to say no.

DR. RINGEL: No.

DR. WHITMORE: No.

DR. CLYBURN: Yes.

DR. SKINNER: No.

DR. PATTEN: Yes.

DR. TEN HAVE: No.

DR. DAVIDOFF: No.

DR. BIGBY: No.

DR. WOOD: Yes.

DR. NELSON: With your indulgence, no for some, such as growth velocity, yes for others, such as cutaneous manifestations.

DR. SNODGRASS: No.

DR. MATTISON: No.

DR. SCHMIDT: Yes.

DR. EPPS: No.

DR. TAYLOR: Yes.

DR. WILKERSON: No.

DR. STRATAKIS: No.

DR. BLASCHKE: Without belaboring it any longer, I will say yes.

DR. WOOD: All right. Question No. 5.

With regard to dermatologic local cutaneous effects, at what level of severity do risks outweigh the benefits of topical corticosteroid use in an OTC setting?

Dr. Bigby.

DR. BIGBY: This question is actually directed to Jon. It seems to me that the simplest question to ask is should the more potent topical corticosteroids be considered for over-the-counter use, period, as opposed to--I mean why didn't you ask us that question?

DR. WILKIN: Well, I guess because we were interested in the answer to that question.

[Laughter.]

DR. WOOD: Thank you. Next question.

DR. WILKIN: The point about at what level of severity of local cutaneous effects, because I mean you might have mild erythema, on the other hand, you might have really severe atrophy, and we were asking for something that would qualitative or quantitative from the Committee, where they thought something that had the potential to do X or Y, or

whatever, that those are the products that should not go over-the-counter.

DR. WOOD: Let's hear from the dermatologist first on this. They are the people who should be able to answer this best.

Dr. Whitmore.

DR. WILKIN: Stria, telangiectasias, acne eruptions.

DR. WOOD: Dr. Wilkerson.

DR. WILKERSON: I think certainly in blacks, the hypopigmentation issue is big. I just wanted to add that every good sermon has three points and every good advisory committee has five questions, so that is the answer to Dr. Bigby's question.

DR. WOOD: Dr. Schmidt.

DR. SCHMIDT: I think the most important one is stria because it is something that is permanent. You know, the rest of these things resolve with time and then the other thing, and I don't want to belabor this, but I really think that contact dermatitis, you know, to some of these

things, you know, I think that if something induced contact dermatitis in a lot of patients, I think I would consider not having that either.

DR. WOOD: Any other comments?

DR. RAIMER: I think sometimes atrophy can be permanent, too, especially in an older person, so I think stria or severe atrophy that doesn't resolve.

DR. WOOD: Dr. Skinner.

DR. SKINNER: I was thinking some of this probably could be done with good labeling. It would just be so restrictive, you know, don't use it on the face, don't use it in the axilla, don't use it in the antecubital popliteal fossa, don't use it in the groin. You know, with that I think you could avoid most of the trouble with the cutaneous effects.

DR. WOOD: Any other comments? Yes, Dr. Nelson.

DR. NELSON: As a non-dermatologist, what would strike me as most important here is reversibility, and not necessarily severity. If

something could appear as severe, but if it's reversible when stopped by the individual who is using it, that is much different than if it could be mild, but then be reversible, so I think it's the reversibility.

If I think of myself as a consumer buying it, I see it, I stop it, I would want it to go away, would be the key rather than how severe it might look for that period of time.

DR. WOOD: Any other comments? Yes, Dr. Epps.

DR. EPPS: I should also mention hypertrichosis, which some people get, too.

DR. WOOD: Any other comments? All right. We are through, ten past 3:00, guys. Thanks a lot.

DR. FINCHAM: Alastair, thank you for shepherding us today through all this. Nicely done.

[Whereupon, the meeting was concluded at 3:10 p.m.]

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