FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ADVISORY SUBCOMMITTEE

OF THE

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

8:05 a.m.

Thursday, October 30, 2003

The Ballrooms
The Hilton Hotel
620 Perry Parkway
Gaithersburg, Maryland

ATTENDEES

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEMBERS: (Voting)

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

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

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

ROBERT STERN, M.D.
Beth Israel Deaconess Medical Center

SPECIAL GOVERNMENT EMPLOYEES-CONSULTANTS: (Voting)

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

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

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

ATTENDEES (Continued)

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

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

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

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

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

FEDERAL EMPLOYEES: (Voting)

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

CHARLES RABKIN, M.D.
National Cancer Institute, NIH

LOIS TRAVIS, M.D.
National Cancer Institute, NIH

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

PHYLLIS WINGO, M.D.
Centers for Disease Control and Prevention

INTERNATIONAL GUEST: (Non-voting)

PATRICK SALMON, M.D.
European Medicinal Evaluation Agency

ATTENDEES (Continued)

FOOD AND DRUG ADMINISTRATION STAFF:

SUSAN CUMMINS, M.D.
BARBARA HILL, PH.D.
LOIS LA GRENADE, M.D.
DIANNE MURPHY, M.D.
SHIRLEY MURPHY, M.D.
BINDI NIKHAR, M.D.
THOMAS PEREZ, R.PH., M.P.H., Executive Secretary
MARILYN PITTS, PHARM.D.
JONATHAN WILKIN, M.D.

ALSO PRESENT:

DAVID J. MARGOLIS, M.D., PH.D.

C O N T E N T S

TRACKING CANCER RISK AMONG CHILDREN
WITH ATOPIC DERMATITIS
WHO ARE TREATED WITH TOPICAL CALCINEURIN INHIBITORS

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C O N T E N T S (Continued)

P R O C E E D I N G S

(8:05 a.m.)

DR. CHESNEY: I think it's time to get started. I wanted to welcome everybody back from yesterday and particularly welcome all of you who weren't with us yesterday. I think it was a very, very interesting session, and we look forward to adding to it today.

Just a couple of preliminary comments. I think we learned a lot about atopic eczema, but we also learned two other unique aspects which is that Dr. Wilkin taught us that lanthanos means hidden from view. In my mind, my brain went looking for laudanum. So that's why I made that bizarre comment, and it took Dr. Fost's brain about 10 minutes to find the right file. As you get older, you discover that brains work strangely. But anyway, thank you for that comment, Dr. Wilkin.

(Laughter.)

DR. CHESNEY: Also he reminded us of the word "elegant," that we should always think to design studies elegantly as mathematical solutions are derived which is most efficiently and neatly.

I also wanted to take time this morning to thank the many people at the FDA who prepared the materials for us so elegantly. It's everything that you wanted and not much more, and we really appreciate that. So I hope I

have everybody's name here appropriately. In the Division of Dermatologic and Dental Drug Products, it's Luke Markham and Lisa Mathis who were the medical team leaders, and Mary Jean Causemafamaro, who is the chief of project managers and Margo Owens, who's a project manager. And then in the Division of Drug Risk Evaluation, Mark Avigan, who's the acting Director of the Division of Drug Risk Evaluation. Then, of course, in the Office of Counter-Terrorism and Pediatric Drug Development, which is pronounced OCTAP.

DR. DIANNE MURPHY: OCTAP.

DR. CHESNEY: Thank you.

(Laughter.)

DR. CHESNEY: Of course, Dr. Susan Cummins, who's a medical team leader, and Rosemary Addy who is the project manager. So on behalf of the committee, we really thank you very much for preparing everything so efficiently for us.

Our first speaker for today is Dr. Nikhar. We heard from her yesterday. She's a pediatrician and a medical officer with the Division of Dermatologic and Dental Drug Products. Today she's going to briefly review the topical calcineurin immunosuppressant inhibitors.

Thank you. My colleagues remind me that our Executive Secretary, who's trying to get the computer to work this morning, needs to read the conflict of interest,

but before that, I guess we need to go around the table and have everybody introduce themselves. So forgive me for forgetting that. Dr. Murphy, do you want to start?

DR. DIANNE MURPHY: Dianne Murphy, Office Director for the Office of Pediatric Therapeutics and OCTAP.

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

DR. LA GRENADE: Lois La Grenade, epidemiologist, Office of Drug Safety.

DR. CUMMINS: Susan Cummins, Division of Pediatric Drug Development.

DR. SANTANA: Good morning. Victor Santana, pediatric oncologist from St. Jude's Children's Research Hospital in Memphis, Tennessee.

DR. FOST: Norm Fost, Professor of Pediatrics and director of the bioethics program at the University of Wisconsin.

DR. GLODE: I'm Mimi Glode, Professor of Pediatrics, Infectious Disease, Children's Hospital and University of Colorado School of Medicine in Denver.

DR. DANFORD: David Danford, Professor of Pediatrics, Section of Cardiology joint division, Creighton University and the University of Nebraska Medical Center in Omaha.

DR. FINK: Bob Fink, Director of Pediatric Pulmonology at Children's Medical Center in Dayton, Ohio.

DR. ANDREWS: Elizabeth Andrews, pharmacoepidemiologist at Research Triangle Institute in North Carolina.

DR. TEN HAVE: Tom Ten Have, biostatistics and epidemiology, University of Pennsylvania.

DR. CHESNEY: Joan Chesney, pediatric infectious diseases at the University of Tennessee Health Science Center in Memphis and St. Jude Children's Research Hospital.

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

DR. EBERT: Steve Ebert, Professor of Pharmacy and infectious disease pharmacist, Meriter Hospital, Madison, Wisconsin.

DR. GORMAN: Rich Gorman, engaged in private practice of general pediatrics in Ellicott City, Maryland.

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

DR. STERN: Rob Stern, Professor of Dermatology, Harvard Medical School, and Chief at the Beth Israel Deaconess in Boston.

DR. MATTISON: Don Mattison, NICHD.

DR. WILFOND: Ben Wilfond, peds pulmonary, National Human Genome Research Institute in the Department of Clinical Bioethics at the NIH.

DR. RABKIN: Charles Rabkin, medical epidemiologist from the Division of Cancer Epidemiology and Genetics, National Cancer Institute.

DR. TRAVIS: Lois Travis, epidemiologist from the Division of Cancer Epidemiology and Genetics, National Cancer Institute.

DR. CHESNEY: Thank you.

Now Tom Perez will read the conflict of interest statement.

MR. PEREZ: Good morning.

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

The subcommittee will discuss how to approach long-term monitoring for cancer occurrence among patients treated for atopic dermatitis with topical immunosuppressants.

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

institutions.

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

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

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

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask

in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. CHESNEY: Thank you. Dr. Wingo has just joined us. I wondered if you'd mind introducing yourself for the record, please.

DR. WINGO: Yes. I'm Phyllis Wingo and I'm from the Centers for Disease Control in the Division of Cancer Prevention and Control there.

DR. CHESNEY: Thank you. I would like to introduce a visitor. Dr. Patrick Salmon is here from the European Medicinal Evaluation Agency. I wondered if he would just stand for a moment so everybody could see who you are. Thank you.

Now, my apologies again, but we need to have comments from Dr. Murphy and Dr. Wilkin as to our mission today.

DR. DIANNE MURPHY: Dr. Wilkin tells me he has no new vocabulary word for us today.

(Laughter.)

DR. DIANNE MURPHY: So I simply wanted to welcome everybody again. It's one of our glorious autumn days today that we were missing out on yesterday.

I'll just note, in contrast to yesterday where

we had a molecular entity of which we had decades of experience, we have today many of the same issues in a molecular moiety of which we have really much more limited experience, though we do have a clearly defined signal that is already noted in the label. I'm not going to say much more. I think the presenters will be able to outline for us what the question is that we're bringing to the committee today in reference to our ability to again define the best risk management approach to the use of these products.

Thank you.

DR. CHESNEY: Dr. Wilkin, do you have any introductory comments?

DR. WILKIN: Again, I would welcome the committee. Yesterday was a very fruitful day for those of us at FDA, a lot of constructive, very helpful insights, things that we hadn't thought of before, things we'll now be looking for, and we're looking for that again today.

DR. CHESNEY: Thank you.

Dr. Nikhar, my apologies for your preliminary introduction, but we're all very, very interested in hearing about these topical immunosuppressants.

DR. NIKHAR: Good morning. My talk today covers an overview of topical immunosuppressants. These were discussed in brief yesterday.

Starting with a brief introduction, this is the newest pharmacological class for atopic dermatitis. These drugs were introduced in this decade. They have a direct immunosuppressive action in diseases with an immunological basis, and there are two currently FDA-approved products: tacrolimus, FK506, the trade name being Protopic; and pimecrolimus, SDZ ASM 981, the trade name being Elidel.

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

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

Elidel cream 1 percent was approved in December of 2001. It is indicated for patients 2 years of age and older for short and intermittent long-term therapy in the treatment of mild to moderate atopic dermatitis.

Both drugs were not approved for use in children less than 2 years of age, and systemic absorption can take place in both adult and pediatric age groups from the topical application of both drugs.

And currently the effects of topical immunosuppressants on the developing immune system are unknown.

Now moving on to review some of the pharmacokinetic studies done for both drugs. Starting with tacrolimus, here studies were done in both children and adults. Pooled results from two PK studies in 49 adult moderate to severe atopic dermatitis patients indicate that tacrolimus is absorbed after the topical application of .1 percent Protopic ointment. Peak tacrolimus levels ranged from undetectable to 20 nanograms per ml after single or multiple doses of .1 percent Protopic ointment, and 45 out of the 49 patients had peak concentrations less than 5 nanograms per ml.

A PK study of .1 percent Protopic ointment in 20 pediatric patients, aged 6 to 13 years, showed tacrolimus concentrations below 1.6 nanograms per ml in all patients. The absolute bioavailability of topical tacrolimus is unknown. Using IV historical data for comparison, that is, comparing it to Prograf, the bioavailability of tacrolimus from Protopic in atopic dermatitis patients is less than .5 percent. And the lowest tacrolimus blood level at which systemic effects can be observed is not known.

Moving on to pimecrolimus, here too studies

were done in both children and adults. In adults treated for atopic dermatitis with 13 to 62 percent body surface area involvement for periods up to a year, although most patients had blood concentrations at or below the limit of computation, detectable pimecrolimus blood concentrations were less than 2 nanograms per ml. In 26 pediatric patients between 2 to 14 years of age with atopic dermatitis and 20 to 69 percent body surface area involvement who had twice-a-day application for 3 weeks, blood concentrations of pimecrolimus were less than 3 nanograms per ml.

What is significant is that 20 out of the 23 children investigated had at least one detectable blood level as compared to adults with 13 out of the 25 investigated had a detectable blood level over a 3-week period. In 22 pediatric patients, aged 3 to 23 months, with 10 to 92 percent body surface area involvement, a higher proportion of blood levels ranging from .1 to 2.6 nanograms per ml was seen. The inference drawn was that this increase may be due to larger surface area to body mass ratio seen in younger subjects.

A higher incidence of upper respiratory symptoms/infections was also seen in the 3 to 23 months age group relative to the older age group in these PK studies. So a causal relationship between these findings and Elidel

use cannot be ruled out.

Although all the factors that lead to higher systemic levels are not known, these are some of the factors that may contribute: a higher body surface area, younger age groups, especially the 3- to 23-month age group as seen with pimecrolimus, and reduced skin barrier function, for example, with Netherton's syndrome. Netherton's syndrome is an autosomal recessive condition characterized by generalized erythroderma, extremely high IgE levels and atopic diatheses, hair shaft abnormalities, and reduced skin barrier.

Now moving on to some of the pediatric clinical studies that were also done prior to drug approval. The use of Protopic .03 percent ointment was studied in children 2 to 15 years of age by conducting two phase III studies. In these studies, varicella zoster and vesiculobullous rash were seen more frequently in patients treated with Protopic ointment .03 percent compared to the vehicle.

Elidel cream .1 percent was studied in two age groups, the 3- to 23-month age group and the 2 to 17 years age group.

In the 2 to 17 years age group, nasopharyngitis, influenza, viral infections, pyrexia, cough, headache, and eczema herpeticum were increased over

vehicle in the 1-year safety study.

The 3- to 23-month age group had a short-term 6-week study followed by a 20-week open-label study as well as a 1-year safety study. In the short-term study, pyrexia, upper respiratory infection, nasopharyngitis, gastroenteritis, otitis media, and diarrhea were seen more frequently compared to compared to vehicle. The adverse event incidence for those in the open-label phase of the study who switched over to Elidel cream from vehicle approached the incidence of those patients who remained on the cream.

In the 6-month infant safety study, adverse events occurring more frequently in the Elidel cream group compared to vehicle included pyrexia, upper respiratory tract infection, cough, vomiting, hypersensitivity, rhinitis, viral rash, rhinorrhea, and wheezing.

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

These are the proposed mechanisms of action for both drugs. Both tacrolimus and pimecrolimus inhibit T

cell activation by binding to the same cellular receptor, the FK-binding protein, or macrophilin-12. The tacrolimus or pimecrolimus FK-binding protein complex further binds to calcineurin which is an enzyme vital for early activation of both T helper cell types 1 and 2.

The following are the adverse effects of topical immunosuppressants. Local effects commonly seen are: burning, pruritus, erythema, irritation, edema, and urticaria.

These are some of the systemic effects: pyrexia; upper and lower respiratory tract infection; nasopharyngitis; viral skin rashes, for example, molluscum contagiosum, herpes simplex and zoster, eczema herpeticum; influenza; and further, otitis media; gastroenteritis; vomiting; diarrhea; streptococcal pharyngitis and staph infection; and skin infection not otherwise specified. Now, lymphadenopathy has been seen with both drugs, and although the etiology is reactive in most cases, in the absence of a clear etiology or in the presence of acute infectious mononucleosis, discontinuation is recommended and close monitoring of such patients is then required.

The advisory committee has copies of both labels and these give a further breakdown of adverse events comparing active treatment to vehicle in different age groups.

I would like to mention the adverse effects of Prograf that are in relevance to the adverse effects of this class of drugs. Patients receiving Prograf are at an increased risk of developing lymphomas and other malignancies particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression. A lymphoproliferative disorder related to Epstein-Barr virus infection has been reported in immunosuppressed patients, and the risk of this lymphoproliferative disorder appears greatest in young children who are at risk for primary Epstein-Barr virus infection while immunosuppressed.

Now moving on to the potential long-term adverse effects of topical immunosuppressants. Animal studies have shown an increased incidence of malignancies with both topical tacrolimus and pimecrolimus. Lymphomas were seen with both pimecrolimus and tacrolimus. Follicular cell adenomas were seen with pimecrolimus, and skin tumors with concurrent UV radiation exposure were seen with both drugs. These will be mentioned in further detail by Dr. Hill in the next presentation.

So since the systemic use of calcineurin inhibitors is associated with the formation of lymphoma and skin malignancies, low systemic exposure from topical calcineurin inhibitors over a course of time leading to a

cumulative dose effect may lead to melanomas, non-melanoma skin cancers, Hodgkin's and non-Hodgkin's lymphomas.

In conclusion then, the concerns that we have about the long-term side effects of these drugs are as follows. Children from the age of 2 years and upwards with off-label use expected in even younger children will be using these medications on a short or intermittent long-term basis.

About one-third of children with moderate to severe atopic dermatitis may continue to use these drugs into teenage and adult years, thereby having a long duration of exposure.

Currently, we do not have long-term safety data on either tacrolimus or pimecrolimus, and so post-marketing evaluation of topical immunosuppressants is needed to evaluate this potential risk. And means of setting up these prospective studies need to be discussed.

And that brings me to the end. Thank you.

DR. CHESNEY: Thank you very much. We'll have time for questions and answers for the presenters after we've heard these three presentations.

As an editorial comment, I realize now the only children I've seen with atopic dermatitis who have been on these immunosuppressants have been under the age of 2 years, which just emphasizes the point you made, that they

will be used whether they're approved or not in that age group.

Our next speaker is Dr. Barbara Hill. She's a pharmacology/toxicology reviewer with the Division of Dermatologic and Dental Drug Products and was the primary reviewer for the topical immunosuppressants being discussed today. In addition to her doctorate in pharmacology and toxicology, she completed a post-doctoral fellowship at the National Cancer Institute of the NIH. Dr. Hill will review the animal toxicology data for the topical immunosuppressants.

DR. HILL: Good morning. My name is Barbara Hill, and as was mentioned, I'm a pharmacology/toxicology reviewer in the Division of Dermatologic and Dental Drug Products.

In today's talk, I'm going to compare the animal toxicology data available for two topical immunosuppressants known as calcineurin inhibitors that have recently been approved for the topical treatment of atopic dermatitis. As previously mentioned, these two compounds are Protopic ointment -- the active ingredient in this is tacrolimus which was approved in December of 2000 -- and Elidel cream. The active moiety is pimecrolimus, which was approved in December of 2001.

I will compare the two structures of these

chemical moieties, discuss the general toxicology associated with these compounds, and briefly summarize the genetic toxicology, photoco-carcinogenicity and carcinogenicity studies conducted for both drug products, and then conclude with an overall summary of the available animal toxicology data.

On this next slide are the structures for tacrolimus and pimecrolimus. Even though their chemical formulas are different, as you can see on this slide, their overall chemical structure is very similar, which is not surprising since they both bind to the same protein and inhibit calcineurin.

The potential immune target organs of toxicity that have been identified in chronic animal toxicology studies include thymus, lymph nodes, and spleen, and so based on this information, the nonclinical toxicology results indicate that both compounds can be categorized as classic immunosuppressive agents.

The results of the genetic tox studies conducted for both compounds is summarized on this next slide. For both compounds, an appropriate battery of in vitro and in vivo genotoxicity tests were conducted, and the results of those studies showed that they were both non-genotoxic agents.

However, it's important to note that not all

carcinogens are direct acting genotoxic, meaning DNA-reactive agents. There's a second class of compounds referred to as indirect acting carcinogens, which do not interact directly with DNA and the carcinogenesis is based on another mechanisms. A couple of examples that fall into this category are hormones and immunosuppressive agents.

In the next few slides, I will summarize the results of photoco-carcinogenicity studies conducted for both drug products. The objective of this study is to determine in a hairless mouse model if dermal test article application combined with simulated sunlight exposure can reduce the time to formation of skin papillomas compared to simulated sunlight exposure alone. A positive effect in this assay is referred to as an enhancement of the UV skin photo-carcinogenic effect, which is defined as shortening of the time to skin tumor formation.

The results for both compounds are summarized on this slide. For tacrolimus, it was demonstrated that for the vehicle ointment alone, it enhanced the UV photo-carcinogenesis in this assay and that tacrolimus ointment had an additional small effect beyond what was noted for the vehicle ointment. For pimecrolimus, it was demonstrated that for the vehicle cream alone, it showed an enhanced UV photo-carcinogenesis in this assay and that pimecrolimus cream had no additional effect beyond what was

seen for the vehicle cream alone.

The results of the findings from this study were that a precaution was included in the label of each drug product advising patients to minimize or avoid exposure to natural or artificial sunlight while using the drug product.

This next slide summarizes the carcinogenicity studies that were conducted for both drug products. For tacrolimus, an oral rat carcinogenicity study, an oral rat carcinogenicity study, and a dermal mouse carcinogenicity study conducted with the final marketed formulation were conducted.

It's important to note that for our division, we recommend that the dermal studies be conducted with the final marketed formulation because it's important to understand the potential carcinogenic effect not only with the active ingredient, but with the combination of excipients used in the product as well.

For pimecrolimus, an oral rat carcinogenicity study, an oral mouse, carcinogenicity study, and a dermal rat carcinogenicity study, once again with the marketed formulation, were conducted. In addition, a series of high-dose studies were conducted in the mouse where the active ingredient pimecrolimus was dissolved in ethanol and applied dermally to the mouse for a duration of 13 weeks.

A couple of definitions before I go on to show you the results of these studies. The first is that a treatment-related tumor is identified as a statistically significant increase in the incidence of the tumor in treated animals compared to vehicle control animals. The treatment-related tumors that are expressed in both labels are expressed as a multiple of human exposure based on AUC comparisons to the maximum recommended human dose. In other words, the multiples of human exposure are based on the systemic exposure obtained in animals compared to that obtained in the clinical studies under conditions of maximal use.

This next slide summarizes results of oral carcinogenicity studies conducted for both drug products, particularly focusing on any lymphoma signal that was noted. The first two rows summarize the results of the oral rat and oral mouse carcinogenicity studies conducted with the active ingredient in Protopic ointment.

In the first row in the oral rat study at a dose of 3 milligrams per kilogram per day, which is equivalent to 9 times the maximum recommended human dose, the results of this study were negative, meaning no lymphoma signal was noted.

In the second row in the oral mouse study at a dose of 5 milligrams per kilogram per day, which is

equivalent to 3 times the maximum recommended human dose, the results of this study were also negative.

But it's important to note that it was determined that for both these studies an adequate systemic exposure was obtained after oral administration. Both these studies were conducted by administering the active moiety in feed, and there was a limitation as to how high the dose exposure you could get. You'll see a comparison of that in the next slide when I show the results of the dermal studies conducted for Protopic.

The third and fourth row of this table summarize the results of the oral mouse carcinogenicity studies conducted with the active ingredient in Elidel cream. At a dose of 45 milligrams per kilogram per day, which is equivalent to 258 to 340 times the maximum recommended human dose, a lymphoma signal was noted. And a dose of 15 milligrams per kilogram per day was identified as a NOEL dose. This is the dose at which no effect level was determined for the formation of lymphoma. This was equivalent to 60 to 133 times the maximum recommended dose.

The next slide summarizes the results of the dermal carcinogenicity studies, once again focusing on any lymphoma signals seen. The first two rows summarizes the results of the dermal mouse carcinogenicity studies conducted with Protopic ointment. This was conducted, once

again, with the final marketed formulation, and at a dose of 3.5 milligrams per kilogram per day, equivalent to 26 times the maximum recommended human dose, a lymphoma signal was noted. And the NOEL dose, at which no lymphoma was noted, was identified as 1.1 milligram per kilogram per day, which is equivalent to 10 times the maximum recommended human dose.

If we go back to the previous slide, you can see that in oral studies conducted to support Protopic, in the mouse study the highest systemic exposure they could obtain was 3 times the maximum recommended human dose. So it's not surprising that no lymphoma signal was noted in this, whereas we did see a lymphoma signal in the dermal mouse carcinogenicity studies conducted to support Protopic ointment.

The third row of this table summarizes the results from the dermal rat carcinogenicity study. At the highest dose possible, 10 milligrams per kilogram per day, equivalent to 3.3 times the maximum recommended human dose, the results of this study were negative, meaning no lymphoma signal was seen. But this dose was once again the highest that could be obtained, and it was limited based on the highest amount that could be dissolved in the formulation. So we weren't able to get to a high enough dose to potentially see a lymphoma signal.

The last three rows of this table summarize the results of the special high-dose dermal mouse studies. These studies were, once again, conducted with pimecrolimus dissolved in ethanol and applied dermally to the mouse for a duration of 13 weeks. At a dose of 25 milligrams per kilogram per day, which is equivalent to 47 times the maximum recommended human dose, a lymphoma signal was noted. The NOEL, where no lymphoma was noted, was identified as 10 milligrams per kilogram per day, which is 17 times the maximum recommended human dose. At a higher dose of 100 milligrams per kilogram per day, which is equivalent to 179 to 217 times the maximum recommended human dose, lymphoma was noted, but at a shorter duration of treatment of 8 weeks.

So, in summary, the results of this slide show that the lymphoma signal is dependent on dose and duration. At a higher dose, you see it at a shorter duration of time, and at a lower dose, you see the signal at a higher duration of time. The typical duration of treatment for carcinogenicity studies is 2 years.

This next slide summarizes other tumor signals seen in carcinogenicity studies conducted to support Elidel cream. The first four rows of this table summarize results from the rat oral carcinogenicity studies. At a dose of 10 milligrams per kilogram per day, which is equivalent to 40

times the maximum recommended human dose, benign thymoma was noted in male and female rats. At a dose of 5 milligrams per kilogram per day, which is equivalent to 32 times the maximum recommended human dose, benign thymoma was also noted in male rats.

The NOEL dose in female rats was identified as 5 milligrams per kilogram per day in this study, which was equivalent to 21 times the maximum recommended human dose, and the NOEL dose in male rats identified as 1 milligram per kilogram per day, which is 1.1 times the maximum recommended human dose.

The last row of this table summarizes the results from a dermal rat carcinogenicity study conducted with Elidel cream, the final marketed formulation, and at the lowest dose tested of 2 milligrams per kilogram per day, which is equivalent to 1.5 times the maximum recommended human dose, follicular cell adenoma of the thyroid was noted.

On the last few slides of this presentation I will provide an overall summary of the animal toxicology data available for both drug products.

First, Protopic ointment and Elidel cream are topical immunosuppressants based on the study results noted in general toxicology studies.

Neither tacrolimus nor pimecrolimus exhibited a

genotoxic signal.

Both Protopic ointment and Elidel cream contain cautionary wording in the labels to avoid sunlight exposure based on the results of the photoco-carcinogenicity study.

A lymphoma signal was evident in a dermal mouse carcinogenicity study conducted with tacrolimus ointment. A lymphoma signal was evident in an oral mouse carcinogenicity study conducted with pimecrolimus. A lymphoma signal was evident in the 13-week dermal mouse studies conducted with pimecrolimus dissolved in ethanol.

The estimates of human systemic exposure data are highly variable and are dependent on the maximum body surface area that is treated in an atopic dermatitis patient. In other words, if you have an atopic dermatitis patient with a larger body surface area involvement, you would expect to treat that patient with a larger amount of the topical immunosuppressant and potentially have a greater systemic exposure.

Also, it's important to note that systemic exposure is also dependent on the severity of the disease and the disruption of the epidermal barrier. If you have a disruption of the epidermal barrier, you would anticipate a greater systemic exposure.

It's also important to note that the biologic plausibility of lymphoma formation in local lymph nodes

cannot be ruled out at this time. It is acknowledged that demonstrating this effect could be technically challenging, but it is possible that you could have a lower systemic exposure but a higher local exposure to lymph nodes, and that may also increase the risk for lymphoma formation.

Other tumor signals noted in the carcinogenicity studies include a benign thymoma noted in the oral rat carcinogenicity study conducted with pimecrolimus and follicular cell adenoma of the thyroid noted in the dermal rat carcinogenicity study conducted with pimecrolimus cream.

So, in conclusion, based on the carcinogenic signals noted in the nonclinical studies, registry studies were recommended as a phase IV commitment for both Protopic ointment and Elidel cream to try to determine the potential cancer risk associated with clinical use of these products.

Thank you for your attention.

DR. CHESNEY: Thank you very much, Dr. Hill. You covered an incredible amount of material very elegantly, and we look forward to asking you questions.

Our last speaker for this session is Dr. Marilyn Pitts. She is a pharmacist and safety evaluator with the Office of Drug Safety of the FDA. Dr. Pitts will present the post-marketing adverse event reports for these products.

DR. PITTS: Good morning. Today I will describe the post-marketing adverse event reports of the topical calcineurin inhibitors. I will provide background information including drug use data, as well as describe our methods of identifying the adverse event reports. I will separately describe the AERS adverse event profile associated with pimecrolimus and topical tacrolimus. I will provide a description of adverse event reports found in the pediatric population and the cases with the most serious outcomes, death and hospitalization, and the malignancy and nonmalignancy cases, as well as the pediatric infection cases.

There are two topical calcineurin inhibitors available to the U.S. market: pimecrolimus marketed as Elidel and topical tacrolimus marketed as Protopic. Pimecrolimus was approved December 2001 for patients 2 years and older, and topical tacrolimus was approved December 2000 for patients 2 years and older. However, only the 0.03 percent preparation of topical tacrolimus is approved for children between the ages of 2 and 15 years.

Both pimecrolimus and topical tacrolimus are approved as second-line agents only. Pimecrolimus is for mild to moderate atopic dermatitis, and topical tacrolimus is for moderate to severe atopic dermatitis. Again, both agents are not approved for children of less than 2 years.

We obtained prescription drug use data and drug appearance data from IMS Health. Prescription drug use data measures the number of prescriptions dispensed for each agent and is different from drug appearance data. Drug appearance data is determined by patient visits to office-based practitioners in the continental U.S. Since approval, there have been more than 3.2 million prescriptions of pimecrolimus and more than 2 million prescriptions of topical tacrolimus dispensed. Based on drug appearance data, we see that more than 50 percent of all pimecrolimus is used in children between the ages of newborn and 2 years. Similarly, appearance data demonstrates that a significant amount of topical tacrolimus is used in children with almost 10 percent being used in children between the ages of 2 and younger.

To identify possible adverse events associated with the topical calcineurin inhibitors, we queried the AERS database. The AERS database is an electronic database that originated in 1969 as the Spontaneous Reporting System, or the SRS system. In 1997, it was replaced by AERS. Approximately 3 million adverse event reports for drugs are located in the AERS database.

We separately searched the AERS database for all reports of pimecrolimus used by using pimecrolimus as a suspect agent. In addition, we separately searched for

topical tacrolimus by searching for topical tacrolimus only as a suspect agent. We will review each of these searches separately.

The following information concerning topical pimecrolimus represents our post-marketing experience since approval of the product in 2001.

For pimecrolimus, we found 79 reports. There were 64 reports of U.S. origin and 15 reports of foreign origin. There were 53 females and 23 males. Pediatric cases amounted to almost one-half of the pimecrolimus cases. The majority of the adverse events reported for all ages are found in the product labeling and 90 percent of the adverse events reported involved the skin. We were particularly interested in the cases with the most serious outcomes, and for pimecrolimus that represented hospitalization and the cases of tumor growth and then the pediatric cases.

There were 32 pediatric adverse events associated with pimecrolimus. The majority of the patients received pimecrolimus for atopic or allergic dermatitis. As well, the majority of the cases were of U.S. origin. The cases were evenly split between males and females. The patients ranged in age from 2 months to 15 years, and there was a median age of 2 years. However, there were 14 patients that were less than 2 years old.

The adverse events seen in this population were primarily of skin reactions. However, there were 2 cases of nonmalignant tumors and 7 cases of infections.

As well, there were 4 hospitalization cases. Patients that were hospitalized were all less than 2 years of age. They were 4 months old, 6 months old, 9 months, and 18 months old.

An example of a hospitalization case involved an 18-month-old child who developed a Staph. aureus positive adenitis and was admitted to the hospital and treated with drainage, irrigation, and intravenous antibiotics. Unfortunately, the report did not tell us the time of onset of the adenitis relative to the pimecrolimus use.

A second case was of a child who was 9 months old who was admitted to the hospital and treated for osteomyelitis, osteitis, and a soft tissue infection. However, the soft tissue infection occurred 20 days after starting the pimecrolimus.

There were 7 cases of infections associated with pimecrolimus use. 4 of the cases were U.S. and 3 were foreign. The children in this subpopulation ranged from 9 months to 15 years with a median age of 18 months. The two hospitalizations were previously reviewed. The infections seen or reported included abscess formation, bronchitis,

eczema herpeticum, and keratitis, scarlatina, soft tissue infection, Staph. aureus positive adenitis, and strep throat.

There were 2 cases of nonmalignant tumor growth in the pediatric population. One case was of a 5-year-old who developed a granulomatous lymphadenitis 49 days after starting pimecrolimus. The second case was of a child of an unknown age who developed a facial tumor after starting pimecrolimus.

The following information concerning topical tacrolimus represents our post-marketing adverse event experience since approval of the product in December 2000.

There were 183 cases found with topical tacrolimus. 164 were of U.S. origin and 19 were foreign cases. There were 103 females and 74 males. 36 of the cases occurred in children 16 years old and younger. 95 percent of the adverse events seen in the overall population are found in the product label, and 50 percent of the reports involved a skin reaction.

The cases that we particularly interested in were three cases coded as death, the pediatric population, the 5 malignancies and infection cases. Interestingly, there were also 4 cases of renal failure or insufficiency associated with topical tacrolimus use. As a reminder, this is a labeled adverse event for the oral and the

intravenous preparation but not for the topical.

There were 3 topical tacrolimus cases coded with death as an outcome. 2 of the cases occurred in adults and 1 case occurred in a 3-year-old child.

The 3-year-old use topical tacrolimus for 9 months prior to expiring from an overwhelming staphylococcal pneumonia and sepsis. The patient had used both 0.03 percent and 0.1 percent strengths of topical tacrolimus.

There were 36 pediatric cases of adverse events associated with topical tacrolimus use. The patients primarily used topical tacrolimus for atopic dermatitis. 35 of the cases were U.S. and 1 was foreign. There were 7 cases where the patients were less than 2 years old.

For cases reporting the concentration or strength of topical tacrolimus, one-third of the cases reported using the adult formulation in the pediatric population. The adverse events reported primarily included skin and application site reactions. Additionally, there were 2 cases reporting detectable serum levels and 10 cases of infections associated with topical tacrolimus use.

In the 10 pediatric infection cases, 9 were of U.S. origin and 1 was of foreign origin. The patients ranged in age from 13 months to 16 years. The median age was 4 years. There was 1 death which we previously

presented, and 3 cases of hospitalization. The infections that were reported included pneumonia/sepsis, eczema herpeticum, Staph. aureus sepsis, chickenpox, warts, strep sepsis, herpes zoster, herpes simplex keratitis, erythema, and erythema infectiosum.

There were 5 malignancies associated with topical tacrolimus use. All of these malignancies occurred in the adult population. None occurred in the pediatric population. 4 of the malignancies were in the U.S. and 1 was foreign. The median age of the patients was 52 years, with a range of 28 to 56 years. 2 of the 3 cases reported an outcome of death. The onset of the malignancies was 1 month to 6 months, with a median of 3.5 months. The malignancies that were reported included anaplastic large cell lymphoma with metastases, B cell lymphoma, Kaposi's sarcoma, and 2 cases of non-Hodgkin's lymphoma. Again, systemic preparations are labeled for possible lymphoma development.

We have reviewed the AERS post-marketing adverse event reports for both pimecrolimus and topical tacrolimus. We found cases of serious outcomes with both agents. The most serious outcome associated with pimecrolimus reported was hospitalization and the most serious outcome reported with topical tacrolimus was death. Additionally we found pediatric cases of nonmalignant

tumor growth with pimecrolimus and adult malignancies with topical tacrolimus, as well as local and systemic infections with both agents.

The pediatric AERS adverse event reports demonstrated off-label use in children younger than 2 of years of age for both pimecrolimus and topical tacrolimus. In addition, the pediatric adverse event reports also showed that the adult formulation of topical tacrolimus has been used in children.

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

These three presentations are open for questions and answers. Dr. Mattison.

DR. MATTISON: Just a comment, Dr. Chesney, to back up your editorial observation. We've looked at data from other prescription benefit management companies and also have information suggesting substantial use in kids under 2 years of age for both of these agents.

The questions, though, relate to the way that the preclinical animal studies were done. I couldn't tell from the data that was presented if the animals that were used were adult or immature in these studies.

DR. HILL: They were adult.

DR. MATTISON: They were both?

DR. HILL: Adult.

DR. MATTISON: They were adult. Because I

guess I would be concerned about creating a preclinical animal study that paralleled use in developing humans and given that they're approved from age 2 on up, I would be really interested in seeing some juvenile or immature animal and then lifetime experiments with these agents.

The second question relates to endpoints. Given the data suggesting substantial likelihood for modification of response to infectious agents, what about also including in the developing and adult animal studies infectious challenges?

DR. HILL: Both points are very good. Typically for the carcinogenicity studies, they're conducted over the duration of the age life of the animal, but you're not specifically focusing on starting with the pediatric and then maybe stopping after a little period of time and seeing if lymphoma happens. Those would be special studies and actually a very good suggestion.

The challenges with infectious agents, like a host resistance model and things of that nature, typically aren't done for drug products unless you see something that you don't understand. And we did understand that these were immunosuppressive agents, so we didn't feel that those kinds of studies were necessary.

DR. CHESNEY: Dr. Santana and then Dr. Stern.

DR. SANTANA: I have two questions. One is for

you and the other one is for Dr. Pitts.

Tell me a little bit more about this animal model. It kind of goes in the direction that was being asked before. What is the time of development of lymphomas in these mice? You told us they developed lymphomas, but you didn't tell us the time ranges in which they're occurring from exposure to event. That's one question.

And the second is, have you looked at the immune function of these mice, and do you see changes in lymph nodes, spleen, et cetera, that would predict or preamble the development of lymphomas?

DR. HILL: Let me address the second part of the question first. That goes back to the results of the general toxicology studies. What we did see is we did see effects in the thymus, in the spleen, in the lymph nodes, that are indicative of immunotoxic effects which are classic for immunosuppressive agents. So that was a very clear signal.

And then for the design of the carc studies and the formation of the tumors for lymphoma, the way a typical carc study is conducted is you have exposure over the duration of a lifetime of the rodent, which is typically a 2-year exposure, and then we analyze the tumors usually at the end unless there are animals that have to be sacrificed in the interim for lymphoma formation.

The lymphoma formation, which is very clear in the special high-dose studies that were conducted in the dermal mouse, is really a matter of dose and duration. If you give a higher dose, you're going to see it at a shorter duration, and if you give a lower dose, you're going to see it at a longer duration. So with the lower doses, quote/unquote, that were given in the carc studies, you see the lymphomas later, but with the higher doses, we saw it even as early as after 8 weeks of treatment. So it really very much is dependent on dose and duration.

DR. SANTANA: Are there incidence rates for those developmental lymphomas? You mentioned I think summary cases, but I didn't get a sense whether it's a high incidence, it's a low incidence. I didn't get a feeling for numbers-wise what are we talking about.

DR. HILL: In my opinion it's a high incidence. It's 50 percent or higher and that's a high incidence for tumor formation, but that was just specifically for the lymphomas.

DR. SANTANA: Then my second question, if the chair would allow, relates to these adult patients that were in one of the last slides that were shown that develop lymphomas. Do you know more about the comorbid histories of these adults in terms of their risk of developing lymphoma in comparison to developing lymphoma and getting

this agent? Do we know whether they were immunosuppressed from HIV, they were immunosuppressed from other conditions?

DR. PITTS: We do know more. One of the patients, the Kaposi's sarcoma, was an HIV-positive patient. Another patient -- I have the data. I can get the details for you, but yes, most of the patients had other concurrent illnesses.

DR. SANTANA: So these were not purely atopic dermatitis patients that were getting this agent. They had other conditions.

DR. PITTS: They had other confounders that were present.

DR. SANTANA: But the drug was always used as a primary indication to treat their atopic dermatitis. Am I correct?

DR. PITTS: Yes.

DR. SANTANA: Thank you.

DR. CHESNEY: Dr. Stern, then Dr. Rabkin, then Dr. Danford.

DR. STERN: I had one comment and a couple of questions. When we talk about potential immune targets, I think we should very much talk about the skin. If you look at the role of photo-carcinogenesis and risk for skin cancer, the skin is clearly a very active immunologic end organ.

With that in mind, I had two kinds of questions. We know from our experience with transplant patients, using these drugs or similar drugs -- in one case the same; in another case, similar drugs -- that there are a couple of problems that are of greatly increased incidence. This goes a little bit to the question next to mine.

One is papilloma virus infection, and I'm wondering if we've done experiments there. I think that's of particular interest and importance because, in fact, in dermatologic practice, these agents seem to have their greatest advantage on the face and in the genital area, and they're clearly carcinogenic, HPV types in the latter area, and in immunosuppressed individuals, we know that not only are warts more of a problem, but in carcinoma in situ and eventually genital carcinomas. So I'd be interested about how we're addressing that.

The other thing is in extrapolating from experience with systemic immunosuppression, your studies, as I understand it, were really essentially simultaneous studies. Yet, if you look at the transplant experience, it's immunosuppression following substantial mutagenic exposure. If you look at Australians versus Swedes, one of whom prior to transplantation had on average much higher exposure to ultraviolet, the Australians compared to the

Swedes, and yet both countries, probably more in Australia, have very strong programs for their transplant patients of keeping them out of the sun. Once they're immunosuppressed, the absolute incidence, age-adjusted, is somewhere around 20-fold higher in Australian transplant patients controlling for age. So I'm as concerned about the subsequent exposure although, because of my first comment, I do think that simultaneous or day-after exposure because of inhibiting apoptosis with immunosuppression is likely to be important in terms of the body not getting rid of cells that have mutated.

DR. HILL: You raise a couple of good points. I'd like to address the virus for the skin tumors. Animal studies are conducted so that they're animals that are virus-free. Typically we don't ask for studies where we would have them exposed to the virus and then expose them to the active moiety. My personal opinion is I would anticipate you'd see an increased risk of the skin cancer in that case.

Then specifically for the increased carcinogenic risk, once again we don't have an animal model that would specifically address that because we don't have pre-initiated mice or rats and then expose them to it with UV exposure and then see if there's an increased risk. So those are not really animal studies that we've done because

I think it's pretty well established -- I don't know how much additional information we might get from that.

I just wondered if you had any more specifics. Maybe you were thinking of a specific study.

DR. STERN: I know very little about papilloma virus beyond the clinical and couldn't even speculate about how to design those. But for photo-carcinogenicity studies, I would think the mouse model would work where you take a set of mice and you irradiate them to an exposure where you expect some tumor yield farther out, so you don't continually irradiate them, and there are pretty well-established markers.

I'd probably do three groups. One group irradiation and vehicle only, stopping the irradiation well before you expect a large yield. The second group irradiation and the immunosuppressant and continued irradiation. Actually, I'm sorry. Four groups, as I think about this. The third group, just the same irradiation and a switch from vehicle to active, and the fifth group, just irradiation and active and then a switch to vehicle after the irradiation stops. I think it would be very interesting to see the various yields in those four groups. And you wouldn't need huge numbers of mice to power this, and you'd have your answer in a year basically.

DR. HILL: Thank you.

DR. CHESNEY: Dr. Rabkin, then Dr. Danford, and Dr. Ebert.

DR. RABKIN: I'd also, Dr. Hill, like to echo the point about the fact that these mice are viral free. Were they housed in SPF conditions with very little bacterial challenge? Because that's one of the problems --

DR. HILL: That's correct.

DR. RABKIN: One of the problems with these animal studies is that it's a very artificial environment, and it's very sensitive to the amount of bacterial or other agnogenic stimulation from the environment.

DR. HILL: Well, to support that, though, they're conducted under GLP conditions so that there is a standard across the board for everything. There have been instances where we have recommended specific types of studies that are different under different conditions, but we didn't do that for any of these drug products.

DR. RABKIN: Then my second question is about the difference that you noted between the sexes of the rats with the sensitivity to thymoma or thymoma development. Is that due to differences in their background rates or differences in the rates in the treated animals?

DR. HILL: It's hard to tell, but part of it might be due to the differences in systemic exposure between male and female rats.

DR. RABKIN: Just in absolute terms of the incidence of thymoma, does that have an equivalent incidence in untreated animals?

DR. HILL: Could you rephrase the question?

DR. RABKIN: You mentioned that the detectable level refers to increase over background rates.

DR. HILL: Correct.

DR. RABKIN: And the increase was present at a lower dose rate in male rats compared to female rats. Is that because the untreated male rats have a low rate relative to untreated female rats or is it because the male rats had a high rate at a different threshold than the female rats?

DR. HILL: I'm not entirely sure but it's possible that the male rat could have a greater sensitivity.

DR. CHESNEY: Dr. Hill, while you're up there, I wondered if I could ask my question.

DR. HILL: Certainly.

DR. CHESNEY: Then we'll go on.

You mentioned that in your opinion, the incidence of lymphoma in these animals was 50 percent or higher. That sounds very impressive --

DR. HILL: Depending on the dose too, dose and duration. If you have a lower dose and longer duration,

the incident rate may not have been that high, but for the higher dose studies, that's true.

DR. CHESNEY: For those of us who are the uninitiated, could you compare that to any other drug that has a similar high incidence of lymphoma development or tumor development?

DR. HILL: For tumor development in general, my opinion is that the lymphoma formations seen in these studies was higher than general tumor formation seen in other studies. It's hard to make a direct comparison because you have to make sure that you have exactly the same sets of standards when you're doing them. It's better to run the studies side by side. So when you're comparing across studies, it's difficult to say. But in general, I would say that the lymphoma signal was strong enough that I would consider it a valid signal. Sometimes you can get a little bit above background and statistically and biologically it's a signal, but this was high enough above background and statistically significant that it's a strong signal in my opinion.

DR. CHESNEY: Thank you.

Dr. Danford.

DR. DANFORD: Imagining for a moment how this drug might be used clinically, I'm picturing a child with atopic dermatitis who's treated with a high potency topical

steroid, and then when we discover that the clinical response is not what we want, then fairly promptly switch to one of these agents. I'm wondering is there any animal data or any of the adverse effects data that speaks to the issue of possible synergism between the exposure to steroids followed in rapid succession by one of these agents.

DR. CHESNEY: I think you just need to stay up there, Dr. Hill.

(Laughter.)

DR. HILL: You raise a very good point. There are no animal studies that look at co-administration of corticosteroids -- well, maybe first corticosteroids and then switching to the topical immunosuppressant or maybe concomitant use of those two, although I think the division would agree that that's an important consideration and perhaps studies to do that would be very useful to see the results.

DR. CHESNEY: Dr. Ebert, did you have a question for Dr. Hill also?

DR. EBERT: Yes. Mine is related to the doses that you used and looking at the relative human doses and that those are generally expressed in terms of milligram per kilogram per day. We've talked a lot in here about the fact that children, due to their larger body surface per

weight, tend to be at greater risk. I'm wondering whether, especially with the derm exposures, you've thought about normalizing the doses to humans based on a dose per meter squared as opposed to a dose per kilo.

DR. HILL: Actually the information I presented was -- I presented the milligram per kilogram dose, but the maximum recommended human dose, the multiples of human exposure are actually based on AUC comparisons, so systemic exposure. So the comparison is the systemic exposure achieved in the animals versus systemic exposure in humans under maximal use conditions. Typically what we selected was in pediatrics in particular because it did have a greater systemic exposure. So we looked at the PK data and our biopharmaceutics reviewer determined what was the greatest systemic exposure under maximal use conditions, and we used that to calculate the multiples of human exposure. So that incorporates really the body surface area because it's systemic exposure.

Does that address your question?

DR. EBERT: I think so. I guess I'm just saying that if you were to use dose per meter squared as opposed to dose per kilogram, my guess is that your multiples would be smaller than you're seeing.

DR. HILL: They may be, but when there is systemic exposure data available in humans and in animal

studies, it is preferred to base it on that. When you don't have any systemic exposure data, then we do it based on body surface area, and it would be based on milligram per meter squared per day doses.

DR. CHESNEY: Dr. Ten Have, then Dr. Gorman, and Dr. Mattison.

DR. TEN HAVE: Thank you. I have two questions, the first one for Dr. Hill regarding the photo-carcinogenesis result showing that the vehicle seemed to be photo-carcinogenic versus a much smaller carcinogenic effect for the actual moiety element. Did you try to control for differences between the vehicle and the moiety in the lymphoma animal studies? It looks like that may have happened with the Elidel being dissolved in ethanol.

DR. HILL: Well, in the carcinogenicity studies, in order for a tumor to be determined significant, it has to be statistically significantly elevated above the incidence seen in the vehicle control. So that controls for the vehicle there.

The studies that were conducted with pimecrolimus just dissolved in ethanol were additional studies that the sponsor conducted on their own. We didn't necessarily recommend those studies, but that data was useful to help us to get a feel for the dose and duration before you saw lymphoma formation.

I just want to make a comment about the photoco-carc studies, because you mentioned the vehicle. In the literature, it's been demonstrated that vehicle can sometimes have a very great effect on enhancement of photo-carcinogenic effect because frequently what happens with these vehicles is you basically have an increase in the amount of UV exposure that gets to the skin. The vehicle is part of the drug product and that's what's going to be used. So if you see something increase in vehicle, it's important for the drug product. Possibly the reason why you don't see such a great increase with the active in the vehicle is that you may have, in this system, maxed out what you would see. In another system, you may see a greater effect.

DR. TEN HAVE: Yesterday we saw a vehicle that was not ointment, but instead I believe peanut oil. So there are alternatives I think there.

The second question is for Dr. Pitts regarding the AERS registry search. Two questions here. One is what was the time period for the data that you retrieved from the AERS data set?

DR. PITTS: For the pimecrolimus, it was from marketing till August of this year, I think August 21st.

DR. TEN HAVE: That would be how long?

DR. PITTS: From December 2001 to December

2002.

DR. TEN HAVE: About a year.

DR. PITTS: About 18 months or so.

And then for topical tacrolimus, from December of 2002 to I think August of this year, about the same period.

DR. TEN HAVE: A second question is the time of onset for the malignancies associated with topical tacrolimus -- the onsets range between 1 and 6 months.

DR. PITTS: Yes.

DR. TEN HAVE: And there was a discussion about the comorbidity of these patients, and I'm not sure what the latency period is for these malignancies. Can you comment on those onsets in terms of the known latency period for these malignancies?

DR. PITTS: I think Lois can give me a little better information in terms of the latency of the actual, but for these particular cases, the 28-year-old had a history of HIV, onset of 1 month. A 50-year-old had an onset of 4 months. Another patient had an onset of 6 months, and another patient, an onset of 3 months. So I think somewhere in the Prograf label, there may be some language about an acceleration or a decrease in time to occurrence, but I can't tell you what the natural history is. I can't but I think someone else may be able to help

us with that.

DR. RABKIN: I can address that a little bit.

DR. PITTS: Thank you.

DR. RABKIN: Both of those malignancies are seen very rapidly after the onset of severe immunosuppression in the transplant setting and other situations in which people have sudden loss of immune function. So post transplant, within several months, lymphoproliferative disease that's EBV associated is seen and these can rapidly progress to lymphoma, and similarly Kaposi's sarcoma can be seen very rapidly after transplant associated immune suppression and can be occurring within months. That's in contrast to the usual latency for carcinogenesis which tends to have a much longer period, including in the setting of immune suppression, the carcinomas that occur tend to be much later.

DR. CHESNEY: Thank you. Dr. Gorman, Dr. Mattison, and Dr. Fink.

DR. GORMAN: I have a specific question for Dr. Pitts concerning one of the cases in the tacrolimus database on slide 16, the 3-year-old who at 9 months had streptococcal pneumonia. Was that a domestic case, a United States case? Was the child immunized with a commonly available vaccine against streptococcal disease?

DR. PITTS: That was a foreign case. There's

not a whole lot of detail to the case. The patient I know had used both products, the 0.03 percent and 0.1 percent, and we had the onset information. So I have no idea in terms of the immunization history.

DR. GORMAN: Thank you.

The second question is for Dr. Hill, and it is looking for a slightly different viewpoint on information. Is there a dose response to this agent? If I understand these agents correctly, they bind to proteins that then interfere with a phosphatase activity. Is there a dose at which that activity falls to zero? So when we're dosing mice and rats and children repetitively with higher and higher doses, do we effectively run out of benefit and then only increase the risk?

DR. HILL: It's a good question. We don't have data that could really address that at this point. There haven't been studies conducted in animal models in vivo looking at when you give different doses and you see lymphoma formation, when is the cutoff period where you still see calcineurin inhibition, an efficacy effect possibly, and then when it progresses on to lymphoma. Most of the calcineurin inhibition has been in vitro and it's very difficult to extrapolate in vitro to in vivo situations.

DR. GORMAN: Is there a whole cell model that

might begin to answer that question?

DR. HILL: Could you rephrase the question?

DR. GORMAN: Is there a model either animal or in a test tube that will give you a dose-response curve that will tell you when you've maxed out on the response for this particular group of agents?

DR. HILL: Well, I think it would be difficult because I don't know of an animal model that could mimic atopic dermatitis. So it would be difficult to get that efficacy signal as well as the lymphoma risk.

DR. GORMAN: Thank you.

DR. CHESNEY: Dr. Mattison, then Dr. Fink.

DR. MATTISON: Three questions. One relates to the bioavailability. In Dr. Nikhar's presentation, on the sixth slide, she indicates that bioavailability of topical tacrolimus is unknown. Given that that's the case, how are systemic exposures estimated or evaluated for this drug?

The second question relates to practice. Yesterday we heard that it was thought that common practice among dermatologists is to encourage fairly aggressive use of these topical agents initially and then tapering as the skin response occurs. Is that also thought to be the case with these?

Then given that these agents are used in immature individuals, what do we know about the interaction

of these agents with the development of the immune system? Do they alter immune system development?

DR. NIKHAR: I will try and answer your PK questions. As far as the IV bioavailability, it's about .5 percent, and as far as the oral administration of Prograf and so on, the information I have is that in adults with an average about 53 body surface area involvement treated with Protopic, the exposure of tacrolimus is about 30-fold less, and that's seen with oral immunosuppressive doses in kidney and liver transplantations.

Then as far as your second question goes, yes. The use is limited to about 6 weeks or less depending upon clinical response at present.

And the third question, the answer to that is that it's still being evaluated. I can't really talk more, but some studies are being conducted looking at the immune system, the interaction with vaccines, and so on.

DR. CHESNEY: Dr. Stern, you had something immediately pertinent?

DR. STERN: To take up your point, I think the issues about these are -- and I'd like to make a comment and then ask a question. It's my perception as a practitioner that in fact there's a perception in the community at large, in spite of that labeling, that among parents particularly, that these agents are safer than even

mild topical corticosteroids. That goes to my question of do we have IMS data that tells how many of these prescriptions are by primary care physicians versus by specialists, because if an agent is supposed to be for people who are intolerant or nonresponsive to first-line agents, we'd expect a high proportion of specialists prescribing.

In my own practice, which does not have very many children, but lots of adults, I see this being given as a first-line drug to people where the diagnosis is not necessarily even within the indications and certainly not people who have had mild to moderate potency steroids because of, I think, as we've seen by sales, a very active place in the marketplace, if you read the journals.

So I'd like to know is this really being used and promoted in a way that is consistent with the indications or is there evidence to suggest that the perception of prescribers and in fact patients is that this is safer than topical steroids and used more widely?

DR. CHESNEY: Dr. Pitts.

DR. PITTS: I can answer the question about IMS data. We don't currently have IMS data on these specialties that are prescribing. I think we can probably request that information, but right now we don't have that, and I don't have any further information.

DR. CHESNEY: Dr. Fink. Dr. Wilkin, did you want to add to that?

DR. WILKIN: I share Dr. Stern's perceptions on I think what may be out there. I'm not implying that the manufacturers are presenting it this way, but I saw really bold headlines in one of the throwaway journals: "Move over Steroids." Then the article talks about topical calcineurin inhibitors.

I think there is a great enthusiasm for things that are new. This is not just for drug products. This is for everything. In fact, I like occasionally to read things about ancient Rome, and Tacitus who wrote Agricola -- I think it's in chapter 29 or 30 -- is talking about the young centurions and the Romans that want to make a name for themselves, and there's this great opportunity beyond the unknown borders of the frontier and it's very exciting. And the line is, omne ignotum pro magnifico. Anything not understood is seen as glorious.

(Laughter.)

DR. WILKIN: I think quite literally everything new, whether it's a new drug product or anything else, there's a lot of hope that goes into it. So I think that plays into it.

Then I think there has been some, if you will, pharmaco fear mongering about the topical corticosteroids.

They have definite things that we have to think about that would be considered potential adverse events, but they really have been a stable workhorse. I think a lot of physicians really understand the good and the bad and understand the balance and how to use them very effectively. But I think what we're talking about, the steroids versus topical calcineurin inhibitors, really plays out in a lot of other areas of new drugs versus drugs that have been on the market, new technologies versus -- I don't think it's limited to pharmaceuticals.

DR. CHESNEY: Thank you. I had actually just given that same line to Tom, but it was in chapter 28. So I just wanted to correct that.

(Laughter.)

DR. CHESNEY: Dr. Fink.

DR. FINK: This is a question I guess for Dr. Hill or Dr. Wilkin. Given the fact that you have a fairly strong animal signal for lymphoma and that you have at least human case reports of occurrence of skin malignancies and that you're treating a non-life-threatening condition, how much stronger does the signal have to be before the drug is considered inappropriate for a non-life-threatening condition? I'm sort of wondering if you see it in 50 percent of rats, but the drug was still approved for use, if it were at 75 percent, does it become unapprovable? At

what level would this drug be considered nonapprovable for a non-life-threatening disease even though it's one that clearly is quite bothersome to the individuals affected?

DR. WILKIN: I think the compelling piece for approval is that there is this safety margin, in other words, the difference in the AUCs. Our concern with the topical calcineurin inhibitors is we know from the systemic exposures that it seems to be cumulative dose that has something to do with the eventual development. We don't have in the short-term studies really good evidence that these events are occurring. We made them second-line therapies. We have in the labeling the information about the animal studies. I think it's labeled so that physicians can make good choices, and not every patient can take topical corticosteroids. So I think there's a place for these products.

Our goal is to learn more, and when we learn more, we may have a better understanding of the risk-benefit calculus that we may say they're first-line therapies or we may go in the other direction and be more restrictive. I think it's the issue of uncertainty right now.

DR. CHESNEY: Dr. Ten Have.

DR. TEN HAVE: This is a question for Dr. Wilkin and maybe Dr. Rabkin. What is a margin of safety

with these doses? Because we had a wide range of margins ranging from 258 to 340 times the maximal dose in humans compared to the rats down to 26 versus 17 times. Do you have a range that you work with in terms of safety?

DR. WILKIN: I just gave away my only copies of the labeling. I think we have incorporated these safety margins in the labeling. They're being copied because we actually are going to share parts of this with the committee. Maybe we could defer and come back to that.

DR. DIANNE MURPHY: I think what we're going to be doing is handing you the patient package insert because we're going to incorporate into the first question this risk management issue so that we can get some feedback on that.

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

DR. EBERT: It's kind of a corollary to Dr. Stern's question earlier, but it seems as though part of the issue here is whether the adverse effects are associated with suppressing the immune system versus inherent carcinogenicity of the compound. Given the limitations of the AERS data, do we have any ideas as far as the nature and types of adverse effects for topical corticosteroids versus these calcineurin inhibitors? Are the same types of adverse effects coming up for those agents as well? Mostly yesterday I think we talked more

about adrenal insufficiency, but are there some of these same neoplasms that come up in that database?

DR. CHESNEY: We did receive in our blue handbooks for the committee copies of the package inserts already.

DR. STERN: And the patient information as well.

DR. CHESNEY: And the patient information. It's under tab 4 for those of you who wanted to check it out.

DR. PITTS: Dr. Ebert, you're referring to the malignancies? I don't believe we saw those particular reports for the topical corticosteroids.

DR. STERN: And I do believe there's a fairly substantial animal and human data of photo-carcinogenicity with topical steroids, which is largely a negative one essentially. Beyond vehicle effects, there's little to suggest that for photo-carcinogenicity, topical steroids are a problem.

DR. CHESNEY: Dr. Epps, but I think Dr. Wilkin wanted to make a comment.

DR. WILKIN: In response to the earlier question, what are the safety margins, if you turn to that tab 5 and go to page 11, you'll see the carcinogenesis, mutagenesis, and impairment of fertility section for the

labeling for one of the products. Towards the bottom of the large paragraph in the middle of the page, it says, no lymphoproliferative changes were noted in this study at a dose of 10 milligrams per kilogram per day. Then in parentheses it says, 17 times MRHD, and you have to read further where it says that's the maximum recommended human dose based on AUC, which is area under the curve, comparison. So those would be the safety margins that we've placed into labeling.

DR. TEN HAVE: So most of those margins were above the safety margin of 17 in the studies that were presented.

DR. WILKIN: Yes.

MR. PEREZ: That's tab 4, by the way, page 11.

DR. WILKIN: Oh, yes. It's tab 4. If I said another tab, excuse me on that.

Yes. In fact, you can read through and read what some of the other findings were, and the longer I look at this, I can see 17 times for the mouse dermal carc. No increase in incidence of neoplasms was observed on the skin or other organs up to the highest dose of 4 milligrams per kilogram per day. And that's 27 times.

We don't have some sort of standard at FDA on the safety margin. It has a lot to do with the risk-benefit calculus. I would think that we could find

approval for a product that might be used over a short-term basis that is rescuing a patient who is in severe distress from something that is potentially life-threatening and they might actually have a safety margin that literally is less than 1. But we do take the numbers and think about the potential benefits from a product and try to weigh that.

DR. CHESNEY: Dr. Epps.

DR. EPPS: I guess I have kind of a comment for Dr. Hill and I guess a point of information. To piggyback on what Dr. Danford said, patients who are referred to me as a subspecialist usually are tried initially on a class VI or VII steroid and then switched over to some of the immune modulators rather than a potent topical steroid.

Also, I do think it's aggressively promoted to primary care providers as something that doesn't cause atrophy and something that is perhaps safer or an alternative because there are quite a few patients who have never even tried steroids. They don't use emollients. They don't use any of the other things that we use to treat atopic dermatitis. So for a study, if you're going to do something in addition to the strong topical steroids, which we use in older kids, followed by some of the newer ones. You could do weak ones perhaps in animals.

Also there are people out there who are

compounding these new drugs with steroids. So you may want to find out if there's something synergistic going on, whether that affects what's happening. Is it as effective or is it increasing with suppression? So I would look at that too.

DR. CHESNEY: How can you do that? How can you just compound it with anything you want?

DR. EPPS: Write the prescription and a compounding pharmacist does it.

DR. CHESNEY: Dr. Ebert, could you comment on that? I didn't realize that they could mix it with anything they want to.

DR. EBERT: Yes. Extemporaneous compounding is a relatively common procedure.

DR. CHESNEY: Hello.

(Laughter.)

DR. CHESNEY: So much for all our perseveration about some of these issues.

Dr. Fink.

DR. FINK: Just a comment I guess. In some classes of drugs, a safety factor of 17 -- if it was an antibiotic, it's hard to imagine a physician prescribing 17 times the maximum recommended human dose or a patient swallowing it. But as we heard yesterday, with some of these topical agents, they seem to be fairly commonly used

at doses that may approach or exceed 10 to 20 times what most of us would consider a prudent dose if not a maximum recommended human dose.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: One of these agents is also approved in an oral form. It's for a more life-threatening indication. Are there ongoing studies in that particular formulation that might give us some information in a forward-looking mode?

DR. HILL: If you're referring to animal studies in particular, no, there are not any studies currently ongoing.

DR. GORMAN: I was thinking of phase IV post-marketing studies for those agents. If we're looking for signals of tumors, perhaps we could look at the oral forms to at least know where to look.

DR. STERN: Well, there's a large literature on the calcineurin inhibitors or rather in solid organ transplant patients. And there are not just signals, there's clear evidence for both squamous cell carcinoma and for lymphoma, both the so-called post-transplant part, but also in terms of other forms of lymphoma with long-term therapy.

Let me briefly summarize the data on the calcineurin inhibitors used in relatively low risk

patients. If you take a group of Swedes and you transplant them and you maintain them generally at fairly low doses of a calcineurin inhibitor, sometimes in conjunction with another immunosuppressant, often in conjunction with some corticosteroids systemically, you see a small increase in the risk of squamous cell carcinoma or a modest increase in the first 2 years. Beginning about 2 years after use and at least as far as the studies I've seen, not very dependent as much on dose, but as on duration of immunosuppression, you start to see an increased risk such that the relative risk compared to what's expected by year 5 exceeds a 100-fold increase in squamous cell carcinoma.

It's also interesting, although I'm interested about the papilloma virus, if you look at genital neoplasms that are often papilloma virus associated, there are modest increases in risk also in a time-dependent fashion, but on the order of sort of 5 to 10, not 100-fold. So there's no doubt that long-term immunosuppression with this class of agents is in fact the sine qua non for making squamous cell carcinoma in the skin in susceptible individuals.

If you take Australian transplant recipients who stopped going out in exposure, their incidence rate approaches 38 tumors per 100 persons per year of squamous cell carcinoma, in other words, an average of one tumor every 3 years for every person who is transplanted, again

beginning 2 to 5 years after transplantation.

If you take patients of particular interest to me and in fact some in a therapy that is mainly used for psoriasis and cutaneous T cell lymphoma, oral psoralin photo-chemotherapy which is a very excellent photo-carcinogen and in fact is used in some animal photo-carcinogenicity studies as the positive control for systemically administered agents, if you take those individuals who've had more than 200 PUVA treatments, which is a level that is shown to be associated with a substantial, about 10- to 20-fold, increase in risk by itself, and you treat them with cyclosporine, a drug that's approved for the treatment of psoriasis, generally used at fairly low doses, typically about 2 to 3 milligrams per kilogram, rather than the higher 5 milligrams or so per kilogram used in transplant patients, you see a 6-fold increase in their risk compared to what they had on the basis of PUVA alone, and you see an incidence approaching, after 2 years of exposure, 1 per person per year of squamous cell carcinoma of the skin.

So it's not a question of whether immunosuppression in the skin will lead to an increased risk of squamous cell carcinoma. It's a question of how much, how soon, at what doses, and what the level of risk will be, and how we moderate that.

I think there are some very interesting questions in the pediatric age group. One of the interesting things is that, to the best of my knowledge, there are no robust data. There are two things. There are no robust data on basal cell carcinoma risk in transplant patients. There's some suggestion of modest increases in risk, but certainly not the same as squamous cell carcinoma.

But we believe that the key interactions between sunlight, probably UVB, and skin cells that predict basal cell carcinoma risk are either after a very long latency or after childhood exposure. If you look in nature at when sun exposure matters in terms of squamous cell carcinoma, it's cumulative and in fact recent exposure has a real impact on subsequent risk. If you look at basal cell carcinoma, the level of childhood risk, after controlling for other risk factors, is the principal determinant.

So one question is with these patients in childhood, are we changing something in terms of apoptosis of cells that are going to go on to basal cell carcinoma 20 or 30 years later independent of their continuous use?

Similarly, with melanoma, at least as I read the transplant literature, there's relatively little evidence to suggest a very substantial increase in melanoma

risk with long-term immunosuppression. There are some studies that suggest modest increases in risk with very long exposure, but it's nothing like squamous cell carcinoma. But again, if you look at when are probably the salient mutagenic events occurring for melanoma, it's also probably early in life, the same kind of thing with most types of melanoma, childhood exposure rather than cumulative life-time exposure seems to be the main, at least UV determinant of melanoma risk. So if you're changing how you're handling UV insult at that presumably susceptible period, you may impact lifetime risk of melanoma in a way different than we've been able to observe or not observe when we follow adults who are immunosuppressed for long periods.

DR. CHESNEY: On that sobering note, I think we're right on time, and we're scheduled for a break. If everybody could return at 10 o'clock, we'll resume at that point.

(Recess.)

DR. CHESNEY: Could we get started please?

The first speaker for the second half of the morning is Dr. Lois La Grenade. Dr. La Grenade is an epidemiologist in the Office of Drug Safety, the Division of Drug Risk Evaluation. She is a British-trained dermatologist and epidemiologist, and she will present on

the design considerations to be considered when studying the risk of cancer from use of topical calcineurin inhibitors.

DR. LA GRENADE: Good morning. I am Lois La Grenade, and up until a minute ago, my slides were perfect. I don't know what has happened.

(Laughter.)

DR. LA GRENADE: But in the interest of time, we'll proceed with the presentation and I hope that you can follow as I can.

As you've heard, I'm an epidemiologist in the Office of Drug Safety, and my presentation this morning will discuss some of the design issues that are important in studying the risk of malignancies with topical calcineurin inhibitor use in children.

For the first part of my presentation, I will discuss the methods that are available generally in observational epidemiology. Then in the second part, I will focus more closely on the methods that would be appropriate to study the risk of cancer with long-term use of calcineurin inhibitors.

In observational epidemiology, we have a limited number of design methodologies. First of all, there's the case-control method, and there's the cohort method, and then there are registries which are really

surveillance tools.

Case-control studies are basically retrospective in nature. That is to say, we start the study after the disease of interest has already occurred from the suspected exposure. We then compare cases who are people with the disease of interest to controls who are people without the disease of interest. What we compare is the frequency of the exposure of interest between the cases and the controls.

Because the advantages of a case-control study are that it's fairly inexpensive compared to the others, it can be done relatively quickly within a few months or at most a year or two usually. And it's generally useful for studying rare events, particularly those with a common exposure.

However, because of its essential retrospective nature, there are a number of disadvantages. It's subject to a number of important biases, recall bias being a very common problem, and this is because the disease occurs so long after the exposure occurred, you then have to go back and try and get information on the exposure. Very often cases may systematically recall the exposure differently from the controls, and this leads to what we call recall bias.

It's also subject to selection bias. The cases

may not be representative of all cases. The controls may not be representative of all controls.

And it may be unsuitable for studying diseases with a very long latency period such as cancers.

It's also difficult to study diseases with a very rare exposure.

Cohort studies, on the other hand, are prospective studies. In a cohort study, we compare essentially exposed to non-exposed persons. We start with a defined group of people and they may be defined by a common exposure, by a common disease, or by a place of residence. The Framingham study in Massachusetts, is an example of a cohort study defined by a place of residence, the Town of Framingham in Massachusetts. And you follow your cohort through time for the ascertainment of the disease or diseases of interest.

The advantages of a cohort study are that the exposure and the case status are determined prospectively. So recall bias is minimized. All cases can potentially be captured, so selection bias certainly in regard to cases can also be minimized. Another advantage of a cohort study is that you can study several diseases or outcomes at the same time.

Cohort studies are most closely related to the experimental design where a toxin is administered and then

you follow the subjects for outcomes. As a result, there is a high acceptance of results generated by a cohort study by the scientific community. And cohort studies often are used to confirm findings that are found in quick and dirty case-control studies.

Now, the disadvantages of a cohort study is that they tend to be very expensive. They require large sample sizes, particularly so for rare disorders, and they take a long time, many years, sometimes many decades. Because of the length of the cohort study, we often have subjects dropping out for one reason or another with resulting problems from losses to follow-up.

One of the ways of overcoming this disadvantage of length of a cohort study is to use a retrospective cohort study, and the way this is done is that you use a preexisting cohort, for example, an occupational cohort or a drug-exposure cohort. Then you look in that cohort for cases of the disease of interest, and then you compare the frequency of the disease of interest or the incidence in your cohort to population incidence rates in a method called the standardized incidence ratio. This is a method what was first popularized in occupational epidemiology.

Registries, which as I said, are surveillance tools are rarely little more than rosters of subjects, subjects who are identified by a common exposure, and those

are exposure-based cohorts, and occupational cohorts would fall into this category as well.

Or registries can also be disease-based. Our State and national cancer registries are examples of disease-based registries.

Registries may either be complete or incomplete. Complete registries are usually mandatory, and all subjects with the exposure under investigation or the disease under investigation are captured and entered into the roster. Incomplete registries are usually voluntary, with subjects choosing whether or not to participate.

Registries can be used in a variety of ways in epidemiology. Exposure registries can be used as cohorts, in which cases can be ascertained and incidences calculated within the exposure cohort. Case-based registries can be used as a source of cases for case-control studies. In general, complete registries are far more useful in epidemiology and they can be used to determine incidence rates for diseases as is done with our cancer registries. Incidence of rare events can also be calculated in a rare exposure registry.

Now we turn from general methods to the methods that would be appropriate for the specific topic of investigating the risk of malignancies with calcineurin inhibitor use in atopic dermatitis.

There are very special problems with cancer studies because cancer is a rare event, and particularly in young people, in adolescents and young adults. Cancers have a very long latency period usually in that many years, sometimes many decades elapse between the exposure and the clinical appearance of the malignancy. For this reason, the prospective method, either the cohort or the registry, is ideal.

Case-control studies, as I said, are generally used for quick and dirty studies, studies where a signal has been generated by case reports of an association between a previously unsuspected exposure and a particular disease.

In designing a cohort study for this purpose, it should be prospective, as I said. The exposure assessment could then be done accurately and in a standardized fashion. We could collect information on dose and duration of topical calcineurin inhibitor use. And dose and duration information on these two factors is very important in cancer studies and in trying to do causality assessments. The cases can also be ascertained as completely as humanly possible and as accurately as possible. In addition, in a cohort study we could collect data on confounding and other risk factors as well.

Cohort studies are expensive and require a lot

of effort, and they're generally indicated where there is good evidence of an association between a disease and exposure. This good evidence could come from clinical studies, from case-control studies, or from other studies, for example, animal studies, and I will put forward the view that we have good evidence in this case. We have good evidence from clinical studies in humans with oral calcineurin inhibitor use for organ transplants, and we have good animal toxicology data.

Cohort studies are also indicated when a new agent that requires monitoring for its possible association with several diseases is introduced into a society. Again, I think that the case of calcineurin inhibitor use in topical treatment of atopic dermatitis fulfills this criterion.

Fletcher and Griffin in 1991 wrote an article entitled International Monitoring of Adverse Drug Reactions of Long Latency, and in it they wrote, that for adverse reactions of long latency to be detected methods have to be used that permit observation of the patients to be followed for many months or years. An essential requirement is the establishment of a cohort of patients who can be accessed later on at specified intervals.

These are some of the important issues that we have to consider in designing a cohort study for the

development of malignancies with calcineurin inhibitor use. In the next few slides, I will spend a little time discussing each one of these features.

The background you have largely heard from Drs. Nikhar and Hill, who have spoken before me this morning, but I thought it useful to summarize it basically in these slides.

First of all, with the vehicles of both topical calcineurin inhibitors, we have found enhanced photo-carcinogenicity. In animal carcinogenicity studies, there has been a signal for both lymphomas and other systemic malignancies. Use of oral calcineurin inhibitors in solid organ transplants has shown that there is a high incidence of lymphoma and cutaneous malignancies particularly. The risk is greatly increased, as Dr. Stern has told us earlier this morning.

The objective of the study would be as outlined in the approval letter for both products which required a phase IV commitment study to investigate the risk of developing cutaneous and systemic malignancies in children with atopic dermatitis who have long-term intermittent treatment with topical calcineurin inhibitors.

Now, the outcomes of interest would be malignancies. Cutaneous malignancies, including melanomas and non-melanoma skin cancers, and systemic malignancies,

including lymphomas, both Hodgkin's and non-Hodgkin's, and other systemic malignancies.

I want at this stage to introduce a question of whether, bearing in the light of the information that we have, we ought to consider the use of an additional endpoint, for example, actinic keratoses. I will come back to this point later on in my presentation.

We have to choose a study population. If this were to be a traditional cohort study, we would choose a cohort of children -- and we define children as being aged 2 to 16 years -- who had atopic dermatitis, and we'd follow this cohort for the next 10 to 15 years and document during that time the type of treatment each child had received, the response to treatment, the presence of confounding or other risk factors such as sunlight exposure, skin type, disease severity and extent, and so on. And we'd document the occurrence of malignancies as they appeared. At the end of the follow-up period, we would compare the incidence of malignancies in subjects treated with calcineurin inhibitors to that in subjects not treated with calcineurin inhibitors.

But there are difficulties with this traditional cohort approach. For one thing, we'd require very large sample sizes. It would take a very long time, and we may find at the end of the follow-up period either

that most patients had used both calcineurin inhibitors and non-calcineurin inhibitors or vice versa, that only a very small population had used calcineurin inhibitors as treatment. What we might find in that situation is that it would be difficult to compare. We would have reduced power and we may, at the end of all that time, end up with no answers.

An alternative method would be to use the occupational cohort or the exposure cohort type of methodology. We could enroll a cohort of calcineurin inhibitor users, aged 2 to 16, children who had used it for atopic dermatitis, follow the subjects I think for a minimum of 10 years, possibly longer, and we could use as our comparator age-specific population incidence rates for cancer. These we would get from our cancer registries or data from national sources. We could then calculate the standardized incidence ratio in a method similar to the occupational cohort method. I believe that Dr. Stern himself has used this method in a long-term cohort of PUVA-treated patients for psoriasis, studying this exact question, the development of malignancies in the PUVA-treated patients.

Now, there are difficulties, nevertheless, with this approach. We have no U.S. national incidence data for most cutaneous malignancies. Dr. Wingo is present today

and she will speak to us later on exactly what we can and cannot do with our national and State cancer registries. But it's my understanding that we have limited information on cutaneous malignancies, other than for invasive melanoma.

We may, therefore, have to extrapolate from data from other countries which do collect such data such as Finland or from regional data in the United States. We have, for example, the southeastern Arizona skin cancer registry which does collect information on incident non-melanoma skin cancers.

Now, this slide is courtesy of the SEER cancer statistics web site. What it shows is the age-specific incidence for all cancers by gender. I use this slide to illustrate the very low incidence of malignancies in the age groups younger than 20. The incidence begins to rise in the mid to late 20s.

This slide is similar, but I've used data from the southeastern Arizona skin cancer registry and I've shown here the age-specific incidence by gender for squamous cell carcinoma. Again, we see that it is low in the very young age groups and it doesn't begin to rise until about age 30 or so.

Similar for basal cell carcinoma. It doesn't begin to rise until about age 30.

This low background incidence rate of malignancies in young children and young adults is going to have problems or implications for a sample size and power later on. This is the reason for my showing them.

What I've done, because of the issues that we are going to have with power and sample size, I've done a number of specimen calculations on the various scenarios using different background rates for malignancies.

This particular slide uses data for all malignancies and some of my information is not showing at the bottom of the slide, but it's for all cancers in the 25 to 29 age group. The incidence is 6 per 10,000, and the data is taken from SEER. What we have done is calculated possible sample sizes for the traditional cohort method where we would have two comparison groups with atopic dermatitis. We can see that to detect the relative risk of 3, we would need a sample size of just over 20,000. To detect a relative risk of 4, we would need a sample size in total of 12,000, and a relative risk of 5, a sample size of 8,000.

If we want to study all malignancies in the 0 to 19 age group -- again this is SEER data -- but using a single group using the occupational cohort analogy here, we would find that to detect a relative risk of 4, we would need 14,000; of 6, 8,000; and of 8, 6,000 in a single

group. So this is probably doable.

However, if we looked at lymphoma, which has a much lower incidence rate -- and this is lymphoma, all types, in the 0 to 19 age group. The background rate is 24.1 per million population annually. We can see that to detect a relative risk even as high as 4, we would need 115,000 patients, and to detect a relative risk of 10, we would need 32,000 subjects.

Given these problems with the sample size and power, I thought it might be useful to look at the problem from another angle. Perhaps we could have a fixed sample size and then see what would be our probability of not detecting a case when in fact we had a given relative risk.

So here I've done sample calculations for a sample size of 10,000. If we try to detect a relative risk of 4, we would have a 38 percent probability of not seeing a single case. If we tried to detect a relative risk of 8, we would have a 15 percent probability of not seeing a case, and conversely an 85 percent probability of seeing a case. If we had a larger sample size, say, 20,000, we would have a lower probability of not seeing a case for a given relative risk. So one approach might be that we could decide on a sample size and then decide what level of certainty or uncertainty we'd be comfortable with.

This slide just demonstrates graphically the

same thing that was illustrated in the table slide previously, that the higher our relative risk goals, the lower the probability of us not finding a case for a given sample size.

Another way in which we could boost our power and sample size would be to have a multi-center or even a multinational cohort study, and I'm hoping that Dr. Salmon who represents the EMEA today will speak to this issue of the multinational participation in a cohort study.

I come back to the possible use of additional endpoints in the form of actinic keratoses. Actinic keratoses have traditionally been regarded as precursors of malignancies. In fact, they are abnormal proliferations of keratinocytes confined to the epidermis. More recently we've studied them in greater detail and have found, to a large extent, the cell types in actinic keratosis is identical to that of squamous cell carcinoma and abnormal cells in actinic keratosis possess the same P53 mutation as is found in squamous cell carcinomas. Recently there's a movement to have them regarded as squamous cell carcinomas in situ.

In some studies, up to 60 percent of all squamous cell carcinomas have been found to arise in preexisting actinic keratoses, and actinic keratoses are very rare in young people. They usually are a marker of

sun exposure and for that reason it might be useful for us to include it as an endpoint. If we didn't have a duration of the study long enough to pick up squamous cell carcinomas later on, we could use it as a predictor perhaps of who would go on to develop squamous cell carcinoma. Certainly we don't normally see actinic keratoses in very young people and it would be a signal that all was not well.

We need to define our exposure both from a minimum definition at enrollment to use as an enrollment criterion. We need to define what we mean by long-term intermittent exposure to calcineurin inhibitors. Some of the suggestions that we have toyed with in our division and the Derm Division is whether 6 weeks exposure, continuous or intermittent, would constitute a minimum definition of long-term intermittent, whether we should extend it to 3 months, whether we should use a dose amount, the use of 30 grams intermittently or continuously over a 6-week period. All these are things for discussion.

Now, we also need to define exposure assessment during the study itself. How are we going to assess the exposure? One method is to use the issuing of a prescription plus self-report of use by the caregiver or by the subject him or herself once they were old enough. We could also use a combination of methods used in clinical

trials to return unused portions of the tubes, to weigh the unused portions of the tubes, but in deciding how to define exposure assessment during the conduct of the trial, we'd have to consider the additional burden to participants and consequent losses to follow-up that might result versus the obtaining of more accurate information.

Another question is how would we ascertain malignancies. We could use histopathological definitions. We could use international classification of disease codes as our definitions. If we had an exposure cohort on whom unique identifier information had been collected at baseline, we could link with our national and State cancer registries certainly to ascertain systemic malignancies. But we could not do this certainly in the United States in most instances for cutaneous malignancies because we have only limited data on cutaneous malignancies in our cancer registries. Self-reporting of cutaneous malignancies has not been shown in most studies to be reliable.

So we're left with the problem of how to ascertain cutaneous malignancies. We couldn't use, as I've said, linkage to State and national cancer registries because these do not routinely collect the information. Non-melanoma skin cancers, specifically basal and many early squamous cell carcinomas, are often treated in office or patient settings, so we could not use hospital records

or hospital discharges to ascertain cutaneous malignancies either. In addition, basal cell carcinomas and actinic keratoses may be treated with a variety of locally destructive methods with no samples even being taken for histology. So if we use pathology logs to ascertain cutaneous malignancies, we would be missing a substantial number of them.

Bearing all these things in mind, I would suggest that ascertainment of cutaneous malignancies should best be done by periodic, possibly annual, physical examination of the skin by a physician, preferably by a dermatologist. I say preferably by a dermatologist because in at least one study recently in Ireland, they compared general practitioner diagnosis of lesions that were subsequently found to be malignant on histology with the pre-histology diagnosis by a dermatologist, and general practitioners got it right 22 percent of the time compared to dermatologists who made the correct diagnosis of a malignancy 87 percent of the time on clinical grounds.

Physical examination is particularly important if we want to capture all the malignancies or as many as possible in a short enough period of time so that we can have an early and accurate assessment of the risk.

The duration of follow-up is another important point. I would recommend a minimum of 10 years for each

subject. Ideally this should be longer, but I think to reflect a minimum latency period of cancers, a minimum of 10 years would be suitable. It could be that the latency period is shortened and we would get results sooner than 10 years, but I think the minimum is 10 years.

Now, a very important aspect of such a study would be minimizing losses to follow-up because this is an important source of bias in cohort studies. Entire papers have been written on how to minimize losses to follow-up in cohort studies. I'm not going to spend a lot of time on this except to say that vigorous methods will need to be pursued to reduce losses to follow-up. I believe that Dr. Andrews, who speaks later on in the morning, may address some of these issues.

We'll also need to incorporate statistical methods for handling losses to follow-up. In our statistical analysis plan, we would be able to calculate crude and adjusted incidence rates within our cohort and to calculate the standardized incidence ratio. Depending on the numbers, we might also be able to explore dose-response relationships and the effects of other confounding factors such as disease severity and that sort of thing, but that depends on how many cases we would find.

Now we turn to whether the registry design were used to investigate this problem. A registry would have to

be mandatory with all users registered. If this were done, we would at least know the number of all the patients or close to the real number of all patients who had used calcineurin inhibitors topically. If we could ascertain all the malignancies, the registry would probably be the fastest method for getting incidence rates.

Unfortunately, however, there are problems with the registry method. There is generally poor acceptance of mandatory registries by both physicians and patients alike, and sometimes they go to the extent of avoiding use altogether to overcome the problem of having to be registered.

Registries are also expensive, perhaps not quite as expensive as cohort studies, but they're expensive nevertheless, and we have probably nowadays patient privacy issues to deal with.

Although we would get accurately the number of people who had used topical calcineurin inhibitors, we would not be able, in a typical registry, to get information on the dose and duration of exposure, nor would we be able to get information on disease severity, on skin types, and that sort of thing, other confounding factors. Again, we come back to the problem that it's not possible to ascertain most skin cancers.

So in this slide, I thought I would summarize

important factors that we require in a study to investigate the risk of malignancies with calcineurin inhibitors and how each of the possible design methods measured up.

Exposure assessment in a cohort study would be good. It would be fair in the registry situation because we wouldn't have detailed information on dose and duration of therapy, for example. And in a case-control study, this would be not very good largely because of the retrospective nature of the study.

Outcome assessment would be good in a cohort study, but incomplete in a registry because we would not be able to ascertain completely cutaneous malignancies. Likewise, it would be incomplete in a case-control study.

The duration of both the cohort and the registry studies would be long. A case-control study would be short, but we'd have to wait 20 or so years down the line before we could conduct it.

The cohort is probably the most expensive, with the registry coming in a close second, and a case-control study being relatively inexpensive.

Both the cohort and the registry would require large sample sizes. A case-control study would require probably a much smaller sample size, but again, we'd have to wait for a considerable time before we could undertake such a study, and I do not believe that the public health

would be served by waiting 20 years to undertake a case-control study.

Risk factors and incidence could be calculated fairly well or could be assessed fairly well in a cohort study. We'd have incomplete incidence in a registry and we couldn't calculate incidence in a case-control study.

The relative risk we could calculate in a cohort study, not in a registry, and the metric that we calculate in a case-control study is an odds ratio which is an approximation of the relative risk but is not itself the relative risk.

We could calculate the standardized incidence ratio in a cohort study and for systemic malignancies in a registry, but not in a case-control study.

On balance then, it would seem from the scientific point of view the cohort study would be the method to choose because it has advantages over the other two methods.

Nevertheless, if we chose a cohort study, practical issues remain: the duration of follow-up, power, and sample size considerations, how to ascertain the endpoints, how often, who should do this. We'd have to explore measures to reduce losses to follow-up, and we'd have to decide what level of uncertainty was acceptable.

Finally, I'd like to acknowledge the help of

Dr. Yi Tsong, statistician, acting Director of Quantitative Methods Research in the Office of Biostatistics, and he is present today to answer any statistical questions that you might have.

I'd like to also acknowledge the help of Dr. David Graham, Associate Director for Science in the Office of Drug Safety.

Thank you.

DR. CHESNEY: Thank you very much, Dr. La Grenade, another very elegant presentation.

Our next speaker is Dr. Elizabeth Andrews, and she will discuss the practical and methodological issues for these studies. Dr. Andrews is an epidemiologist and Vice President of RTI Health Solutions. Prior to joining RTI, she developed the worldwide pharmacoepidemiology programs for Glaxo SmithKline. She brings many years of practical experience with drug safety monitoring for a variety of short-term and long-term events.

DR. ANDREWS: Thanks very much for asking me to present today on methodologic and practical issues in doing a registry. Dr. La Grenade has given us a lot to think about in terms of designing a study to answer this question.

I'm going to take a slightly different approach and step back and ask a number of questions relating to

methodologic design and analysis as well as the practical issues where the rubber meets the road.

So, first of all, we need to think about when we would do a long-term follow-up study, and there are three general circumstances.

One is when adverse events may not be manifesting until months or years after treatment, which is the case in this particular case relating to cancer.

Another example would be when adverse events might have been ambiguous in clinical trial programs and in short-term therapy but might manifest themselves clearly with long-term use. Yesterday's discussion gave us a great example of adrenal suppression in long-term topical steroid use.

And a third example would be when adverse events may be too frequent to have been observed in clinical trials. Again, the issue at hand meets this criterion.

It seems there are several key questions we have to be able to address before we can design a study. Are these drugs, the calcineurin inhibitors, associated with cancer at a level that would warrant modifications of current prescribing and treatment recommendations? We need to answer that question.

We need to know what the baseline level of the

risk of skin cancer and lymphoma is in the pediatric population, and as we've heard, we don't know a lot about that, specifically around skin cancer.

And then we need to answer the question of what is the estimated increase in risk that must be detected for safety assurance; namely, what is our threshold for action?

With that in mind, how are we going to measure that increase? Do we measure it through a relative risk or do we use a public health measure of risk difference? For example, if the baseline 10-year risk of either lymphoma or skin cancer in kids is 2 per 10,000, that's the best estimate I could derive from the figures I looked at. And if we observe through this long-term follow-up study a risk of 10 per 10,000, that translates into a relative risk of 5. It sounds pretty scary. If we look at the risk difference, that's a risk difference of 8 out of 10,000 over 10 years, translating into 1 new case of skin cancer per 1,000 patients exposed over a period of 10 years.

We need to understand what potential increase in risk meets this threshold for action at a policy level. What's the regulatory need at this point?

And what level of increased risk would be acceptable from a patient and family perspective to receive the benefits of the treatment?

As we continue to discuss the goals of the

study, we need to think of whether the study will be an etiologic study or a surveillance study, and that's already been discussed to some extent. In a typical etiologic study, we're attempting to either detect or rule out some specific increase in risk that we can define a priori. We use a standard study design and we power the study to achieve our objectives.

In a surveillance study, however, we tend to take a different approach, and that has implications for design as well as analysis. We use a general standard study design, but in our analytic methods, we need to think about how we review the evolving data over time in a qualitative, as well as quantitative way.

An example of a surveillance study that I thought I would use today is the international acyclovir pregnancy registry. This is a study that was established back in 1984 to look at the exposure to oral acyclovir, a drug used to treat herpes infections, following inadvertent exposure in pregnancy. Those patients were identified and followed up to term and beyond. The outcomes were identified through patients' physicians to identify infants with birth defects.

The frequency of birth defects in that study was compared to a population expected rate, and that comparison was based on data collected in a generally

similar manner to the way the data were collected in the registry. That study, after about 15 years, concluded that the overall frequency of birth defects was similar in the acyclovir exposed patients as in the general population, about 3.2 percent with a very tight confidence interval compared with an expected rate of about 3.2 percent.

Now, you might not expect an increase in the risk of a specific birth defect to actually be manifest in an increased risk of overall birth defects, analogous to our situation here with cancer and all cancer versus individual cancers. In this particular study, we determined after following over 1,000 thousand pregnancies that the study had the ability to detect a 7-fold increase in the risk of specific birth defects that occurred in 1 out of 1,000. The study was at that point closed to new enrollment because it was difficult to continue enrollment, and also because of the marginal utility of additional data collection in reducing the uncertainty around specific birth defects was very low.

Another key point in thinking about a study of calcineurin inhibitors and cancer is whether to have a comparison group. Dr. La Grenade pointed out a number of useful points here. This also goes back to the goal of the study. Is it to detect a possible signal or is it to reduce the uncertainty relating to a possible increase in

risk?

A single-arm registry can be very useful to identify incidence of events over a defined follow-up period. And it can identify if and when the event rate exceeds a threshold of an expected rate, if you can measure that threshold. It can identify characteristics of the patient population that you might want to look at if you were doing a more formal comparative study that might be confounders. In order to take this approach, however, we need a very well defined estimate of the expected risk which we have for lymphoma, but which we do not have for the non-melanoma skin cancers.

A study with a concurrent comparison group can do some other things. It can certainly establish whether the incidence of events is similar between the exposed in the comparison group. It can explore the role of potential confounders which would have been measured in both groups, and it also can help assess a signal that arises in the exposed group.

I've identified a potential scenario, and that is if we are looking at a baseline rate of 2 per 1,000 cases of cancer over 10 years, what if in the first 3 years we observe 2 cases out of 5,000? Well, that's more than would be expected. Have we crossed the threshold? What do we do with that information? It would be very useful to

have comparative data at that point so that we could begin to look at the distribution of confounders rather than wonder if we have exceeded a threshold.

An example of a study that did use a comparison group is the Rheumatoid Arthritis Azathioprine Registry that was started in 1984. The issue here was that azathioprine, an immunosuppressant, was used in transplantation and was associated with potential increased risk of lymphoma and other lymphoproliferative malignancies. Transplantation is associated with a significantly increased risk of cancers. Azathioprine was being used for rheumatoid arthritis at a much lower dose. The lower dose use of azathioprine also was associated increased risk of lymphoma.

This is a study that enrolled patients over a period of 10 years in Canada, enrolled patients who initiated therapy with azathioprine, and for each azathioprine patient, another 2 patients who were initiating therapy with another disease modifying antirheumatoid drug. Patients were followed up for a minimum of 5 years each for additional exposures and serious events like lymphoma, all cancers, and some acute events. Specifically excluded from these outcomes were non-melanoma skin cancers because of the potential detection bias, as well as the potential to under-ascertain

these events.

The study was designed to enable the study to detect an increased risk of around 3-fold with full follow-up. The most recent information that I reviewed was after the end of the 10 years, and there should be another 5 years of information.

So this study is analogous to the situation that we're dealing with here in a number of ways and is an example of a study that absolutely had to have a comparison group because there would be an expected significant increase in lymphoma in the azathioprine group compared with the general population because there's an increased risk of malignancy in patients with severe rheumatoid arthritis.

So we need to consider potential study designs that can include longitudinal follow-up studies, case-control studies. These can be done with de novo data collection. They can be done in existing databases, and there can be variations on the design.

You've already heard a little discussion about design of cohort studies. There are a number of examples of looking at long-term events. The azathioprine registry is one example. Patient registries; large, simple trials follow this scheme.

And case-control studies. While I think that a

case-control study would be extraordinarily difficult in this particular case, I thought I would point out that there are a couple of cases where case-control studies have been useful in looking at antecedent drug exposure and outcomes where there has been a significant latency period. One case is looking at neural tube defects in infants and antecedent exposure to folic acid, and don't forget the DES and vaginal cancer story. I'll also point out the point that Lois made earlier, which is you can't define an incidence rate from a case-control study.

So if we decide to set up a study, perhaps a longitudinal follow-up study, we need to think about how to recruit patients. We need to think about what are those methods for identifying patients. Will we go to referral centers? Will we do something to recruit patients directly? As we think about this, will these methods select patients who are typical of users or will they be a highly skewed cohort, and does it matter? Will the patients be newly treated, or can we include people who've already been on drug in the past?

When we look at inclusion criteria, in terms of indication and severity of disease, will we try to increase the efficiency of the study by selecting high-risk patients, patients perhaps with substantial sun exposure? Will we perhaps look for older patients who might have a

higher rate of background cancer? Maybe adults. Or should the study be representative of the typical user population? That depends on what you'd like to extract findings to.

And if there is to be a comparison group, will this comparison group have the same baseline risk as the exposed group? Well, in a nonrandomized study, we know the answer is no. They will have a different risk. Maybe that's okay, but you need to know what the differences are by collecting enough information to measure this and understand what analytic methods will be used in the analysis to control for this, for example, propensity scores.

In looking at exposure, there's the question of what's the minimum exposure that's required in order to qualify someone for the study, and then how much information on exposure to these and other drugs will be needed over the course of the study, what level of detail. And then what periodicity of follow-up will be needed over that 10-year period or 5-year period in order to make sure that we've adequately captured the information?

In measuring outcomes, well, how will we do that? Will we allow outcomes to be reported by the patient? Will we abstract medical records from the patient's treating physician? Will there be required physical exams periodically to identify skin cancers that

might otherwise not be identified? Will we link the patient records with cancer registry, National Death Index, or other data files that are already in existence with outcome data?

What level of detail will we collect?

And what biases might be expected in our data collection? For example, in the calcineurin inhibitor group, we might expect to see a higher rate of reporting of skin cancer even if there isn't an increase, if there is that perception, just as in a study of topical steroids we might see a higher reporting of short stature irrespective of the truth.

So we need to consider confounding, other treatments, other conditions. I would give some thought to the occurrence of asthma frequently in atopic dermatitis patients that might be distributed equally across the comparison groups. It's certainly worth considering.

And there will be other variables that will be published in the literature after the time the study has started, and there will be the semi-annual discussion of whether the study needs to be modified to take into account the new data on potential confounders.

I think it has already been mentioned in the writing of the analysis plan, one needs to consider analytic methods that will handle time-dependent variables.

If patients are enrolled over a series of years, then those patient characteristics at enrollment will be different from year 1 to year 2 to year 3. Medication exposures will change over time. We need good methods for grouping, lumping, considering different exposure categories. Potential confounders may change over time. And there will be the unanticipated events and practice patterns that will change, and the study will need to be able to handle that in the analysis.

So having said that, the ideal study design would be a long-term follow-up study in which there was an exposed and unexposed group that was recruited with the same baseline risk. Exposure measurement would be handled perfectly. Dose and duration of all relevant treatments and all potential confounders would be ascertained. Outcome measurement would be complete in both groups. Follow-up would be sufficient to observe all of the outcomes of interest. Maybe that's 10 years. Maybe it's 20. And the power. Well, the study would need to be able to detect or rule out an increased risk of whatever your notion of the threshold for action is over the expected or observed in the unexposed group.

However, the ideal is rarely practical, and that's what I intend to address next. In thinking about where the rubber meets the road in study designs, we can

turn to some examples and think about bigger issues of how do we implement a study like this. We can look at a number of examples, but there are two characteristics of studies that are inversely related that I think are important here.

One is study complexity and the other is study size. Here I've taken study size from small, being 1,000 or so, up to large, tens of thousands of patients. And then there are studies that are very simple that may collect data annually by mail up to a highly complex study where we may be doing routine skin examinations on an annual basis.

We do these highly complex studies all the time. These are our randomized clinical trials, and there is a reason they're small. We do large safety studies that tend to be very, very simple, but the studies up in the upper right quadrant where we do highly complex follow-up with physical exams with large numbers of patients are typically studies that have been designed to address major public health issues like the Women's Health Initiative, the Physicians' Health Study, the ALLHAT study.

So some of the things that need to be considered in going into this enterprise are the cost of the study, not insignificant.

Equally important would be the opportunity costs to all involved. That means the time and effort, as

well as money, that will be spent by regulators, sponsors, physicians, and patients in addressing this question at the expense of other things they might be doing.

We need to also consider the potential indirect impact of doing the study. If a major study is launched to look at calcineurin inhibitors and the risk of cancer, what will the impact be on physician treatment choices knowing the study is out there? Will it impact adversely prescribing behavior, complaints behavior by patients and their family, and will there be some additional impact on reimbursements?

Then my fourth question here is when is it reasonable to do this kind of a study? What are the benchmarks and what is standard practice? There's not a whole lot of experience to share in this respect.

Well, the key issue in making a study like this successful is a high retention rate over multiple years of the study. There are a number of tools to help maximize follow-up, and I'll get into some of them.

Retention really has at least two components. One is the ability to track and locate patients. Can you find them? And the other is participation. If you can find them, are they still willing to participate in your study? Tracking can be done in a number of ways and can be done very, very successfully. It involves keeping up with

a patient and maybe a neighbor, next of kin, knowing when they move, and getting new contact information. It also involves linking patient identifying information against publicly available data that can help track them down, all conducted with IRB approval.

There are a number of studies that show that you can locate people at a high rate over many years. One example is the Piedmont Health Survey of the Elderly which was able to track 99 percent of an elderly population over a period of 10 years, and there are other examples showing very high rates of tracking over many years even without intervening contact.

I think there are special issues relating to follow-up of kids over time into adulthood. Many of them -- and I hope mine will be one of them -- will leave home when they go to college.

(Laughter.)

DR. ANDREWS: That just proves that's another issue of tracking. So we need to consider those various factors that make the study more complex.

Study participation. Are people interested and willing to follow up? Really, there is a lot of literature and there are a lot of examples. I didn't bring many specific examples, because everywhere I turn, the answer I get is the epidemiologist's answer to everything, which is

"it depends." And it really does. It depends on the mode of data collection. If data collection is done by mail surveys, the response rate is going to be very, very low. Not always. I'm involved in a study where we're getting over 95 percent follow-up in quarterly mail surveys.

It depends on the periodicity of contact. Participation increases when there's a frequent level of contact.

Salience of the study to the patient is key here, and so it needs to capture the interest of the patient and the parent.

Incentives are critically important. They don't have to be large incentives, but appropriate to keep people involved.

And the burden on the participant has to be minimized.

Now, there are special considerations in pediatrics. You have both the patient and parent participating, so that's two people or maybe three people who have the opportunity to say I've had it, I want out of the study. You also have changes in consent over time, giving you more opportunities for people to think about whether they want to continue on in the study.

So my advice would be to plan for annual attrition, but that should be based on the methods that are

selected and you can select a study design that can optimize patient follow-up. Probably you would use a mixed mode of data collection. Certainly in-person interviews is very helpful, but maybe considering mixed modes of data collection, mail, telephone, visits.

One other issue of practical consideration that is incredibly important and that is the issues of IRB approvals and HIPAA privacy concerns. We're all struggling with this new environment now in which IRBs would normally have approved studies that looked quite reasonable and are having second thoughts. When you take a study design that looks a little novel, you may have to go through two or three iterations before convincing them that it really is a worthwhile study.

A key issue that was raised in Dr. La Grenade's presentation was the issue of a mandatory registry. I would just point out that if the study is to be a study, then an IRB will not approve a study in which treatment is conditioned on participation in research. So that would be an issue, and I would suggest that a mandatory registry probably is not a viable option.

We need to consider in the design who gives assent and consent, when that occurs, how often that occurs, how does it change over time.

What IRB approvals will be needed? Will there

be a central IRB and lots of local IRBs?

And if the study involves chart abstraction to validate outcomes, then you might need to consider HIPAA waivers in the institutions where the charts would be obtained.

So in conclusion, considering a study design like this requires some epidemiologic expertise in addition to folks who have been in clinical trial design because the design and the analytic methods and the practical methods really approach more an epidemiology study design or survey.

The key focus in the design must be a long-term retention strategy.

The study must minimize burden to the patient or the dropout rate may be so high as to render the study meaningless.

And the successful design will be a compromise between the ideal and what's actually practical.

But fundamentally, back to basics, the design must be tailored to the ultimate goal of the study, and I'm not sure that we're clear what the ultimate goal of the study would be.

Thank you.

DR. CHESNEY: Thank you very much, Dr. Andrews, for a very clear discussion of the issues involved in long-

term follow-up studies.

Our last speaker for this morning is Dr. Phyllis Wingo. She is an epidemiologist and Chief of the Cancer Surveillance Branch of the Cancer Division of the Centers for Disease Control and Prevention. Her primary responsibilities include the National Program of Cancer Registries and the design, conduct, and analysis of descriptive epidemiologic research on trends in cancer incidence, mortality, survival, and patterns of cancer patient care.

DR. WINGO: Good morning, everyone. I'd like to thank Susan Cummins for inviting me to talk about cancer registries in the United States. Before I start my presentation, I think it's important to make clear we've been talking a lot about exposure registries, and now I'm going to switch gears slightly and talk about disease registries.

Briefly I'm going to talk about the cancer registry infrastructure that currently exists in the United States. I think it's a very strong infrastructure, and as I will show you, it is nationwide, and we do have data for every State. I'll talk about what kinds of data are available in the population-based cancer registries.

I'm also going to talk a little bit about data quality, and the reason I'm going to talk about data

quality is that part of the registry infrastructure is fairly new, and because it's fairly new, not all of the States are in a place where they should be participating in special research studies, but many of them are. And I'll describe that to you.

I'll do that description through the combined publication of cancer data that currently exists. This publication combines information from the very long-term SEER program, as well as the National Program of Cancer Registries from the Centers for Disease Control.

I'll also give a little bit of information about follow-up. Again, this is follow-up of cancer patients as opposed to follow-up of persons exposed to a particular drug. And I'll then try to summarize.

I'm not going to go through a 70-year history of cancer registries in the United States. What I would like to say is that cancer registries have been around for a very long time. They started with a bone sarcoma registry in the 1920s that was set up by the American College of Surgeons, which is still around today. The standards that were set in these early days and the focus that this group had on data quality are factors that influenced the development of population-based registries and, as I said in my opening remarks, still affect what we're doing today.

I also will talk a little bit bout the SEER program, which has already been referred to in some of the presentations this morning, and talk a little bit more about the newer program from the Centers for Disease Control so that people know what it is and what it offers and where it is in its state of development, and then what kinds of data are available from the two systems combined.

The SEER program, or the Surveillance Epidemiology and End Results program, is funded by the National Cancer Institute. They just celebrated 2 weeks ago -- I was up here for their 30-year celebration. They are the gold standard for cancer registries in the United States, and they are the kind of registry that all the other population-based registries aspire to be like.

They have data from the diagnosis year beginning in 1973. For most of their history, they have covered five States and six metropolitan areas, and in the year 2000, 4 of the CDC program States that are in the turquoise color here joined the SEER program also. They're actually funded by both programs, and now the SEER program covers 26 percent of the U.S. population.

The National Program of Cancer Registries, or NPCR, is the program that's funded by the CDC. It is a relatively new program. It's only been around for 10 years. The first year of diagnosis for some, but not all

of the States, because not all of the States started in the program with that first diagnosis year, is 1995. It covers 45 States, 3 territories, and the District of Columbia. It covers 96 percent of the U.S. population.

The bottom line is the SEER program plus the NPCR program cover all 50 States in the United States and the District of Columbia.

As I said, I'd like to talk a little bit more about NPCR. It was created by the Congress through the Cancer Registries Amendment Act in 1992, which authorized the CDC to minister to this program, and the legislation set into place requirements for establishing cancer registries in States where one currently did not exist. At that time, 10 States did not have a statewide population-based registry, and to enhance registries in the other States where there already were registries, but they did not have adequate resources to do a very solid job of getting complete reporting that was high quality and timely.

As part of the congressional law, as part of the Cancer Registries Amendment Act, each State had to put into place a State law that established a statewide population-based registry. In addition, each State also had to develop legislation and regulations for reporting and for protection of confidentiality.

Here's the issue of data quality. Our acronym is CTQ. Completeness. We need complete reporting of all cases that occur within the States. We need timely data. We need high quality data.

At the time this program was created, the registries that existed in the United States did not have standardized definitions for reporting cancer. They did not have standardized data elements. They did not have standardized data collection procedures. So part of the congressional legislation was to mandate that data be collected in a uniform way, and States are required to report out annually.

Just again to repeat, each State has to have authorizing legislation. The State legs and regs require comprehensive reporting. They allow access to records. They require the reporting of uniform data, confidentiality protection, promoting ultimately, when the data are of sufficient quality, access to the data by researchers, and authorization to conduct research, and protection from liability.

The laws obviously from State to State vary a great deal. In some States, there are a lot more teeth in the laws than in other States. We had a State, for example, that was not able, with the existing laws, to get all of the hospitals to report cases, and when the Medicare

folks stepped in and said, well, that's very nice. We will hold up your Medicare payments unless you report your cancer cases. And all of a sudden, we had -- this came from the State. This didn't come from us -- complete reporting for that State. Whatever works I guess, and different States have different methods for getting things to happen.

What kinds of data are available in the population-based registries? There has been some allusion to this already. Basically, as our previous two speakers pointed out, the reportable cancer case is defined in the Cancer Registries Amendment Act as each form of invasive cancer with the exception of basal cell and squamous cell carcinomas of the skin, and each form of in situ cancer, except for carcinoma in situ of the cervix. The cervix piece was added after the law was written, but as I mentioned, population-based registries in the United States do not capture basal and squamous cell skin cancers. They do capture melanomas and other nonepithelial skin cancers as well as the melanomas that we've talked about this morning.

What kinds of data elements are available? The demographic information is as listed on this slide. Most of these data are retained at the State level. Data that are sent to CDC, sent to NCI have personally identifying

information stripped off, such as age, address, census tract, and so on, Social Security number. So at a national level we have only the basic statistics for describing the burden of disease in this country and in each State. Special studies have to occur at the State level where there would be access to personal identifying information.

The registry also contains basic clinical information, including date of diagnosis, date of admission or first contact, the source of that information, date and type of the first course of definitive treatment, usually surgery. There's also limited information on hormone therapy, chemotherapy, and immunotherapy, basically a yes/no kind of did you receive it, that may or may not be available in the medical record of the hospital, information on date of death and underlying cause of death.

Pathology information is required for all of the tumors identified through these programs, including primary site, morphology with behavior and grade, the sequence number of the tumor, laterality, and diagnostic confirmation.

Data quality, as I said, is really important again because not all of the States that participate in the NPCR program have achieved the quality standards that have been set by law. I'm not going to spend a lot of time on those. You can look at the details of these requirements

and how they are evaluated. I'll just go through them fairly quickly. But these are important attributes for determining whether or not we will include a particular State's data in the national estimates of the burden of disease. These are also measures that should be considered when you're looking at doing research using the cancer registry in a particular State.

We look at measures of completeness and we evaluate those in a variety of ways related to case sharing with bordering States, case reporting from all facilities, audits.

Death clearance. One way of finding cases is through death certificates only, and if you identify a case through a death certificate, you don't have the information about the tumor unless you do follow-back and get that information from the pathology reports.

Dealing with duplicate reports of cases is also part of measuring completeness.

Issues of timeliness. We want cases reported within 6 months of diagnosis, and we look at a variety of dates that are collected to evaluate the timeliness of cancer data.

We put time frames around these. In other words, we don't want just quality data. We don't want just complete data. We don't just want it in a timely way. We

want them to do all of these things, including follow-back within a certain period of time. We want States to find at least 90 percent of unduplicated cases within 12 months and 95 percent of unduplicated cases within 24 months.

We also do a variety of data cleaning operations on the data to check for consistency and validity between various variables in the data set.

There is an external group. It's called the North American Association of Central Cancer Registries, also called NAACCR, that does a variety of things with population-based registries in the United States. One of the things they do is evaluate the quality of population-based cancer registries. They have been doing certification of data beginning with the 1997 year of data submission, and as we have come through time, you can see that the number of States that they now certified as of this year's data submission has gone from 9 to 36. So we value this external evaluation of the quality of cancer registry data.

So what's available? Right now, we are in the process of, for the second time, jointly publishing with the NCI data from the SEER program and high quality data from the NPCR. These data are for the year 2000 diagnosis year. This report contains crude and age-adjusted incidence rates per 100,000 population for adults and per

million population for children 0 to 19. This report covers 84 percent of the U.S. population, and it will be out next week.

The quality issues that we looked at for including States in this report are listed on the slide. I'm not going to go through each one again. It has to do with completeness of reporting, cleaning the data, clearing death certificate only cases, quality of race, sex, and age data.

There are data from 41 statewide and 6 metropolitan area registries that met these criteria, and these are the States that are included. As you can see, we have generally poor representation in the Southeast.

The report has basically three kinds of data. It has national cancer incidence data by site, sex, and race. As I said, it covers 84 percent of the U.S. population for the year 2000. It includes more than 1 million new diagnoses of cancer and more than 10,000 new cases of cancer among children ages 0 to 19 years.

Here are the ranked age-adjusted incidence rates per 100,000 population for men in the United States, and you can see that non-Hodgkin's lymphoma among men in the United States lists as the number 5 cancer, followed by melanoma as number 6.

I don't have the endocrine cancers listed here,

cancers of the thyroid and thymus. This was mentioned in one of the presentations this morning, but there are also data for about 5,000 males and about 13,700 women in this data set with new diagnoses of endocrine cancers in the year 2000.

Here are the top 15 cancers for females in the United States. Non-Hodgkin's lymphoma is sixth on this list behind some female cancers, and the usual top three, again followed by melanoma.

I pulled out the lymphoma incidence rates and the counts for both Hodgkin's and non-Hodgkin's disease. The rate in males in the United States for the year 2000 is 22 per 100,000 and in females it's 14 per 100,000.

Looking at invasive skin cancer incidence, this is melanoma and other nonepithelial skin cancers, there's a rate of 25 per 100,000 in males and 18 per 100,000 in females.

Here I have some information on the occurrence of cancer in children by gender. As I said, there are slightly more than about 10,000 cases in this data system for children of these ages with a rate of 166 -- this is per million. We've changed the denominator in reporting the childhood cancers -- per million population in males and 147 per million population in females. There are the data also for lymphomas listed there.

In addition to these national kinds of data for both adults and for children, there's another part of the report that contains the State-specific data for the top 20 cancers as well as regional data. Here you can see the population coverage for these regional data. It's really quite good, as you've already seen, except for in the South. There are the regions as listed there.

The third part of this report contains gender- and race-specific data that are ranked within those groups for each State. I'm not going to present those data, just make you aware that in fact it exists.

Follow-up in the registries is not about follow-up for exposures but in fact for vital status. All registries that participate in the two federal programs do linkage with State death certificate files, Social Security files, the National Death Index to confirm deaths from cancer and other causes for patients that are already ascertained in the cancer registries.

The SEER registries and a very few of the NPCR registries also do follow-up to determine alive status. The SEER registries do this to maintain having a current address on the cases in their registries, and so they link with the other kinds of files that are listed here on this slide. I guess what I would say is that this is an important activity for keeping up with a current address,

although there are other means of doing that for doing special studies.

I'd just like to summarize, make a couple of points. We do have population-based cancer registries in all 50 States and the District of Columbia. As I tried to illustrate to you, the quality of the data varies across the States. That quality is also a reflection of individual State's experience and ability to do special studies. But I think it's a community that has made remarkable progress over the past 10 years such that there are now good quality data available in 41 States.

Follow-up is good for death status. It's limited for alive status.

So I think we do, in fact, have a very strong nationwide cancer registry structure in place and that we do have data available at many levels, including at the national, regional, State, and local levels, for monitoring the burden of disease, planning comprehensive cancer control programs and conducting special research studies.

Thank you for you attention.

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

Questions for our three speakers of the second half of the morning. Dr. Stern.

DR. STERN: I wanted to bring out a couple of issues which I think were well covered but I think deserve

a special concern with these agents. We've talked about the difficulty of -- we expect these risks to be in some way dose and duration related.

Now let me speak about the risks of skin cancer. One added confounder is the fact that we also expect that the risks of skin cancer are likely to be a result of local rather systemic effect primarily in these agents. Therefore, in order to understand the relationship of dose to risk, which in these studies is perhaps the most persuasive evidence for an increased risk is looking at the entire cohort and seeing how risk varies with exposure over time, one also has to think about site of application. And I would have to say that after trying to reasonably quantify exposure to topical agents over the last 28 years and a little bit longer in clinical practice, reasonable quantification even on an annual basis in patients who have been educated of what they're using in the last year, how often they use it, and where they use it has at least certainly eluded all of my capabilities. So I just think it's not an easy task, and I'm sure there are other folks who can do it better but I've never succeeded in a way that I thought that I could well quantify really relative exposure over time and particularly exposure by site.

That was one and I have a bunch of other points that I think will be better raised in that. I think the

issue of actinic keratoses as an endpoint is an interesting one and one I've also thought about. I have some concerns about it in both ways. One is the clinical diagnosis of actinic keratoses varies substantially person to person.

The second is that there may be some confounding due to disease in these individuals. At least in people with seborrheic dermatitis, which is in fact one of the conditions that Elidel is used off label for, in my experience in sun-exposed areas, telling seborrheic dermatitis from actinic keratoses could be very difficult, except in Dr. Wilkin's hands I think, but for some of us it can be very difficult, although I understand the Greeks found it an easier differential diagnosis.

(Laughter.)

DR. STERN: Clearly people, if they're educated to this, may lead to over-diagnosis, beyond the point of it being a squishy endpoint subject to ascertainment bias.

My other concern is at least as one looks at the transplant literature, if you think about lesions, if you think about the actinic keratosis, there's a probability over time it will go forward. In fact, what may be happening in transplantation is that whether they go through a transitional stage of actinic keratoses or first manifest themselves with tumors, the duration of being clinically a pre-malignant -- a carcinoma in situ either

clinically or histologically may be shortened. One of the things you see is a shortening. Therefore, if you look at an intermediate lesion, if you look at the in situ lesion -- and you're, after all, measuring prevalence as caught on doctor's exams, say, once a year -- you may be under-representing the real number because the real interest is those that go on.

So I'm just not sure that it's either a feasible endpoint or really that a negative finding or a small increase in risk of actinic keratoses would really be -- you'd know how to extrapolate that finding, be it positive or negative to what the real interest is, what's the increase in risk of squamous cell carcinoma.

DR. CHESNEY: Dr. Fink.

DR. FINK: I would just like to bring up what I think may be a major confounder to study design and would, I guess, argue for the inclusion of a non-treatment control group. In the spring of this year, the Pulmonary Allergy Drug Advisory Committee of the agency reviewed the preclinical data on omalizumab, or anti-IgE. And cancers, including non-melanoma skin cancers, were of concern there. One of the issues of that data, although not definitive, pointed out that it appears that elevated IgE levels -- these would be in atopic asthmatics with IgE's above 200 -- actually had a protective effect for epithelial cancers.

So in those studies, there was a question as to whether you are losing a protective effect and the comparison to SEER's database or the SIR's methodology would be inaccurate.

What was seen there is that the control population had a significantly decreased risk of epithelial cancer compared to SEER. And the anti-IgE treated group came up to the population norm. So there was a loss of protective effect. If that is also true for atopic dermatitis where IgE is elevated, you really have to have a control group that is untreated to detect that loss of the anti-IgE protective effect.

DR. CHESNEY: Dr. Glode.

DR. GLODE: This is a question for Dr. Andrews. When you discussed the rheumatoid arthritis study as possibly analogous -- and I could see the analogy that perhaps dermatologists would enter patients, et cetera -- I just wanted to ask you if this type of study design has, over time in general, been validated, been helpful because I see the problems as time goes on with other drugs being introduced into therapies, for example, obviously with rheumatoid arthritis, other immune modulating drugs. So it comes back to the issue again of your comparison group sort of changing over time perhaps in terms of their risk for malignancies. But has this study design, which looks like it doesn't have to involve too many patients, for example,

given us good information historically?

DR. ANDREWS: That particular study proved very useful in looking at some of the short-term toxicities. It was also useful, as other drugs were being developed and there was the need to look at short-term infection. It was able to provide a comparison group for an uncontrolled clinical trial population. So there were a number of uses for the study data over time.

Yes, treatment patterns changed a lot, and the analytic strategy had to accommodate that fact. So you didn't have a single ever azathioprine-exposed population. You had azathioprine plus methotrexate, whatever. It was very complex.

We were able to achieve a very high rate of retention. I think one of the factors that made that a very successful study had to do with practice of medicine in Canada. Patients with rheumatoid arthritis tend to be seen by rheumatologists repeatedly. So the rheumatologists were actively engaged and contributed data for many, many years. I think in the States most patients might have seen rheumatologists once or twice, but would be treated by their primary care physician. So everything conspired to a good, feasible study in that case. And because the anticipated rates of lymphoma and other outcomes are fairly high in that population, we didn't need a huge sample size.

DR. CHESNEY: Dr. Gorman and then Dr. Santana and then Dr. Danford.

DR. GORMAN: Is not the goal of this study, when we were talking about goal-setting, which I found re-informative perhaps rather than refreshing, but re-informative -- we're looking immune-modulating effects on a systemic basis. While we're waiting for the 20-year cancer incidence to change or the 5-year cancer incidence to change, could we not be looking as well on the perhaps not as serious but equally telling dermatological changes such as recurrence of zoster or invasive viral diseases or invasive bacterial diseases? Could they be not incorporated in the same design whether it be cohort or surveillance?

DR. CHESNEY: Do you have any one special to address that to?

DR. STERN: I'm sorry to be talking so much, but this is an area of interest of mine.

At least with UV and PUVA in carcinogenesis, acute UV is associated with flares of HSV but not herpes zoster, but in terms of chronic exposure, they're not good predictors for cancer risk. They're good predictors for acute immunomodulation in the skin, but they're not good predictors for cancer risk probably because some of those phenomena are more when a person has exceptional exposure

as opposed to steady exposure. Steady exposure is important for cancer. Bringing out HSV is when you get a sunburn is when you get herpes simplex reactivation, and they may be correlated, but they're certainly not good predictors.

DR. GORMAN: Well, perhaps not herpes simplex, but zoster is something that would be a sentinel event in a pediatric practice as being an unusual -- not rare, but unusual -- occurrence. Incidence rates that were different I think would have a signal-to-noise ratio that would rapidly be high even if it's not a predictor of eventual cancer.

DR. STERN: I guess when I think of zoster earlier than usual, it's usually again in the background of fairly profound immunosuppression or fairly acute insult like radiation therapy to a ganglion, to an area where there's latent virus, and it doesn't seem to be so much of a problem when we just modestly but chronically immunosuppress individuals, whereas those kinds of insults do seem to be a problem with long-term exposure in terms of carcinogenesis.

So again I think there is obviously some correlation between cumulative dose and peak doses, but to me, most of those signals have to do with exceptional acute doses or very profound immunosuppression, which if it

occurs, is certainly like to be associated with a high risk of cancer if it occurs on a long-term basis, but I don't think is directly analogous to what we expect to these less profound but chronic exposures.

The question really is when we get down lower in the magnitude of immunosuppression, how much is that going to alter things long-term. I think that is a bit different than the acute conditions in the skin, at least as I'm aware of them.

DR. DIANNE MURPHY: I'd like to follow up on that question, though, because in the limited controlled studies that were done, we already saw this come out statistically. So I think the question is really one of background noise and ability to pick this up from your experience because we had to label it because we already saw it in the rather limited numbers of studies that we had. So I think that's what you were trying to get at, not as a particular cancer, but just a shorter-term signal that some sort of additional immunosuppression is going on here that's more systemic.

DR. GORMAN: That is the question I want to answer. If I can be convinced or unconvinced whether -- if we're going to down-regulate children's immune systems for atopic dermatitis, I want to know that, and I think that's the question that we look at with the signal of cancer long

term, dermatological cancers or perhaps lymphoma long term, but there are other markers perhaps not as sensitive and perhaps not as life-threatening, but perhaps equally important to parents who are taking care of these kids.

DR. DIANNE MURPHY: Just to clarify. The division wanted to make sure everyone realized that that signal is picked up in the less than 2-year-old population.

DR. CHESNEY: Dr. Rabkin, did you want to say something? And then Dr. Santana and Danford.

DR. RABKIN: Similar points to those that have already been raised. I was going to mention that you would need to distinguish between markers of systemic loss of immunity and perhaps even more difficult to discern losses for cutaneous immunity that could have very local effects for which there's very little tools, not that the tools for systemic alterations are that sensitive, but the tools for cutaneous changes in immunity would be even more difficult to discern and the clinical signs are also more nebulous.

Also, I'd like to make the point that the effects of these conditions, regardless of treatment, on immunity and risk of diseases such as lymphoma are uncertain. So the importance of a comparison group is very real and even with the comparison group, in the absence of the usual specter of a randomized clinical trial, it's going to be very difficult to ascribe any particular

differences to the treatments, as opposed to differences in the disease.

DR. CHESNEY: Dr. Santana.

DR. SANTANA: I just want to make two general comments.

First of all, as a practicing oncologist, if there's anything I can do to prevent a patient from getting a malignancy, which is very rare in pediatric malignancies that we have that opportunity, we should do. Obviously that comment is biased in the sense that we rarely have these opportunities and it has to be taken in the context of what other conditions the patient may have in which the use of the particular agent was necessary in order to ameliorate or cure their primary disease.

Having said that, I do want to publicly applaud Elizabeth Andrews' presentation about bringing the issue of stewardship forward. Many of us who live in academic ivory towers who have a lot of access to support to do our studies sometimes don't recognize this issue of stewardship. And as we think whether it is appropriate for this particular class of drugs to conduct these studies that will consume time, that will consume talent, and that will consume money, the three cornerstones of stewardship, that we carefully do that because I don't think I've heard yet this morning during the presentations that the goals of

the study were defined, and if I'm now going to be a good steward of these three elements, I want to make sure that the goals are clearly defined so at the end of the study, all these three variables have been accounted for and then we can publicly say that we were good stewards of the trust and the monies that people gave us to do this.

DR. CHESNEY: Dr. Danford.

DR. DANFORD: I'm also impressed by the amount of money and effort and time that's going to be invested in a study such as this, and I am interested, in that context, whether there are any anticipated practice pattern changes that might occur during that extremely long time frame. I am wondering, therefore, if the FDA is in any position to comment as to whether there are, in the drug development pipeline, agents that show exceptional promise for the treatment of this condition. And if there are, would the development of such agents render the studies we're contemplating moot?

DR. WILKIN: Well, apologies. I was having a side bar. I missed the question.

DR. DANFORD: The question is this is a long, difficult, and costly process that we're talking about. Is FDA aware of any alternative agents in the drug development pipeline that might be safer, more effective and drastically change practice patterns in the next 20 years

that would render this investigation essentially moot?

(Laughter.)

DR. SANTANA: Predict the future is what he's asking you to do.

(Laughter.)

DR. DIANNE MURPHY: He couldn't tell you anyway because he'd go to jail.

(Laughter.)

DR. WILKIN: That's exactly right.

But at the beginning before we have very much information, they all look wonderful.

(Laughter.)

DR. SANTANA: Does anybody from the FDA have an idea how much a study like this would cost based on some of the studies that Elizabeth addressed earlier?

DR. WILKIN: Well, I'm not going to talk to the costs because I think there's a wide range depending on how we actually approach this.

I am taken by actually Dr. Stern's reformulation into more of a dosimetry type of approach, and maybe there's something that can be thought of along that line.

DR. DIANNE MURPHY: The only data that we have that really is only marginally relevant is in the report to Congress, aand Rosemary Roberts, you can correct me if I've

got this wrong. In our report to Congress for the FDAMA, the Food and Drug Administration Modernization Act, on pediatric studies we were asked to give an estimate of the cost of studies. I can tell you that we went to PhRMA, we went to a variety of people, and no one could come up with a good number. I will give you the range, the range that was given to us in writing versus the range that was given to us verbally.

(Laughter.)

DR. DIANNE MURPHY: The range in writing was that for a very small study, maybe $500,000. We're talking pharmacokinetic, PK, type studies, a limited number of people, short, quick, not long-term follow-up. To studies involving -- I think the outer figure was -- was it $300 million or $30 million, Rosemary? Do you remember? It was $30 million, something like $30 million for a randomized clinical trial. That was not addressing long-term follow-up trials. That was addressing randomized trials. So the unofficial lowest statement that we got was $50,000 for less than a half a dozen kids to get a PK study, something like that. So those are the sort of huge ball parks for some randomized trials, and that was in this country.

DR. STERN: I hate to always be adding data, but in terms of costs of long-term follow-up of cutaneous diseases in adults, much more simple than in children, at

least what the NIH pays for long-term, as in 25-year studies, in years where we do not have dermatologic examinations, direct costs on the average of about $300 per patient, all direct costs for telephone contact and for following up on all endpoints, cancers, hospitalizations, et cetera. On years when we have dermatologic examinations, it about triples to roughly $1,000. That's an annual cost. In fact, it was cheaper early on because it was easier to get patients to continue and they get to be more complex as follow-up and retain the cohort continues.

So those are sort of, at least in some ways a simpler study where we were trying -- our principal endpoint was really trying to quantify a real event in people's lives, that is, getting a therapy where we could get a record from the doctor, going to an outpatient clinic or a doctor's office for a therapy. And that was the thing we quantified most accurately. That's kind of a ball park of who we've been able to do it over the years, and it's also a little bit cheaper because when you do it for the NIH, you have salary caps and other things that keep down your costs a little bit compared to some other costs.

I think if this were adults and a chronic disease as opposed to a disease where -- what do we expect with many of these children who are initially dosed? I

mean, both the most difficult part of it and the saving grace of this therapy is that most people will only use it hopefully for a number of years, at least using it extensively because atopic dermatitis tends to get better. That's great in terms of lowering exposure. It's terrible in terms of having a sufficiently exposed group among those you originally select, and it's also terrible with respect to being able to keep the cohort together because once people don't have the disease and aren't using it or other therapies to the disease and it's gone from being one of the top three problems in their daily lives, they very much lose interest in these studies.

In my study, where we've done pretty well over the years in terms of follow-up, we had the advantage of ascertaining people at the time almost all with very severe psoriasis, and as a result the disease kept on being high on their platters. They kept on being under treatment, not the treatment necessarily we were initially studying over the years so we could keep them in.

I'll raise one point. Someone talked about incentive. I think one has to be very honest about what are the incentives for the sponsoring institutions. One of the two sponsors here sponsored a study very parallel to mine for another agent, and was very proud with a 49 percent follow-up at the end of 5 years as published in a

journal recently. Those kinds of follow-ups -- you may as well not bother at all when you have that in terms of really well quantifying it.

So I think one of the things we have to think about is we're very concerned with this today, but what are going to be the incentives to the sponsor going forward to be sure -- what's in it for them to get a 90 percent follow-up after 10 years? The first question is, is it feasible for anyone? And the second question is, what's in it for the people who are paying for it?

DR. CHESNEY: Thank you.

I apologize to the three people who are still on the list, but I anticipate lots of discussion this afternoon, and given that people are always having another eye on the airport terminal, I think maybe we should break for lunch at this point and plan to be back at 1 o'clock please. Thank you.

(Whereupon, at 12:02 p.m., the committee was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:06 p.m.)

DR. CHESNEY: Let's get started.

I understand there is at least one person who has requested time, and the FDA does have a new regulation that I have to read before people can speak, and that is that both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, 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 company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of

financial relationships at the beginning of your statement, it will not preclude you from speaking.

And if you have the courage to speak after that, please do so.

(Laughter.)

DR. CHESNEY: Yes, Dr. Margolis.

DR. MARGOLIS: My name is David Margolis. I'm not going to use the presentation. You guys covered everything basically.

My name is David Margolis. I'm board certified in internal medicine and dermatology and I have a Ph.D. in epidemiology.

My conflicts I guess would be that I don't currently have a consulting relationship with either of the companies who I guess would benefit from this, but do have a consulting relationship by employment at the University of Pennsylvania through a project submitted to Novartis which was then submitted to the FDA to do a study similar to ones that have been discussed today. That would go through the University of Pennsylvania through a contract, and I'm employed by the University of Pennsylvania, so I have a conflict I guess with the University of Pennsylvania.

(Laughter.)

DR. MARGOLIS: The reason that I came here to

speak was that about 18 months ago we put together a proposal to do a cohort study to look at the rate of mainly lymphoma in individuals with atopic dermatitis. That was then submitted to the FDA in the spring of 2002, and we received comments in the summer of 2003.

The reason why I wanted to speak at first was that many of the comments were sort of very clinical trial like comments, which were very important, but certainly increased the complexity of the study. After I've sat through most of the morning, I realize that most of those concerns have been addressed in the presentations, and I think the presentations were very nice at pointing out the importance of doing an epidemiologic study and the importance of those study designs.

There were just a couple of things that I wanted to highlight which are not on the slides that I had previously prepared, so it may seem a little disordered, and I apologize for that in advance.

These studies are incredibly important. Somebody did ask about the price and the cost of doing one of these studies. The study that we submitted really looked at lymphoma. Lymphoma is going to be a less complex study because you really can rely on issues of records and the likelihood of diagnosis. It prevents the fact from having to necessarily see the patient on a frequent basis

to look for skin cancers. Even the cost of that study was well over $1 million a year to look at 20,000 to 40,000 person-years of follow-up. So the costs are substantial here.

I think it's also very important to realize what is the goal of the study and what is the major health concern or public health concern here. I'm a dermatologist and I'm sure at some point somebody will scream at me for what I'm about to say. I apologize right off the top, Dr. Stern. But the public health concern here is lymphoma which is a life-threatening disease in these kids, if they were to develop it. Skin cancers aren't in most cases. As Dr. Stern pointed out, the latency for skin cancer is going to be probably well beyond the 10-year period that we're supposedly talking about following these individuals. So in my mind, there's a real need to either do two separate studies or realize that the complexity of the two studies are going to be very different, and the costs, as a result, are also going to be very different.

The other issue, which I also think is very interesting and important was also brought out in some of the FDA presentations, is the issue of exposure. Individuals with atopic dermatitis are likely to be exposed, and as was also pointed out, exposure may be for a very short period of time as the atopic dermatitis may go

away or they may choose a different therapy.

So it certainly is possible to enroll individuals who were exposed to one of these agents, follow them over years, and then stratify an exposure thereby sort of giving you a group of individuals with perhaps similar severity who may never really see the agent again. As was pointed out in one of the presentations, there are some concerns about what should be chronic exposure so you'll have this group in this large cohort who are chronically exposed and another group who aren't, and you may actually have natural exposure patterns.

You will also, by doing that, perhaps have dose-response effects or dose-duration effects that you can also look at over time. So it may not really be necessary to have this second cohort who completely aren't exposed and will never be exposed for 10 years who have atopic dermatitis, which also may be unlikely. So it would be somewhat unethical to impose restrictions on their treatment for years and years and years.

The other important point I think that is very important to bring out is that if these studies were to begin, the amount of information that would be gleaned from these studies would be incredibly important to individuals interested in cutaneous disease. There really are no good long-term studies on individuals with atopic dermatitis.

It's a very common disease, yet we don't have good studies. As was just pointed out earlier, there really aren't even good studies on what the rate of cancer is in these individuals.

We actually also recently completed a study looking at the rate of skin cancers in atopes and actually found almost nothing in the literature to compare it against. There are maybe one or two studies that have actually looked at other cancers as well. That study will probably be published -- well, it's been accepted for publication, but hasn't been published yet.

There's also the information just on what goes on in atopic dermatitis in terms of the atopic diathesis in terms of the onset of asthma, the duration of the asthma, the severity of the asthma, seasonal allergies, drug allergies is also very poorly understood for a disease that's as common and as prevalent as what it is. In one of these studies, you would be able to do that because you'd finally have enough individuals and you'd be following them long enough that it could be done.

In conclusion, I think it's incredibly important that these studies be done, and I think I agree with what's been presented, that there is a signal which says that it should be done. But we need to be prudent and careful in terms of how they're going to be done in terms

of the costs and whether or not they're even feasible. We also need to get started on them before, as was pointed out, other agents are available and the use of these agents becomes relatively less important.

I thank you for your time and consideration.

DR. CHESNEY: Thank you, Dr. Margolis.

I did want to share one other piece of information. Dr. Santana had to leave, but he tells me that 8 months ago the Children's Oncology Group established a registry for cancer in children which will be going through the NCI, but it is the first comprehensive registry of cancer in children. He says there's some regulation that people have to report all cancers in children now to this registry. So that began 8 months ago.

I'd like now to invite Dr. Patrick Salmon, who we introduced before, who's with the European Medicinal Evaluation Agency, just to say a few words about how you all are looking at this issue in Europe. I guess the best thing is to come up here. You don't have a microphone.

DR. SALMON: I do.

DR. CHESNEY: Oh, you do. Well, that's fine then.

DR. SALMON: Thank you very much. As you say, my name is Patrick Salmon. I actually work for the Irish Medicines Board, and I'm here representing the EMEA because

I was the rapporteur for one of these agents that we're discussing today when it was approved by the CPMP around the same time I think as it was considered by the FDA.

The short comment I can make is in fact we share all of your concerns and have been examining these issues in the last year or two. There are various studies ongoing, but none which I think will address the major issues that are being discussed today. As you know, we've had some preliminary discussions with the FDA on this general area and are continuing to do so.

As to how we eventually address these issues, our main concern is that we do and as soon as possible, the main concern being that, as our last speaker just said, these drugs are actually on the market, so patients are being exposed. So we need to sort of try and address the issues as quickly as possible, but as to how we do it, as long as we will get an answer at the end of the study, I think we'll be happy. So I think that would be just a brief comment on what we're doing.

DR. CHESNEY: Thank you very much.

Is there anybody else who would like to speak at the open public hearing?

(No response.)

DR. CHESNEY: All right. Then we'll move on to the main issue for the afternoon which is the questions the

FDA would like us specifically to address, and you received a new version at your place when you sat down. You'll see that there are several pieces to each question and five questions. In looking at them quickly, I felt that there were maybe some redundancies.

I asked Dr. Cummins, who's going to read the questions for us, if she could read through all of them, and if you could in your own minds sort of focus on the main issues.

We've also been asked, when we get to question 2, because it's fairly long, rather than just having general discussion, to start at one end of the table and go around and ask people to address all the issues in question 2, and if the next person says, I agree, that's fine. But again, so that we can get through these in a timely fashion.

So, Dr. Cummins, if you could go through all the questions with us please.

DR. CUMMINS: What I'm going to do is just read these to you quickly in their entirety, every question, and then we'll back through them one by one.

Question 1 is what is a clinically meaningful increase in cancer risk from a treatment for a chronic non-life-threatening disease? And the next part of that question is, does the present patient package insert

appropriately reflect the information concerning cancer risk? And I would just add that in our review of the patient package insert for both of these products that we did over the noon hour, we do not see that either of them contains any information of a potential cancer risk. Please discuss any recommendations.

Question 2. There's a series of facts that precede the asking of the question. Fact 1, lymphoma has been associated with systemic use of this class of immunosuppressants in both preclinical studies and in human use. Cutaneous malignancies are the most common malignancy associated with systemic use of this class of drugs.

Fact 2, topical use of these immunosuppressants results in some, albeit modest, systemic exposure. This may be increased in pediatric patients due in part to increased body surface to mass ratio.

Now, the premise for this question, malignancy may only be discernible via long-term exposure, especially with modest systemic exposure.

So given all that, what is the best way to ascertain the clinical risk of malignancy, e.g., lymphomas or skin cancer, in clinical studies?

Please discuss the merits and drawbacks of each of the following, as well as study design considerations: the duration of follow-up for each enrolled patient,

keeping in mind that the latency period of most cancers is at least 10 years. And the following study design requirements: the sample size needed to detect rare signals and feasibility issues; the approach to ascertainment of skin cancers, e.g., by physical exam by a physician, by physical examination by a dermatologist -- they're also physicians -- by interview or questionnaire; the role of a comparison group; and design strategies to optimize retention.

The next part of question 2, endpoint issues. What are the specific cutaneous and systemic malignancies we should consider? Are there other biologic endpoints such as viral infections of the skin, such as, for example, warts, EB virus infections, or pre-malignancy or early cancer endpoints such as actinic keratoses?

Question 3, FDA has not asked for such long-term studies in topical products before. To require such screening means that we are asking companies to take on very large, lengthy studies with substantial logistical challenges in patient retention, follow-up, costs, and other factors. We've heard a lot about that today. In what situations should we require such studies? And what criteria would you identify as important in deciding that this type of study be done?

Question 4, is there a role for cancer

registries and/or the SEER program in this long-term follow-up project? Please discuss how one might utilize existing registries or programs.

Question 5, what other studies would you recommend, for example, additional animal studies? And what other risk management for this class would you recommend? And just to remind you of the risk management approaches we discussed yesterday, these include additional studies; a boxed warning in the product label; limiting the indication to certain age groups; recommending against use in certain age groups; contraindicating use of the product in specific populations; including a patient package insert to inform the patient or parent/guardian of the risk; requiring that a medication guide be dispensed with every prescription; unit-of-use packaging; issuing a Dear Healthcare Provider letter to groups of healthcare providers most likely to prescribe; or conducting education programs for providers and patients and/or caregivers.

So those are the questions, and I'm going to go back to question 1 so that you can begin your discussion. Again, question 1 is what is a clinically meaningful increase in cancer risk from a treatment for a chronic non-life-threatening disease? And does the present patient package insert appropriately reflect the information concerning cancer risk? Please discuss any recommendations

you may have.

DR. CHESNEY: Dr. Cummins, could I also add the last bullet of question 5, which is what other risk management for this class would you recommend?

DR. CUMMINS: Do you want to put those together?

DR. CHESNEY: I think that falls into question 1 as well.

DR. CUMMINS: Okay. Well, I'll go forward to that, which is what other studies would you recommend, for example, animal studies? And what other risk management for this class would you recommend? I'm just going to leave this list up on the screen so that you have it to refer to.

DR. CHESNEY: Maybe we could start with the easiest part of question 1, which is the present patient package insert says nothing about cancer. Would we recommend any changes in that in terms of risk management?

For those of you who weren't here yesterday, the committee did recommend that a package insert or something comparable be put into the packages for topical corticosteroid use describing hypothalamic-pituitary-adrenal axis suppression and that physicians also be informed about this specifically saying that we don't know what the risk is. Dr. Murphy and Dr. Wilkin pointed out

that if we do that for the topical corticosteroids, that may actually scare people away from using them and into using the topical immunosuppressants.

So we need to decide I think at this point do we need more information for the patient and for physicians in terms of managing a potential risk which is unknown.

Comments. Dr. Fost.

DR. FOST: On that point, it seems to me clear. That is, it would be odd to have the FDA spend a whole day flying people in from all over the country to discuss this, but don't think that doctors or patients need to know about their concerns about this. So it seems to me unavoidable that the patient information sheet and the information that goes to doctors, not just through package inserts but educational programs and so on, need to explain why this is a second-line drug, that there is this great concern about lethal toxicity, no evidence for it in humans yet, or at least not enough to say anything concrete, but based on the animal data, there is serious concern about this, and this is why this should be a second-line drug.

Having said that, I don't know if 10 or 20 years from now the mortality from potent steroids is going to be greater than this or less. As we discussed yesterday, we have no data on that either. We know that there's far more risk because of the huge number of

children that are getting them now and because of the very high incidence of adrenal suppression, but we have no idea whether that degree of suppression is going to result in serious illness or fatality and in how many.

The bottom line of all that for me is that both the inappropriate use of the potent steroids or this drug is inappropriate and should be discouraged. And to me, the patient information sheet and the doctor information through all these sources should be the same for both of them. That is, both should be second-line drugs; that is, potent steroids should be second-line drugs to less potent steroids. And the calcineurin inhibitors ought to be the same; that is, they should be used only in situations in which almost certainly much safer therapeutics are effective.

I don't know how you can get patients' or doctors' attention other than by scaring them, and if they're scared, so be it. That's what we want them to be. I mean, we want them to be a little bit concerned about using these drugs inappropriately. Now, obviously, if a patient has severe atopic eczema and it's unresponsive to other management and it's disabling in all the ways that we know about, then it may be worth the risk, but parents should be informed of that. Doctors should know what they're doing, and they shouldn't be dispensing it in what

seems like a casual way from the anecdotes that we've heard.

DR. CHESNEY: I would totally emphasize the inappropriate issue in the children under 2. We've seen how many prescriptions are being given for that population in particular, and I think that the vast majority of physicians who are prescribing these don't even think about or know about a potential cancer risk. So I would totally agree with Dr. Fost.

Does anybody on the panel disagree with that position? Dr. Wilkin.

DR. WILKIN: It's not so much a disagreement, it's a clarification mostly from Dr. Fost. Before I describe the issue of symmetry of what I heard yesterday and what I heard today, this is largely Dr. Dianne Murphy's interest because she heard the comments about the patient package insert yesterday and thought we might need some parity today and think about that.

Dr. Fost, I thought yesterday your comment was it would be prudent to have statements in the patient package insert to describe good principles of patient use of the product, not using it beyond a certain period of time, limiting it to small amounts and the areas of involvement, consulting a physician if different sorts of things happen. But I thought I heard not mention adrenal

suppression. If there's symmetry, then would that not be the case in the case of the topical calcineurin inhibitors to simply describe limited amounts?

And I'd point out, you do have your patient package inserts. We have things in here that says apply a thin layer -- and then it's the name of the product, and I think it's roughly the same for both products -- to all skin areas that your doctor has diagnosed as eczema. So it's actually asking that the physician point these areas out. Try to cover the affected areas completely. Most people find that a pea-sized amount squeezed from the tube covers an area about the size of a 2-inch circle, approximately the size of a silver dollar. So it even gives some fairly descriptive advice, which I thought was pretty much in line with what you were discussing yesterday.

DR. FOST: Well, I'm happy to clarify it. No, I think it's essential for the steroid creams to inform parents and doctors about the HPA suppression. There's one obvious reason. What you want parents to know is not just that there's a risk but if their child gets sick or has surgery or has trauma, they need to tell their physician who otherwise would never know that maybe they need supplemental steroids. That's why parents need to know specifically about the HPA suppression in language that

they can understand. So that's one reason why it has to be on that insert and the doctor's insert so that he or she knows also.

But second, I think it needs to be on there to get people's attention as a shot across the bow. Just saying something, use this carefully, don't use it when other things are available, is not going to win an election. I think unless you say you can die from this, because it doesn't occur to people that you can die from using a topical cream. In whatever lay language that is on there in understandable language, it needs to be there. And the specific adrenal part of it needs to be on there, and for the CI inhibitors, that it may cause cancer, an untreatable form of cancer.

DR. CHESNEY: Dr. Stern.

DR. STERN: In terms of risk management, we look at these options and some of us wonder about the efficacy in clinical practice of any or all of them. I wonder for a product like this where there are two manufacturers, how did it come that these agents are so popular and so widely used outside of the labeled indications, including when contraindicated. Well, it's a matter of, I think, promotion both to consumers and to physicians. So I wonder whether the two sponsors might come forward and say, we're going to make an effort to make

sure that people understand the labeled indications, which apparently they are supposed to agree with the counterindications. We will not directly market to consumers these products, which I've seen on my television set, and we will be good corporate citizens so that in fact the physicians will rely principally on the peer-reviewed literature and on the package insert rather than the pressure from patients, doc, there's something new for my eczema and I know it's safer than those steroids. So I wonder if what we really have to do are some non-regulatory things if the companies are willing to step up to the plate and make a pledge to help protect our children.

DR. FOST: I want to second that and approve it by acclamation.

(Laughter.)

DR. FOST: As a corollary to it, without knowing anything about this field, I'll just bet that the miracle of CME is at the root of a lot of this also. That is, we've seen this over and over again in these meetings how these drugs that are approved for narrow indications get used expansively through the miracle of pharmaceutical-sponsored CME laundered through MECs. I realize the FDA can't regulate that, but in terms of whatever leverage you can apply for good citizenship, as Dr. Stern points out, the CME on these things should be -- I don't know what's

going on. I'm just guessing, but it ought to be the opposite of promotion of them. It ought to be educational programs that promote caution in their use and limitation on their use unless there are clear indications.

DR. CHESNEY: Unless anybody has any other comments on the risk management issue, I feel like we're all unified on that.

Dr. Fink, you had a comment.

DR. FINK: I agree with everything that's been said. I am particularly concerned about the widespread use of this drug under age 2. I would almost favor registration of providers, but if that's felt to be too restrictive, I think a boxed warning about nonapproval and contraindication of this drug under age 2 is really important. Because of the developing immune system and because of the thin skin and all of the things that impact under age 2, I really think it deserves highlighting, and I think a boxed warning would not be inappropriate.

DR. CHESNEY: Dr. Mattison.

DR. MATTISON: I actually missed some of the earlier discussions, so if I'm repeating something, I apologize.

I don't know that I could even support 2 as a cutoff. I know that 2 is where it's currently labeled at, but given the lack of understanding about interaction

between immune system and central nervous system development, as well as the development of those systems individually, and recognizing that these act quite profoundly on those systems, it seems to me that special concern needs to be given to the use of these agents in individuals who are still developing. So I would even have some difficulty knowing that we could use age 2 as a cutoff.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I'd like to echo Dr. Mattison's comments. If we're answering the question that was presently 5, what other studies would we recommend, my concern is, whether we allow or disallow the use of this drug in earlier age ranges, it will be used in those age ranges. I think we've been completely unsuccessful in regulating drugs once they're out on the market in terms of keeping them from populations we wish not to expose.

Saying that, the question that remains uppermost in my mind, not to minimize the risk of cancer later on or the risk of other dermatological diseases later on, is whether this drug is absorbed systemically in a dose that alters immune function. That's the question that's most important to me in the young age range. I would like to see a study design that allows us to look to see whether we shift the curve of infections to the left -- or to the

right. Excuse me. I'm not an M.P.H. person. Are there more infections in kids who use this drug? Is there an increased death rate overall? Are there increased numbers of infections, more missed school days, and more missed work days by their parents?

I think these are relatively hard outcomes with relatively vague associations. It will be one of those epidemiological studies that allows you to say they're associated with but the causality would not be well defined. But we're talking about an immune modulator and we're looking at outcomes that we see a lot of in kids, and if we see more serious ones in this population, I think we can attribute causality to this agent.

DR. CHESNEY: They've already demonstrated that. Are you talking about a longer-term study? At least the children under 2 did have an increase in a whole variety of different infections.

DR. GORMAN: They did, and then the question is in terms of quantifying that to determine a risk versus benefit for this particular agent I think would be important. If they have an increased number of colds, I might be willing to treat my atopic child with this drug. If they have an increased number of pneumococcal sepsis, I would not personally be willing to treat my child.

DR. CHESNEY: So it would be a larger group,

longer-term, older children.

DR. GORMAN: I'm not going to try to dictate the study design. It would be a larger group and it would be looking for more serious infectious disease outcomes. The varicella data in the very small studies is a fairly large signal. It tells you that there's at least one infectious agent that is much more likely to produce disease in this group.

DR. CHESNEY: You just reminded me of something, and this is for Dr. Wilkin and Dr. Murphy. When I briefly looked over the patient information, I think it says that an increased incidence of colds, nasopharyngitis, strep infection, and so on has been associated with this drug. But I don't think it makes it clear that there may be an association with the immunosuppressive aspects of the drug. When I first read it, I thought so big deal. You get more colds. But I think if parents understood that that was maybe because the immune system is being suppressed, that that would have a much bigger impact on them, I think as Norm said, in language that they can understand.

I'd like to go on to the very first part of question 1 and then come to the other studies of question 5, but I want to be sure that you all feel as strongly as I do that we need to better inform patients and physicians

about all of the issues related to these drugs. I know that you all can do it in the best way that you think. I think it's not appropriate to make it a required medi guide, but in almost every other way that's been mentioned, I think we all feel fairly strongly that this information needs to be made more public than it has been.

Dr. Danford.

DR. DANFORD: I agree with all of that.

The one thing that has not been mentioned is perhaps the medical community needs to come clean with the public about our uncertainty in the matter. We don't know, and maybe we need to let the public know that the FDA is asking for more long-term research on the issue of cancer in these patients and that the answers are unavailable to us now and may be unavailable for decades. One thing that I think may ring some bells of caution in the public's mind is, gee, this could show up a lot later.

DR. SHIRLEY MURPHY: Dr. Chesney, I'm Dr. Shirley Murphy. I'm the other Murphy. It's good to have two blondes. We can switch.

(Laughter.)

DR. SHIRLEY MURPHY: I'm the division Director for the Division of Pediatric Drug Development.

Dr. Wilkin and I were just saying that we thought it would be helpful if we could just go around to

each person and ask them what kind of risk management they would recommend, and if it's the same as another person, just say, agree, just so that we could hear from every single person. Would that be okay with you, Dr. Chesney?

DR. CHESNEY: That's fair. We'll start down at this end of the table.

DR. CUMMINS: Do you want me to advance to that list? Would that be helpful?

DR. SHIRLEY MURPHY: Yes.

DR. TRAVIS: Did you want me just to address question 2 right now?

DR. SHIRLEY MURPHY: I think if you could just tell us from this list what's your first choice or what do you feel just so we have a feeling for all the individuals like changing the patient package insert, for instance.

DR. TRAVIS: I actually had just gone through that and marked off the ones that I would do at a minimum. I'd at least do, to start with, a boxed warning, recommending against use in certain age groups, including a patient package insert to inform the patient or parent/guardian of the risk, require that a medication guide be dispensed with every prescription, the unit-of-use packaging, the issuing of the Dear Healthcare Provider letter, and then education programs as well. Almost all of them at a minimum.

DR. CHESNEY: Everything except the required medication guide. Did you say you would include the medication guide?

DR. TRAVIS: The ones that I had not included is I'm on the fence right now with regard to additional studies because I see the incredible expense involved, and also I'm a cancer epidemiologist, so I study cancer, and I know about the long latency periods. This age group is not at a cancer bearing age now. Their underlying incidence rates are so low that I don't think you're going to really find that much. You're talking about an immense amount of time and money.

Limiting the indication of certain age groups. I had already thought that had been done, so I didn't mention that one.

And contraindicating the use of the product in specific populations, that's beyond the scope, I think, of what I can do given my background. Someone else may want to do that.

And then I had voted yes for the others.

DR. CHESNEY: Dr. Rabkin.

DR. RABKIN: I just wanted to not answer the question that you posed, but I've been trying to get a word in just to remind people about what the issues are here in terms of lymphoma. The parallel with the systemic

administration of high doses of tacrolimus. There, from every indication, it appears that the mechanism by which that's associated with lymphoma is strictly through the induction of immune suppression, and if that's what we're positing as a potential risk for the topical medications, then it would be possible to look for subtle disturbances of systemic immunity, if it's systemic immune suppression and systemic lymphoma that's of concern.

So I'm still aware that although that's a very difficult problem to study, I'm less pessimistic than I would be if we were only to be able to look for lymphoma as an outcome because I agree with the comments that have been made around the room that that's going to be a very rare outcome to be able to detect.

I don't believe that the pharmacology suggests that there's some kind of a cumulative effect of these medications that will be independent of their immune suppressive action. So immune suppression is something where we can find other indicators, not perfect indicators but we can detect that, and in the absence of alterations of immune function, then we may be less concerned about the possibility of lymphoma as a long-term complication of these medications.

DR. CHESNEY: So that could even be potentially under the first part of question 5, which was other studies

you might recommend.

DR. RABKIN: I'm more getting towards Dr. Andrews' question about what needs to be known because I share Dr. Stern's concern that lymphoma may not be the most frequent or most troubling long-term consequence. But if it is systemic lymphoma, that is something that we can do something about.

DR. CHESNEY: Did you want to weigh in on the risk management list? You could agree with the person next to you or --

DR. RABKIN: I'm more agnostic about the evidence that's been presented so far and also not certain of the benefits that could be obtained from some of these, given the state of knowledge being so low. If we say it causes cancer, a lot of people will shrug their shoulders.

DR. CHESNEY: Dr. Wingo.

DR. WINGO: I guess if I had to pick one, just a few items in this list, to put at the top, I would certainly put something about recommending against use in certain age groups, similarly contraindicating use of the product in specific populations, issuing a Dear Healthcare Provider letter -- I would include that -- and the last one on the list, which is the education programs for providers and patient categories.

This is a very complicated problem. It's like

you want to do one kind of study design to look at one outcome and a different study design to look at some of the other outcomes. Again, it takes us back to Dr. Andrews' question of is one more important than the other. Is there one question that we feel like we must answer, and if so, what is it and what's the best study that we can do to answer that question?

DR. CHESNEY: Thank you.

Dr. Mattison, risk management specific recommendations.

DR. MATTISON: I'm comfortable with the proposals that have been suggested prior to my turn to talk.

I'm just going to reiterate a point that I made earlier. I'm concerned about the substantial uncertainties that are addressable and resolvable about the use of this class of agents in immature animals. I'm especially concerned because it's been suggested that one of the mechanisms is to alter apoptosis, or programmed cell death, and normal development depends critically on cells dying at appropriate times in developmental processes. So I think there are major, major gaps in our knowledge about what this class of agents can do during the course of development and would just simply add that as the component of additional studies.

DR. CHESNEY: Dr. Stern.

DR. STERN: When I think about levers, I've already mentioned the one that I think, in fact, would be most effective, which is a non-regulatory one.

Also, in thinking about these levers, given our absence of being able to quantify risks, when I think about the behaviors I would like to change -- we've already heard about very young children but the others are amount of application and duration of application. So perhaps things that convey that at least in my perspective the likely long-term risks of this agent are likely to be much higher with persistent long-term, substantial use than they are with intermittent local use. So trying to use the levers to have people use it as a second-line drug when they really need it and not rely on it chronically.

DR. CHESNEY: Thank you.

Dr. Epps.

DR. EPPS: Thank you. There are several things for those of us who treat atopic dermatitis and those who have had it, obviously there's always a risk-benefit that is always taken into consideration. When we talk about atopic dermatitis at our pediatric dermatology meetings, we always talk about quality of life because that is a huge issue for young people. They don't go to school for months. They're in and out of the hospital. Their own

self-esteem and appearance and missing out of school and delays, it's quite a problem.

Certainly I don't consider axis suppression and risk of cancer equivalent at all. There's always a risk and a benefit, what I tell patients, when there's a risk like that, is it's either 0 or 100. Either you get it or you don't. 30 percent. It doesn't matter. If your kid has cancer, you have it. There's no in between.

So as far as risk management, additional studies, a boxed warning, if you all think it's appropriate. I think it's okay to limit to certain age groups and recommending against use in certain age groups. It should be contraindicated in HIV. There are certain childhood diseases, whether it's ataxia telangiectasia, inherited diseases, which not only feature eczema but also have an increased risk of malignancy. Those should be contraindicated. Package insert is probably okay. I don't think we need to give one with each prescription.

Now, as far as unit-of-use, when we talk to patients, usually we say a pea-size can cover an entire face. So, a small amount can cover a larger area. So sometimes we'll just say just touch the top of the tube and that can cover a certain amount. "Sparingly" is our mantra, as I said before.

I think a Dear Healthcare Provider letter can

be very helpful. It's not just the dermatologists. The allergists prescribe it. The internists prescribe it. Everybody is out there, oh, I have a little rash, by the way, Doc. Oh, let me give you a little something to put on there. So I think everyone should be aware.

Educational programs should be at all levels. Start in medical school. Get it in Goodman and Gilman. Get in the CME, everything. I think the more education and information, the better. I don't know you necessarily need to be an alarmist, but I think people should be aware.

DR. CHESNEY: Thank you.

Dr. Gorman.

DR. GORMAN: I agree with Dr. Epps in the one thing that I think she's disagreed with the other presenters, which is that a medication guide I would also not support.

I would ask in the patient package insert that there be some wording that deals with sharing this medicine with others. There are certain products that the FDA and the manufacturers have done an excellent job in scaring people about touching and sharing. I think this product should be in that group.

DR. CHESNEY: Dr. Ebert.

DR. EBERT: Just to go through the list, first of all, of course, I think I would support additional

studies, as have been mentioned already and certainly will be discussed in the upcoming minutes.

As far as the boxed warning and other issues of labeling, I guess I would also want to look at what is currently available for the systemic product of tacrolimus and whether we have boxed warnings or patient package inserts for that particular product, and if so, if those might be able to be used as at least a template for the topical formulation of the product, and perhaps there might have to be some inferences made that if there is some established side effects associated with the systemic form, then by inference, if there is some absorption of the topical form, one might at least expect to see some of those same adverse effects associated there.

I also support recommending against use in certain age groups, as well as the patient package insert to inform the patient.

As far as the unit-of-use packaging, again, I'm a little bit unclear on that whether that is something that could be incorporated into the patient package insert or whether it has to be a separate entity. I'm not sure if the FDA is at all involved in, for example, limiting refills or prohibiting refills, if that could be something that also could be looked at, that it would require a follow-up visit to obtain another prescription.

Then as was mentioned both yesterday and again today, I think increasing the emphasis on dermatology in curricula or in CME programs and reinforcing the significance of these products is certainly going to be welcome.

DR. CHESNEY: Dr. Ten Have.

DR. TEN HAVE: Not being a clinician nor a behavioral change person, everything sounds reasonable to me.

I do have one question. Somebody mentioned compounding earlier today, and I don't know. Is that a no-no or is that something should be mentioned in the inserts?

DR. CHESNEY: Maybe that's not a bad suggestion given that we hear that people are mixing it with steroids. Maybe there should be some additional information put about use this only as packaged.

Dr. Wilkin.

DR. WILKIN: I was just going to comment that my understanding is that compounding is largely covered by the different State jurisdictions, the boards of pharmacy in the different States and also the boards of medicine, and that either pharmacists or physicians themselves may, on a patient-by-patient basis elect under the standards of medical care to put together two different materials, and that's the compounding.

DR. CHESNEY: Dr. Andrews.

DR. ANDREWS: I'm not too sanguine about the effectiveness of these various risk management interventions. What I would like to see happen is that there should be discouragement against using the drug in the very young.

I'd like to see some education of patients and families about two things. One is the possibility that a topical drug can be absorbed systemically and have systemic effects. Therefore, amount and duration of use are very important. And I'd like some messages about using these drugs sparingly, do not share, some warnings about misuse.

Because I'm not too sanguine about the effectiveness of these things, I would like to see them tested. I think that the wording is really important and I would love to see this kind of wording and the variations go through some kind of cognitive testing process with a variety of potential patients to see what they really understand. You could also test language about potential cancer risk to see the reaction and whether it might be advisable or not to include that in some kind of patient education brochure.

I don't think I'd recommend a medication guide.

I definitely think that some education of physicians is appropriate, stressing the importance of

these drugs as second-line therapy and potential long-term risks.

DR. CHESNEY: Thank you.

Dr. Fink.

DR. FINK: I would agree with much of what's been said. The primary thing I would push for is a boxed warning in that that legally has a greater implication to the manufacturer of the drug to change their behavior in terms of promoting the drug than any of these other steps because I don't know that we can rely upon them to voluntarily change. But if there is a boxed warning that says, not approved for use under age 2, that really puts them on notice in terms of staying away from that indication.

I'm not sure it would be bad to have something about compounding because for these two drugs, there could be a cautionary note, at least in the package insert, that says, these drugs have specifically been compounded in vehicles that promote their cutaneous absorption and any extemporaneous compounding may actually destroy their activity.

DR. CHESNEY: Dr. Danford.

DR. DANFORD: I would point out that we're not so much managing risk here, although that's a little part of it. We're really managing uncertainty about the

character and magnitude of the risk. We don't know what we're trying to manage. So we do need to make that clear to the public in some way, and we need to focus additional studies on reducing that uncertainty as much as we possibly can.

I agree with the remarks that say there should be more education and less advertising, and a Dear Healthcare Provider letter sounds like a very good idea to me.

DR. CHESNEY: Dr. Glode.

DR. GLODE: I would go back to the suggestion someone brought up earlier of just looking at the oral compounds and seeing again for consistency purposes if they have the boxed warning. I'm very much in favor of the patient package insert, and I think that part of what it should inform people is that the basis for approval was essentially short-term safety and efficacy, and what we're concerned about is again the unknown, but the issue of long-term safety when using a drug that has some, but it appears from what we know minimal absorption but some capacity for systemic immunosuppression.

So I'm in favor of the patient package insert, the boxed warning if it's on other formulations, and education and additional studies.

DR. CHESNEY: Dr. Fost.

DR. FOST: I agree with almost everything that's been said. Just one comment on the relevance of whatever is on the present insert of patients who get it in other settings. I'm not sure what the relevance of that is. Those are patients with major diseases highly informed and have long-term relationships with their doctors, have hours and hours of conversations about things, highly literate about medical matters. For sure, they should be told too, but I'm guessing they know five times more than their intern does about all these things. So I don't know that that should be the standard for what's on the package insert for the topical use where it will be a complete surprise to doctors and patients.

DR. CHESNEY: Dr. Wilkin and Dr. Murphy, have we covered risk management?

DR. SHIRLEY MURPHY: I think that was very helpful to hear from all the individuals. Thank you.

DR. CHESNEY: I'd like now to go back to the very first part of question 1, what is a clinically meaningful increase in cancer risk from a treatment for a chronic, non-life-threatening disease? Comments please. Dr. Fink.

DR. FINK: I'm not sure there's any scientific basis to us but I'd throw out less than a 1.5 increase and that if it had a 2-fold increase, I would somehow consider

that unacceptable. So I guess I might pick 1.5.

DR. CHESNEY: That was my reaction. I haven't a clue.

Dr. Stern.

DR. STERN: Well, I think, first of all, all cancers are not created equally, and secondly, all chronic diseases are not equal in their impact. So to me that's an unanswerable question. We use a variety of agents long-term for debilitating chronic diseases that certainly increase the risk of certain cancers by more than 2 and perhaps if you look at least suggestive data for the TNF-alpha inhibitors that are being used for rheumatoid and psoriatic arthritis, there is good suggestion there that there's a substantial increase in lymphoma with long-term risk and certainly a risk of other things as bad as cancer like demyelinating diseases, and I'm not sure which one I'd rather have, quite frankly, in terms of treatment.

So I think that's an unanswerable question. I think you have to look at the risk-benefit. Does the patient really need it? What are the alternatives? What is the burden of the disease, and for things that you expect dose and duration to be a strong part of it, how can I use a strategy that minimizes exposure and hence that? Sure, if the increase in lymphoma risk with 1 year of use was a relative risk of 2, then I'd say that's out of the

ball park for any treatment for atopic dermatitis, but that's not the kind of thing. We're talking about a continuum of severity and we're talking about a dose and duration dependence of risk. So to me it's an unanswerable question.

DR. CHESNEY: Dr. Rabkin.

DR. RABKIN: Dr. Andrews already made this point, but relative risk is perhaps not the best measure when we're worried about patient risk. And there's a lot of attention being shifted to the excess risk, the absolute magnitude. So doubling a very extremely rare occurrence is not of concern. If you're going to assign a level -- and I'm not sure that you can -- if it certainly has all the complexities that were mentioned, you probably wouldn't want to be looking at a relative risk when you're worried about effects on patients.

DR. CHESNEY: Dr. Epps.

DR. EPPS: We also use other medications to treat severe atopic dermatitis and some people use cyclosporine, maybe some other immune modulators orally even to treat, PUVA. There are some other treatment modalities, and I guess what the acceptable increase is there I guess could be applied to this one as well, although it's topical and there are some unanswered questions. But obviously, this disease can be severe

enough that we'd accept a certain amount of risk.

I guess the other problem is that you don't use cyclosporine in everybody, and it's not used as widely.

Also, I should comment that the method of practice or -- I won't say standard of care, but the patterns of practice have evolved since these medications have been approved. First it was second-line, and then well, perhaps you could use it this way. And then certainly there was a recent paper, oh, it decreases flares, and some people interpreted that to mean, well, use it suppressively. Use it all the time whether you have rashes or not. So those are other issues that need to be dealt with because some people are putting it on normal appearing skin, although in the world of atopic dermatitis, I don't think the skin is normal anyway.

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

DR. FINK: Just a comment that I think as we deal with particularly long-term induction of cancer risks, we potentially should look at some of these smoking-related literature and other experiences which says the average human being has no ability to conceptualize a risk that is greater than 10 years down the road. So even if it is high, the average person ignores it. I think we've got to take some responsibility there to say -- I don't know what the number is, but if there's a certain amount of increase,

it's unacceptable.

DR. CHESNEY: Dr. Danford.

DR. DANFORD: Along those lines, I was intrigued by Dr. Epps' earlier comments about how when dermatologists get together, they talk about quality of life in the context of atopic dermatitis. I'm wondering if they talk about it in sufficient depth to have maybe some decision analytical models and quality adjustments to know what sort of tradeoff in length of survival versus quality of life is acceptable to the patient population in question. Although I don't think the first part of question 1 is really answerable, we could make up an answer based on that sort of an analysis I suppose.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I would agree with Dr. Fink on almost everything except what he just said.

(Laughter.)

DR. GORMAN: I think UV exposure is an excellent example of a very minimal increase over baseline risk that has really penetrated the consciousness of the American population.

DR. FINK: It's wrinkles, not cancer.

(Laughter.)

DR. GORMAN: Touche.

(Laughter.)

DR. CHESNEY: Speak for yourself, Dr. Fink.

(Laughter.)

DR. CHESNEY: Drs. Murphy and Wilkin, do you need more of an answer to number 1?

DR. WILKIN: If I could just comment on some of the quality of life instruments that have been proposed to us. Not all, but many of them actually focus on disease-specific pieces, and they're really designed in a way -- they tend to go in the positive direction even in the vehicle group. Do you feel better now that your atopic dermatitis is not so itchy? In general, in these inflammatory diseases that sort of wax and wane, folks get recruited early on when they're sort of at a disease maximum. So even in the vehicle group, they tend to have some improvement. They tend not to focus on the adverse events that might be associated with the product or the difficulties of applying or ingesting or those sorts of things. So I think there are some limitations with the quality of life data sets that we actually get.

DR. CHESNEY: Dr. Andrews.

DR. ANDREWS: I'd like to respond to the earlier question about eliciting patient preferences and do patients understand risks that are low. I think this basic question is sort of unanswerable, but it is potentially studiable, and that is through some methods that ask people

to trade off risks and benefits. It certainly would be an interesting thing to do in a patient population, as well as among physicians who treat these patients, and get an idea of how the risks and benefits are traded off for different levels of disease severity.

DR. CHESNEY: Dr. Fost.

DR. FOST: Well, it's complicated for adults treating themselves, but it's much more complicated for parents making decisions on behalf of their children. They may discount, even if they believe it, a long-term cancer risk in exchange for relief from the burden of caring for a child who's got this chronic skin condition that's driving everybody crazy. So it's just more complicated than finding out what parents want or what kind of risk they'd be willing to accept. That is, they may be willing to accept the risk that we would think was not acceptable. Easy for us to say.

DR. CHESNEY: Actually I think that's a very important point because it's not the 3-month-old that chooses to have this cream put all over their body at 10 times the dose every day for a year. So this is a very intriguing issue.

Shall we go on to question 2, which I'm dreading?

(Laughter.)

DR. CHESNEY: Well, let's see if we can sort out -- well, I'll let Dr. Cummins tell us what you really want us to answer.

DR. CUMMINS: I'm just going to read through the whole thing again, about four slides.

Fact 1, lymphoma has been associated with systemic use of this class of immunosuppressants in both preclinical studies and in human use. Cutaneous malignancies are the most common malignancy associated with systemic use of this class of drugs.

Fact 2, topical use of these immunosuppressants results in some, albeit modest, systemic exposure. This may be increased in pediatric patients due in part to increased body surface to mass ratio.

And then a premise. Malignancy may only be discernible via long-term exposure, especially with modest systemic exposure.

So then we get into the questions. What is the best way to ascertain this clinical risk of malignancy, e.g., lymphomas or skin cancer, in clinical studies?

Please discuss the merits and drawbacks of each of the following, as well as study design considerations: the duration of follow-up for each enrolled patient, keeping in mind that the latency period of most cancers is at least 10 years. Study design requirements: the sample

size needed to detect rare signals and feasibility issues; the approach to ascertainment of skin cancers, for example, by physical exam by a physician or a dermatologist or by interview or questionnaire; the role of a comparison group; design strategies to optimize retention.

And then endpoint issues: reflect on the specific cutaneous and systemic malignancies, whether other biologic endpoints should be collected, such as viral infections of the skin, or other, for example, warts or EBV infections, and/or pre-malignancy or early cancer endpoints such as actinic keratoses.

DR. CHESNEY: Thank you.

DR. CUMMINS: We actually really would like your reflections on all of this, if that's possible.

(Laughter.)

DR. CHESNEY: I guess the bottom line question is the first one. What is the best way to ascertain this clinical risk of malignancy in clinical studies? Who would like to tackle that first? Dr. Fink and then Dr. Glode.

DR. FINK: I don't want to tackle the question. I would like to get a point of clarification from what's been said earlier. If we said that the latency for these cancers is 10 years -- I thought I heard earlier that for skin cancers it was less because if it really is as long as 10 years, then all of the clinical reports of adverse

events to date are unmasking of a preexisting malignancy, not occurrence of a malignancy. That actually may be an important issue because most of those reports, the drugs haven't been on the market 5 years, and is that to say then that none of the reports are new-formed malignancies? They're all unmasking of preexisting pre-malignant conditions? Or is skin cancer different? Because I thought Dr. Stern said skin cancers could --

DR. RABKIN: I made a comment about lymphoma being a very short latency in the setting of immune suppression.

DR. STERN: There are three things you have to take into consideration with skin cancer. One is are you looking at the effects of a primary mutagen or carcinogen, and the second is are you looking at the effects of some way in people who already have mutagenic injury, that their mutated cells that have not undergone apoptosis may go on to cancer. So if you look at the relationship between -- and since everyone is exposed with UV, if you look at the relationship for carcinogens, most of which in the skin have some mild immunosuppressive effects as well, when one looks at the relationship between dose and risk, there seems to be a long period between those two things, a long latency.

If you look at quite profound immunosuppression

in the skin -- and one of the things we don't know -- remember, 5 milligrams of cyclosporine compared to a usual immunosuppressive dose orally, we know that these agents systemically are much less immunosuppressive. But I haven't seen studies of relative immune response on the skin. How immunosuppressed am I where it matters for cutaneous carcinogenesis when I apply one of these products versus when I take 5 milligrams per kilogram per day of cyclosporine? That's data that we could probably have to get some idea in this end organ of interest. What's the extent of immunosuppression?

If these agents were as immunosuppressive as oral calcineurin inhibitors, we would expect in people who are in the susceptible age groups to begin to see a substantial increase after about 2 years of continuous use and by 5 years, get pretty close to where it thresholds.

However, the important thing is, as has been talked about in terms of relative versus absolute risk, the risks of non-melanoma skin cancer before age 35 in people who have not had X irradiation exposures, children who do not have genetic abnormalities that pre-dispose them or some unusual other exposures is very close to 0. Therefore, you're dealing with people who aren't susceptible. How many heart attacks do you see in 18-year-olds who have cholesterols of 400? They haven't gotten

there yet, but if they don't change and they have a bad ratio, what are the odds that that's going to happen in the next 40 years? So it's a very complicated problem and quite frankly, I don't think we can well quantify it for these agents.

DR. FINK: Would you conclude from that then the adverse event report data that were presented here are not necessarily reflective of drug effect? Because none of them were on the drug for as long as 5 years or even 2 years continuously.

DR. STERN: I don't remember a lot of any skin cancers except for two nonmalignant tumors, as I recall, one basically probably secondary to inflammation and another that we don't even have the diagnosis. Then I guess, depending on how you count it, there was an HIV-infected person with Kaposi's, and who knows what's going on there. I don't think we have any data, and I would say that when it comes to skin tumors and spontaneous reporting, I don't think that the Medwatch system would say that's one of their strong points, but I defer to them.

DR. PITTS: Thank you. Well, actually I wouldn't say that there was a masking because I think if you look at the Prograf label, you'll see an acceleration of lymphomas. The other thing is that with the two pediatric patients, one was a granuloma and the other was a

facial tumor without any information. However, with the topical tacrolimus, there were five cases. One was a Kaposi's sarcoma, two non-Hodgkin's, and one was a B cell lymphoma, and then an anaplastic large cell lymphoma. But I'm not sure if that's a masking of a previously existing --

DR. STERN: There were no squamous cells detected which is really, for skin cancer, likely to be the strongest signal from everything we know, and if it had occurred within weeks or months of use, I would have discounted it as ascertainment bias rather than an effect. And the big problem is this is not a susceptible population.

Someone mentioned to me -- and I had forgotten about this -- if you look at the experience of childhood radiation -- and it's interesting. It's mainly basal cell cancer -- if you studied a group of kids who got childhood radiation at age 5 and examined them at age 15, there would be few basal cells. You come back to those people when they're 45 years old, if they're cancer survivors, and in the fields of radiation, some but not all of them will be getting basal cell after basal cell after basal cell. So it's analogous to that problem. I think your 10-year answer is not going to be a robust answer in a childhood study.

DR. CHESNEY: Dr. Rabkin and then Dr. Glode.

DR. RABKIN: By the same token, there are characteristics of lymphoma that would be more likely to be ascribable to effects of these medications if we're thinking it's being generated by the pathway of immune suppression. So EBV positivity you'd anticipate would be universal. The histology would be high grade and diffuse. So it wouldn't be as informative to lump all lymphomas from some system like Medwatch, but rather to collect more information, perhaps going back to these individual records and determining if those lymphomas resemble lymphomas that are seen in other settings that are similar.

DR. CHESNEY: Dr. Glode.

DR. GLODE: My question was just with regard to the clinical trial, I wondered if it would be possible for Dr. Margolis to just share with us in 1 to 2 minutes the study design of his study that the FDA has apparently looked at to look at lymphoma and about how many patients that would enroll or whatever, the power of the study, anything like that just very brief.

VOICE: Dr. Margolis left.

DR. GLODE: Is he gone? Because maybe the study has already been designed and reviewed and it's great.

DR. CHESNEY: Dr. Wilkin, do you have any

information about Dr. Margolis' study?

DR. WILKIN: No. We didn't bring that material. Don't have the detail.

DR. CHESNEY: Does anybody else want to comment on the best way to ascertain this clinical risk of malignancy in clinical studies? Dr. Andrews or Dr. Wingo. She actually volunteered.

(Laughter.)

DR. WINGO: Well, given that you can't study both cutaneous skin cancers and the lymphomas using the same registry, even if you had a registry for the cutaneous melanomas, if you decided that maybe an important thing to look at would be the risk of the systemic drug with lymphomas, you could certainly design a study to look just at that issue and not try to do too much in one study.

Another thought would be that if the data supported this -- and the data are weak. I think that's been part of the discussion today -- you could also make a recommendation for the squamous cell carcinomas that persons who use these drugs should have the recommendation to be screened more frequently, to have the body screens for the development of skin cancers more frequently as opposed to doing a special study to look at that issue.

DR. CHESNEY: Thank you.

Dr. Gorman.

DR. GORMAN: Back to what we know about these agents, if we're going to apply them to the skin -- and we know that the drug is removed through the blood stream. Is it also removed through the lymph, and would the regional lymph nodes then be at somewhat greater risk than a systemic absorption where the only way to get into the lymph node would be through the blood supply? Do we know how this drug is removed from the skin? Because it might make some difference in where the lymphoma would then appear. Perhaps.

DR. RABKIN: I think those are very plausible scenarios, and we don't have knowledge there.

DR. STERN: And it's also not only where the drug is getting to, but in fact there's something in dermatology called SALT. Basically they're interactions and interplay and T cell trafficking between skin and lymph nodes as just part of normal immune response. So in fact, you've got to remember, as I said earlier, when we talk about the effects of immunosuppression, the skin is in fact a very active immunologic organ with a lot of T cell trafficking going back and forth.

DR. CHESNEY: Dr. Danford, you had your hand up.

DR. DANFORD: I think we need to be a little bit cautious about making special recommendations for

people who have been exposed to these topical agents to have examinations frequently by dermatologists, not because I don't think it's a good idea. I think that's probably an excellent idea in clinical medicine, but it may confuse us for the scientific question of are they at special risk for developing these malignancies early because we're not subjecting whatever we're going to use as a comparison group to the same sort of diligent search for the malignancies, and we may falsely uncover a risk that's not there because of differences in ascertainment of the outcome.

DR. CHESNEY: Dr. Andrews.

DR. ANDREWS: If I were pressed to do a study, I would look at the outcome of lymphoma and make use of the State cancer registries for case ascertainment. And I wouldn't limit the study only to children. I would try to get a population where the incidence is higher where it would be more likely to be able to detect a difference.

DR. CHESNEY: Dr. Stern.

DR. STERN: If one were to embark on one study, I think we've heard over and over that there's a big power problem, and one of the things is there are two sponsors, and I just wonder whether rather than encouraging two separate, under-powered studies, one of which will turn out to be positive and negative, whether we might not say if

you're going to do a study, take it all in one shot, and that also might help guarantee a little bit of investigator independence from the sponsoring company. Also, there's a lot of cross-use between these two drugs. In my practice who gets Protopic versus Elidel is what their insurance company is, and that's something that changes over time because most insurers, at least in Massachusetts, have one or the other and not both as a covered drug. So if you're going to do it, which I'm not really terribly enthusiastic about, you may as well do it once jointly for all the reasons I've said.

DR. CHESNEY: Dr. Epps.

DR. EPPS: I would make full use of the Children's Cancer Registry. Perhaps a few questions about calcineurin inhibitors would be helpful even though that's sort of retrospective, but I think that would be at least moving in the right direction. Obviously, longitudinally, it would be very difficult, very expensive. I don't think that looking for actinic keratoses is helpful. As far as viral infections, warts, EBV, probably also molluscum contagiosum seems to be increased as well. I would look at that a little bit, although we already know that they're all increased.

So I agree, I don't think other than our routine dermatologic exams -- a lot of the primary care

physicians do see things that if they aren't sure what they are, they do refer on, so that if we started seeing teenagers and young people with suspicious or skin cancers, then we should certainly be aware and think about it, especially if they're atopic or chronically. A lot of the chronically or more severe atopics we see regularly. You have to certainly not only for insurance purposes because they won't renew their prescriptions forever, but we don't renew the prescriptions forever because as the disease evolves and it changes and certainly therapy should change.

DR. CHESNEY: Dr. Rabkin and then Dr. Wingo.

DR. RABKIN: Deliberately repeating myself, the underlying condition is controversially associated with an increased risk of lymphoma. So if a study like that were to identify those patients to have an elevated risk, it wouldn't be straightforward to ascribe that to the medication.

DR. CHESNEY: Dr. Wingo.

DR. WINGO: I just wanted to make a comment about the Children's Oncology Group cancer registry just to point out that it is not population-based. It's facility-based. There are advantages and disadvantages to going with such a registry as compared to the population-based registries.

DR. CHESNEY: Other comments about question 2?

(No response.)

DR. CHESNEY: That is enough?

DR. SHIRLEY MURPHY: Yes.

DR. WILKIN: Yes.

DR. CHESNEY: Question 3.

DR. CUMMINS: FDA has not asked for such long-term studies in topical products before. To require such screening means that we are asking companies to take on very large, lengthy studies with substantial logistical challenges in patient retention, follow-up, costs, and other factors. In what situations should we require such studies? And what criteria would you identify as important in deciding that this type of study be done?

DR. CHESNEY: Dr. Danford.

DR. DANFORD: I have a question. Leaving the FDA aside and the issue of topical products aside, can anybody think of examples of investigations that have been as long-term as we've proposed and as complicated as we've proposed that have actually come to fruition and provided valuable information for us?

DR. MATTISON: I think the DES study is a good example, a double-blind trial looking at the impact of this drug. There are a host of reproductive and developmental endpoints that would have never been identified actually had the study not been conducted. That's not the only one,

but that's certainly one that comes to mind.

DR. CHESNEY: Dr. Mattison, I have you down here. Was that what you wanted to say?

DR. MATTISON: Oh, sorry.

(Laughter.)

DR. MATTISON: It seems to me that coming back to the mantra that I've been singing here today, long-term studies generically seem to me to be especially important to consider when the endpoints are developmental and may take some substantial period of time for the impact of the agent to be expressed. So I would say that one of the criteria would be use of the agent during developmental time frames or life stages and concern for uncertainty about the impact of those exposures across the course of development.

DR. CHESNEY: Dr. Glode.

DR. GLODE: So my criteria for these topical products would be, first, is there evidence of systemic absorption of the product. Secondly, is there evidence beyond pharmacologic absorption of systemic effect of any kind, and third, are the other formulations that are systemically administered associated with serious and/or life-threatening complications. And if the answer to those questions are all yes, then that's the population that deserves long-term studies I think.

DR. CHESNEY: Yes.

DR. GORMAN: I'd like to echo what Dr. Glode said because I think those are the parameters, and the outcomes with the systemic absorption and systemic effects have to be severe and pose a public health challenge. If I remember Dr. Wingo's data correctly, there are about 20 cases of lymphoma in adults per 100,000, and if 20 percent of Americans have atopic dermatitis, and if they're all exposed to this drug class, and if it just increases the relative risk by a 2-fold effect, which might be hard to determine statistically, that increases the burden of disease, from the back-of-the-envelope calculations, by 25 percent in the American population, which I think is a substantial increase in risk. So if everybody in the 20 percent got it and got a 2-fold increase in their rate of lymphoma, that would increase the total number of lymphoma cases in the United States by 25 percent. I think that's a big number.

DR. CHESNEY: I think the question is in what situation should we require such studies. Dr. Rabkin pointed out the difference between lymphoma being life-threatening and skin cancer not necessarily being life-threatening. So I think a criterion would be that there is a signal for a life-threatening event which would, for me, precipitate the requirement for a more comprehensive study.

Dr. Fink and then Dr. Andrews.

DR. FINK: I think since widespread usage and long-term risk are important, I would almost raise the question that this is one drug or one class of drugs where there's that concern. There are many new bioengineered agents coming into use and we're reaching a period of very rapid drug development, and it would almost strike me that it may be more cost effective to look at undertaking some NIH federal-sponsored, large-term pediatric population studies looking at all risks rather than separating them out drug by drug because it may be environmental risks, it may be drug-related risks, but we're clearly in a very rapid period of evolution both in terms of pharmacotherapy and potentially changes in the environmental risks.

DR. CHESNEY: I had that same thought earlier today, and I think wasn't original. Has Dr. Alexander not been a proponent of long-term childhood studies such as the Women's Initiative?

DR. RABKIN: There actually is in the planning phases implementation of a very large cohort of children to be followed from birth, actually prior to birth, with cancer being one of the important endpoints. But that still may not be powerful enough to detect a side effect of these medications if they're not used as frequently as the manufacturers hoped.

DR. CHESNEY: Could you tell us a little more about that study? It's to look at all life events?

DR. MATTISON: We're about 2-and-a-half to 3 years into what's thought to be about a 6-year planning phase of a study that's called the National Children's Study that would enroll about 100,000 families. It was mandated that NICHD begin planning this in the Child Health Act of 2000. The goal is to look at environmental influences on children's health, growth, and development. There are, in designing the study, substantial concerns by various working groups about pharmaceutical exposures and their impact. As I say, it's in its planning phases right now.

There is an advisory committee that's providing recommendations to NICHD and to the other federal agencies that are participating in this, and there's substantial discussion about even with a sample size of 100,000, how useful this would be for ascertaining exposures that are associated with cancers given that it's likely that this will be some sort of a representative sampling of folks around the United States.

But there are current discussions going on with NCI about the role that this study could play either as a control cohort or as a cohort to look at specific biomarkers in association with exposure.

All of the information about the study is publicly available. There is a public web site called the nationalchildrensstudy.gov, and the current hypotheses that have been proposed by the working groups and other organizations are there, as well as minutes from all the meetings.

DR. CHESNEY: Thank you.

Dr. Ten Have.

DR. TEN HAVE: One more aspect of the criteria for launching these studies may be better animal studies that try to approximate patient reality better. Somebody mentioned that none of the animal studies have been done on young animals. That may be one criterion.

Another one may be lower doses, longer duration trials in animals, again to try to approximate more what's happening in clinical reality.

DR. CHESNEY: Any other suggestions for question 3?

(No response.)

DR. CHESNEY: On to question 4.

DR. CUMMINS: Is there a role for cancer registries and/or the SEER program in this long-term follow-up project? Please discuss how one might utilize existing registries or programs.

DR. CHESNEY: Dr. Andrews.

DR. ANDREWS: I think the answer is obvious. If there is to be a study looking at exposures in lymphoma, then the State registries could play a key role. The SEER program, I don't think, allows you to actually do the linkage. I think that has to be done at the State level. So one could identify the patients and exposures through some mechanism, whether it's through an automated database or through patient recruitment, and link that information with cancer registries for ascertainment of lymphoma.

DR. EPPS: I agree.

DR. CHESNEY: Any other comments about that? Dr. Fink.

DR. FINK: A concern I guess I would have with the use of the registries is they may be helpful, but again going back to some of the data from the asthma field, there have been several nice studies that showed that only about 10 percent of 30-year-olds who had pediatric asthma recall that they had asthma as a child. I'm not sure, if you use a registry approach, what the likelihood is of recalling atopic dermatitis or use of a calcineurin agent for making that association.

DR. ANDREWS: I would agree. I wouldn't start with identifying cases from the registry because I think recall would be hopeless here. I would identify people exposed first and use their exposure status and their

identification to then identify reported cases of lymphoma because we know there is close to 100 percent ascertainment of lymphoma in these cancer registries. So it would be some kind of a longitudinal study where the registries are used to ascertain the outcome.

DR. FINK: Okay, but that's a big registry to take on people who use the drug. That doesn't exist currently.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I think the registry doesn't exist as a registry, but I think the prescription databases, if available, could provide you with those numbers that could then be linked 40 years later to the cancer registries.

DR. CHESNEY: Dr. Santana mentioned before he left, if it was pertinent to bring up, the -- I forget now how you all describe this where you put the label on and you require the physician to register, that process. He said he wondered if that was a situation where physicians using these drugs would have to be registered and the patients have to register. Could you review that policy for those who might not have heard it yesterday? Obviously I didn't remember the details.

DR. WILKIN: Well, there is such a program for thalidomide which is a systemic, very potent teratogen where physicians must take certain CME types of courses and

make assertions that they understand the pharmacology of thalidomide, the teratogenic risk, that they understand the risks of getting pregnant and how those risks might be minimized with counseling. And then pharmacies I believe register, and there's a controlled distribution. The thalidomide goes to the pharmacy and only specific pharmacies. Again, the physician would direct a patient to go to a specific pharmacy to pick it up. There's a program embedded in all of this of getting pregnancy tests in a timely manner in women of childbearing potential. So those are the kinds of things that could be done if that's responsive to the question.

DR. CHESNEY: That would certainly allow registering of every patient who used it, but it seems that it might be a bit extreme.

Dr. Fost.

DR. FOST: Thalidomide is a drug with virtually a 100 percent incidence of an extreme adverse effect if used improperly. So that sort of intensive monitoring is warranted by the severity. Here where you don't even know -- to invest that sort of effort in something that may produce -- well, you don't know what it will produce and it may take you 20 years to find out. There are hundreds of drugs you'd want to ask that kind of question about.

DR. CHESNEY: I agree. I just wanted to bring

it to the table on his behalf.

Dr. Rabkin.

DR. RABKIN: Just to mention an alternative model for investigating pharmacoepidemiologic associations is to take advantage of preexisting healthcare networks that already have computerized records of prescriptions and also track health outcomes. So that's something that a number of pharmacoepidemiologic research groups have been able to investigate with fairly large patient populations.

DR. CHESNEY: Thank you for bringing that up. The Kaiser Permanente group was mentioned yesterday as an example of that.

Other suggestions for question 4?

(No response.)

DR. CHESNEY: Is that enough? Okay.

Moving on to the first part of question 5, Dr. Cummins, maybe we could just ask for any more specific suggestions about other studies that would be recommended.

DR. FOST: Could we just go back to 4 just to add to Dr. Rabkin's suggestion?

DR. CHESNEY: Yes.

DR. FOST: What's the extent of the use of the calcineurin inhibitors in Europe in countries where they have integrated databases, medical databases?

DR. CHESNEY: Dr. Salmon.

DR. SALMON: I have to say I can't answer that question either on a national level or across Europe. I suspect the records are available, but I'm afraid I don't have them.

DR. CUMMINS: The first part of question 5 is what other studies would you recommend, for example, animal studies.

DR. CHESNEY: Other studies that people would recommend that haven't already been brought? Dr. Stern.

DR. STERN: Well, I do think that the amount of animal photo-carcinogenicity experiments that have been done for these compounds compared to the likely magnitude of risk represents an imbalance that could be easily corrected, and I think there are a number of designs that can look at simultaneous and sequential exposures with appropriate controls and at least in some models -- you can't predict extent, but at least predict direction or how much to be concerned would either help to increase our concerns or perhaps even allay our concerns about the use of these in various ways, including controlling for age of animals and levels of exposure and chronicity.

DR. CHESNEY: I think many people picked up on that.

Dr. Wilkin.

DR. WILKIN: Perhaps Dr. Stern can give us a

few more pieces of information on this. We thought about this internally. The rodents, in which we look at this model, are essentially nocturnal animals. So this is sort of a very artificial thing that happens to them. I'm not sure that over time they have all of the evolutionary adaptive advantages in their immune system. In other words, if we got a negative response, what would that tell us, I mean, a negative signal that the calcineurin inhibitor wasn't doing something?

DR. STERN: I don't do mouse work and I don't recall -- and perhaps you do -- for the calcineurin inhibitors, if they've ever been tried systemically in mice with photo-carcinogenicity. I'm not aware of that, if there are positive responses.

I guess what I would look for is, first, I'd look and see if there's a positive animal model of exposing the animal, giving them either placebo or systemic doses of calcineurin inhibitor and seeing if there's an increase in subsequent skin cancer risk, kind of the human model in transplantation. If it hasn't been shown, I'd try that experiment. If that were negative, I'd go home and take back all my comments.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: I'd like to suggest a varicella study. I think dogs are susceptible to varicella. There's

also a vaccine in dogs for that. I would like to see if when this agent is used topically on dogs, whether the death rate from varicella or the breakthrough rate for immunized dogs changes.

DR. CHESNEY: Dr. Fink.

DR. FINK: This wouldn't really be an animal study, but it might be interesting to try and look at, in a small number of young patients, if this drug is going to be used, whether local application of it affects their immune response to vaccinations since that is taken up by localized lymph nodes. I don't know how feasible that is, but it would strike one as something worth looking at.

DR. CHESNEY: I was very intrigued by Dr. Hill's comment that there may be drainage to the local nodes, and I wondered about the feasibility of looking at the local nodes in animals. I have no idea how to do it, but to see if the lymph nodes near a localized area of application look different than nodes at another site or whether it would be possible to label the drug and see how much of it went to nodes and how much went elsewhere in terms of additional studies.

Dr. Rabkin.

DR. RABKIN: We're I think several steps away from the question about what the goal is, though, because even if you do note differences in the local lymph nodes,

it may not be relevant to question as to whether this increases risk of systemic lymphoma.

DR. CHESNEY: I agree, but it was a great idea and I just wanted to say it.

(Laughter.)

DR. CHESNEY: Other comments about additional studies that could or should be done?

(No response.)

DR. CHESNEY: Have we been of any help with these questions? I feel like they were very difficult and complex to try to answer in a short period of time.

DR. WILKIN: Yes. I think we've heard a lot of important suggestions today.

I would like to make just a couple of comments. Originally we started out with the first part of question 1 and not the second part, and it was really a lead-in to these long-term studies. We had planned this session of the advisory committee to talk about uncertainty and how to study for it. I don't know that the FDA group really came with the preparation to talk about risk management per se.

And the other part that we missed today is I think we might have heard a somewhat different portrayal of the actual risk if industry had had an opportunity to go over the data. So I think we're going to take all of the information we've heard, discuss it with the two industries

that currently are involved. Who knows? Maybe there's an opportunity for this group to get a refresher course in what happens at the cellular level and also in dosimetry.

I guess that's one of the other important points today that we had sort of thought about but maybe not articulated in such succinct terms as Dr. Stern, that this is largely a question of dose and duration. And if you'll permit me one more quote, Paracelsus did say that whether a substance is toxic or not depends on what its dose is. We have a lot of topical products that have, frankly, been developed from fairly toxic drugs given systemically. Just as an example, 5-fluorouracil is used on the surface of the skin. I can guarantee that the side effect profile is nowhere close to what we see with systemic 5-fluorouracil. We have active agents in topical products for which industry has never developed a systemic-form product simply because of toxicity concerns. So I think there's an enormous dose aspect to all of this.

We even have a retinoid in a product which is largely going to be used in the setting of pregnancy. It's used for melasma and melasma is virtually a physiologic sign of pregnancy and we know that retinoids given in much higher amounts are actually going to lead to teratogenicity.

So I think one of the things that we always

want to be careful about -- and I think I heard the word "scare" maybe once or twice -- is I think we want to make an important distinction when we are working on risk management to carefully define the line between pharmaco fear mongering or scaring and conveying uncertainty. I think that's something that we also heard the conveying of uncertainty from the committee. And I think we're going to work hard internally, and we may come back and find out from your group if we got it right. But we want to make sure that we haven't crossed over beyond into the crying wolf because crying wolf undermines every precaution and warning and all of the other, if you will, advisory or hortatory things that FDA puts in all of our medication guides and healthcare provider letters and all these sorts of things.

So I think we want to be very careful. We don't want to be overly careful. I mean, we want balance is basically what I'm saying. Dr. Fost actually mentioned that when thalidomide was brought up. He said this is not thalidomide I think, something to that effect, that we need to think of a measured communication response for the information we have got.

So I think the committee has worked very hard today, given us a lot of good information. You've not only wrestled with the science, but probably you've wrestled

with the even greater difficult issue of societal values, that is, how much do we want to know things, how much are we willing to spend, subject kids to different sorts of things to learn about them. It's a difficult area when we're working with uncertainty, and we'll be working with the companies and we may well come back to you to see if we've been able to convey the uncertainty in an appropriate manner.

Thank you.

DR. CHESNEY: Thank you very much for putting it in the broader perspective. I think we realize that when we come, you ask us to look at something very focused, and we don't have necessarily the perspective that you do. But we thank you for bringing it to us.

I also want to thank you for educating us in ancient mores.

I also have a comment that if anybody on the panel needs a cab and didn't sign up there will be a desk in the lobby that's got an FDA label on it and they will help find a cab.

I thank everybody on the panel very, very much for all your comments. I think it was a very informative session. Thank you.

(Whereupon, at 2:55 p.m., the subcommittee was adjourned.)