nyUNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
OFFICE OF THE COMMISSIONER

PEDIATRICS ADVISORY COMMITTEE

SIXTH MEETING

TUESDAY,
FEBRUARY 15, 2005

The Advisory Committee met at 8:00 a.m. in Room 1066 of the Food and Drug Administration, 5630 Fishers Lane, Rockville, Maryland, Dr. Joan Chesney, Chair, presiding.

PRESENT:

P. JOAN CHESNEY, M.D., Chair
ELIZABETH B. ANDREWS, M.P.H., Ph.D.,Voting Consultant
DENNIS M. BIER, M.D., Member
RUTH S. DAY, Ph.D., Voting Consultant
ANGELA DIAZ, M.D., M.P.H., Member
DEBORAH L. DOKKEN, MPA, Patient-Family Representative
ROSELYN E. EPPS, M.D., Voting Consultant
MICHAEL E. FANT, M.D., Ph.D., Member
NORMAN FOST, M.D., M.P.H., Voting Consultant
ELIZABETH A GAROFALO, M.D., Industry Representative
MARY GLODE, M.D., Member
RICHARD L. GORMAN, M.D., Pediatric Health Organization Representative
PAULA KNUDSON, Consultant-Consumer Representative
DONALD R. MATTISON, M.D., Voting Consultant
JOHN WILLIAM MURRAY MOORE, M.D., M.P.H., Member
THOMAS B. NEWMAN, M.D., M.P.H., Member
JUDITH R. O'FALLON, Ph.D., Member
VICTOR M. SANTANA, M.D., Member
ROBERT STERN, M.D., Voting Consultant
JAN N. JOHANNESSEN, Ph.D., Executive Secretary

PRESENT FROM FDA:

SUSAN K. CUMMINS, M.D., M.P.H.
TAPASH GHOSH, Ph.D.
BARBARA HILL, Ph.D.
LISA MATHIS, M.D.
MELISSA MONCAVAGE, M.P.H.
DIANNE MURPHY, M.D.
BINDI NIKHAR, M.D.
MARILYN R. PITTS, PharmD.
ANNE TRONTELL, M.D., M.P.H.
JONATHAN WILKIN, M.D

PRESENT FROM NIH:

JEFFREY I. COHEN, M.D.

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8:07 a.m.

CHAIRPERSON CHESNEY: Okay. I think we are ready to begin and I'd like to welcome everybody to today's program on "Potential Cancer Risk in Children from the Use of Topical Immunosuppressants" and I think we'll start with introductions. Why don't we start with Dr. Day and then go around counterclockwise.

DR. DAY: I'm Ruth Day from Duke University and I'm from the Drug Safety and Risk Management Advisory Committee.

DR. ANDREWS: I'm Elizabeth Andrews, a pharmacoepidemiologist from Research Triangle Institute.

DR. EPPS: Dr. Roselyn Epps, Chief of Dermatology, Children's National Medical Center in Washington, D.C. and I'm serving as a consultant today.

DR. MATTISON: Don Mattison from the National Institue of Child Health and Human Development.

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

DR. STERN: I'm Rob Stern. I'm a dermatologist in Boston.

DR. GAROFALO: Hi, I'm Betsy Garofalo. I'm a pediatric neurologist. I work for Pfizer and I'm the Industry Representative.

DR. GORMAN: My name is Rich Gorman. I am a pediatrician in a private practice in Ellicott City. I am the Pediatric Health Organization representative and the Chair of the American Academy of Pediatrics Committee on Drugs.

MS. KNUDSON: I'm Paul Knudson, Director of the IRB at the University of Texas Health Science Center in Houston and I'm the Consumer Representative to this panel.

DR. FANT: I'm Michael Fant and I'm on the facility of University of Texas Health Science Center. I'm a pediatrician and neonatologist.

DR. BIER: I'm Dennis Bier. I'm a Professor of Pediatrics at Baylor College of Medicine

in Houston.

DR. DIAZ: Angela Diaz, Professor of Pediatrics at Mount Sinai School of Medicine.

DR. MOORE: I'm John Moore. I'm a Professor of Pediatric Cardiology at UCLA.

DR. GLODE: I'm Mimi Glode. I'm Professor of Pediatrics and Pediatric Infectious Disease specialist at Children's Hospital, University of Colorado, Denver.

CHAIRPERSON CHESNEY: I'm Joan Chesney. I'm a Professor of Pediatric Infectious Diseases at the University of Tennessee in Memphis and Director of the Academic Programs Office at St. Jude Children's Research Hospital.

DR. JOHANNESSEN: My name is Jan Johannessen and I'm the Executive Secretary of the Pediatric Advisory Committee.

DR. SANTANA: Good morning. I'm Victor Santana. I'm a Pediatric Hematologist/Oncologist at at St. Jude Children's Research Hospital in Memphis, Tennessee.

DR. O'FALLON: I'm Judith O'Fallon. I'm a

statistician retired from the Mayo Clinic where I worked for 30 years in cancer clinical trials.

DR. NEWMAN: I'm Tom Newman. I'm a General Pediatrician and Professor of Epidemiology and Biostatistics and Pediatrics at the University of California, San Francisco.

MS. DOKKEN: I'm Deborah Dokken. I'm the Patient/Family Representative on the Committee.

DR. MURPHY: Dianne Murphy. I'm the Office Director for the Office of Pediatric Therapeutics in the Office of the Commissioner at FDA.

DR. WILKIN: Jonathan Wilkin. I'm Director of the Division of Dermatologic and Dental Drug Products in the Office of New Drugs, FDA.

DR. TRONTELL: Good morning. I'm Anne Trontell. I'm the Deputy Director of the Office of Drug Safety. Thank you.

DR. MATHIS: Good morning. I'm Lisa Mathis, Acting Director, Division of Pediatric Drug Development in the Office of Counter Terrorism and Pediatric Drug Development.

DR. CUMMINS: Good morning. I'm Susan

Cummins. I'm a Medical Team Leader with the Office of Pediatric Therapeutics in the Office of Counter Terrorism and Pediatrics.

CHAIRPERSON CHESNEY: Thank you. Dr. Jan Johannessen will read the Formal Meeting Statement.

DR. JOHANNESSEN: Good morning. The following announcement addresses the issue of conflict of interest with respect to this meeting and is made part of the public record to preclude even the appearance of such at the meeting. The topics of today's meeting are of broad applicability and 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 interest as they may apply to the general topics at hand.

The Food and Drug Administration has granted particular matters of general applicability waivers for Dr. Day which permits her to participate fully in today's discussion and votes. A copy of the waiver statement may be obtained by submitting a

written request to our Freedom of Information Office. Because general topics impact so many instituions, it is not prudent to recite all potential conflicts of interest as they apply to each participant. The 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.

We would like to note that Dr. Elizabeth Garofalo has been invited to participate as an industry representative acting on behalf of regulated industry. Dr. Garofalo is employed by Pfizer. We would also like to note that Dr. Richard Gorman is participating as a Pediatric Health Organization representative acting on behalf of the American Academy of Pediatrics.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment on. We have open public comments scheduled for 12:00 noon today. I would remind the open public hearing

speakers that they have been allotted five minutes each and we intend to stick to that limit. I would just remind everyone to turn their microphones on when you speak so that the transcriber can pick everything up. Thank you.

CHAIRPERSON CHESNEY: Thank you. Dr. Dianne Murphy who is Director of the Office of Pediatric Therapeutics is going to make some opening remarks and then my understanding is that each member of the FDA who is presenting to us today will introduce each subsequent member.

DR. MURPHY: Welcome to everybody who is here today to assist us in what we hope will be a very productive meeting. I also specifically would like to thank many of the members of the Committee who are here for their second day of government service. Yesterday you provided thoughtful recommendations on approaches to improving safety reporting for the Committee to assist you in your safety oversight activities for pediatric therapeutics. Yesterday the difficulties of discharging your responsibility with the limitations inherent with the tools present was

made clear, but we didn't think that was challenging enough.

So today, we have another difficult task for all of you. We want you to review data that reflects today's knowledge and then we're asking you to help us predict the future risk of cancer for the topical immunosuppressants and then help us how best to decide on how to communicate this level of risk.

What we are dealing with is an unknown degree of risk. Why waiting until the risk is more certain is not acceptable you will hear. It will take too many years before we will have a definitive answer if we are able to define and have a definitive answer. Many people, but particularly children, will have been exposed and we are concerned that it will be too little information too late.

Some will say and I think you will hear a fair argument that the concern is really low and some of the reasons we can feel somewhat reassured are that animal studies are only partially relevant to humans, that high doses have been used in these animal studies and that absorption levels in human are usually low.

Others would say that the concern is high that there are many species including non-human primates or monkeys that have developed cancers, there is a dose effective that's clearly seen in this monkey study, that biologic plausibility is very high, that there are documented high systemic levels in some cases after topical application and that children have larger surface areas and less evolved immune status. These cause us concern.

The use is high. There's been an increase of over fourfold in the last four years and actually it's really quite a bit more than that just trying to take a denominator of one million as the baseline, that almost two millions prescriptions for children were written between June of 2003 and May of 2004, that approximately one-half of million of these were for children under two which the labels presently says it's not recommended for use in that population.

There has been an increase in these products particularly an increase in Elidel more than Protopic. They're finding general use in the population and for Elidel the majority of the use is

currently as you saw in your package by pediatricians.

I think that this slide from Novartis website actually does provide proof that they had a very nice increase in their use of their product, speaking from a business point of view, while it hasn't been quite as marked with topic. That marketing clearly is having an impact when you see when they initiated DTC or direct-to-consumer advertising went up. They stopped it. It went down. It went up when it comes back. So clearly we are dealing with a product that's increasing in use.

The perception of safety. In general, topical products are not usually perceived as associated with the same level of risk as those that are taken orally or given intravenously. So we are dealing also with a general perception of safety. It's a difficult message. How do we provide a clear message when we do have a clearly defined risk?

Bad outcome. Bad outcome would be that applying these creams and ointments to skin turns out that it does contribute to an increase in cancer and people think they have not be provided adequate

information to assist them in the proper use of these products. How do we do that?

So the charge to the Committee today, we've asked you to advise FDA as to your assessment of the risk. We ask you to define the most important risk messages that we need to be able to deliver. We're asking you to identify approaches to maximize the successful communication of these messages and to identify how we measure success in doing that and lastly, what's the timeline? We look forward to your deliberations and again thank you all for your participation here today.

CHAIRPERSON CHESNEY: Dr. Murphy, would you mind introducing Dr. Cummins?

DR. MURPHY: Yes.

CHAIRPERSON CHESNEY: Thank you.

DR. MURPHY: My social skills are limited. I would like to introduce Dr. Susan Cummins. She is a pediatrician who is also a medical epidemiologist who has additional training in behavioral pediatrics. Susan will present a historical approach, try to bring you from where we have been to where we are

today. Thank you.

DR. CUMMINS: Good morning and welcome to all of you. It's a pleasure to have a chance to see you all finally here today. I've been the one who's contacted most of you and asked you to join us. I really appreciate all of you being here today especially the many people who were with us in October 2003 because having that continuity from that meeting to this meeting is extremely valuable to us. So thank you for taking the time from your schedules to join us today.

This morning I'm going to walk you through a brief history of the issues that we're going to be addressing today. I'm going to lay out the landscape for the presentations that follow. So I'm the historian. I'm giving you what happened before and what's happened up to now.

Now as I mentioned, many of you participated in a meeting that we held in October 2003 on many of the issues that will be discussed today. At that time, the primary focus of the meeting was not on how do we communicate risk but rather how do we

evaluate this biologically plausible and concerning potential cancer signal. Today we are going to focus on safety and as I mentioned earlier, those of you who were with us in October 2003 are really helpful especially because you provide continuity from that meeting to this meeting.

This slide lists the chronology of what I'm going to talk about. I'm going to talk about the context that led up to the October 2003 meeting. I'm going to summarize what occurred at that meeting, what was said about the epidemiologic design issues and the constraints in conducting registry studies about these questions. I'll also talk about several key points that were made from the Committee discussion at that time and then I'll talk about the current landscape from October 2003 to the present.

Let me just start with the before October 2003 and I actually want to take you back in time to April 1994 when Prograf was approved. Prograf is an oral and intravenous formulation of tacrolimus. It was approved for the prophylaxis of organ rejection in patients receiving allogenic liver or kidney

transplants, very different population than the one we'll talk about today, and Prograf has a boxed warning about the susceptibility to infection and the possible development of lymphoma and that the text of that boxed warning is shown to you here. Prograf also has labeling in the carcinogenicity/mutagenicity section of the label that people who are exposed to Prograf are at higher risk for the development of skin cancers as well as lymphoma.

Now the drugs that we'll talk about today are the topical immunosuppressant calcineurim inhibitors. There are two products, Protopic or tacrolimus ointment which comes in two strengths and was approved in December of 2000 and Elidel (pimecrolimus) cream comes in one strength and was approved in December 2001. Dr. Nikhar who is a Medical Officer with the Division of Derm and Dental Products will describe these products in more detail for you in a minute.

Both products are approved for the treatment of atopic dermatitis in children two years of age and older and they're approved as second line

agents for that indication. Tacrolimus is approved for moderate to severe atopic dermatitis. Pimecrolimus is approved for mild to moderate atopic dermatitis. Though the mechanism of action for this disease is unknown, both products are described as a classical immunosuppressant and Dr. Nikhar will elaborate on what I mean by that.

At the time of their approval and after, there were animal carcinogenicity studies that were positive and those were presented to you by Dr. Barbara Hill in October 2003. There were a number of positive signals from a number of different species exposed to a number of routes. I've just listed here for you some of those studies. Dr. Hill will review them for you again during her talk.

At the time both products were approved, there was a post marketing commitment made in their approval letters to establish registry studies to assess cancer risk in pediatric patients. I've listed the relevant language here and highlighted in dark blue the key language. For tacrolimus, a registry study of pediatric patients with atopic dermatitis to

evaluate the risk of developing cutaneous or systemic malignancies. For pimecrolimus, again a registry study of pediatric patients age two to 17 with an emphasis on the younger ages, those with atopic dermatitis to assess the risk of developing systemic malignancies.

We at the Agency recognized early on that establishing and conducting these registries was very complex. This was not a simple task. There were many pitfalls in the design and conduct of these studies. So we decided that as a solution to try and tackle those complexities, we would consult the Advisory Committee which we did. We had a meeting with the Pediatric Advisory Subcommittee to the Anti-Infective Diseases Drugs Advisory Committee in October of 2003.

So let me just now talk about what happened at the October 2003 meeting. At that time we had a product review by Dr. Nikhar. Dr. Hill reviewed the animal toxicity data. Dr. Pitts reviewed the post marketing adverse event reports. And we had two discussions on how we might address the registry design issues. There was a presentation from the

Office of Drug Safety, Dr. Lois Lagranade, on study designs, how you might approach this complex research question, "Should you use a case control study versus a cohort study?" Those were some of the issues she presented and the pros and cons of each approach.

Then Dr. Elizabeth Andrews, here with us today, reviewed some of the practical and methodologic issues in conducting these long term registry studies. We also had a presentation from CDC on the role of cancer registries addressing the questions that were before the Committee. Then the Committee discussed the questions that we asked of them.

This slide summarizes some of the complexities and uncertainties that were raised at that meeting about the research questions before it. I think going into the discussion, and I've read now the transcript a couple of times so I feel really embedded in that meeting and it was deja vu to go back and relive it again, it was clear to the Committee that these were really complex epidemiologic problems and despite our efforts to resolve many of these questions, some of these issues are so tough we may

never be able to fully resolve them.

I've listed just some of the key challenges. Everybody talked about the difficulty with measuring and quantifying in every part of this registry design, difficulty with measuring exposure to topical drug products. Dr. Stern, you actually gave a very impassioned speech about how hard this is to do and how you've been trying to really figure out the best way to do for your entire academic career. Measurement of confounders was recognized as difficult and ascertaining cancer outcomes is difficult particularly when skin cancers are not ascertained routinely in population-based cancer registries.

Everyone recognized and was concerned about the long latency period between the exposure that's commonly known that occurs between exposure to a carcinogen and the development of cancer. That would require registry studies of at least 10 to 15 years in duration and because these tumor signals and tumors are rare in children would require populations of a very large size. These studies would need to be conducted at substantial cost and that there would

need to be mechanisms in place to assure very high retention rates.

Also this need to maximize retention was essential. Maximized retention meaning retention at the 80 to 100 percent rate, not retention at 50 percent. Everyone talked about the need for very high retention for any results from these studies to be valid.

After that, the Committee shifted to a discussion of risk management and I've just listed some of the key themes that were brought up by you with a couple of quotes. Many of you mentioned concern that prescribers in public lacked awareness of this potential risk and advised us that we needed to better inform patients and physicians about all of these issues related to these drugs, that this information needs to be made more public than it has been.

There was also a concern that we needed to better assure that the product was used as labeled as a second line drug when really needed and it should be relied upon as a chronically administered agent. Then

there were discussions about strength and warnings including a discussion of a boxed warning and applying other risk communication tools. But at that time, the Committee did not take a formal vote on any of these issues.

So now I'd like to move from October 2003 and also just highlight a couple of proposals that are in the literature about possible uses proposed in the future for these products. Since October 2003, we have additional animal carcinogenicity data. There are additional human cancer cases that have been reported to the Agency and we know that there's been a substantial increase in the use of these products.

You'll hear today about an oral primate carcinogenicity study that was strongly positive for lymphoma and showed a dose response effect. You'll also hear about additional reports of cancer and other serious adverse events in children and adults reported to the Agency in an individuals who've used these products. You've also heard about increasing use of both products including substantial increase in use in children younger than two years, an age group for

which the product is not labeled and we've had limited progress in establishment of these registries.

In addition as part of the landscape, as part of this background, there's been a lot of literature about these products, academic literature in the dermatologic literature, in the pediatrics literature and in the allergy literature. Just doing a very quick search, I easily identified over 123 publications in the last five years and many of the themes focus on the use of tacrolimus and pimecrolimus topical products as first line therapy, the use of these products continuously to prevent flares in atopic dermatitis and that use in children younger than two years of age is safe.

Here are just three literature examples. This first publication in the *Archives of Dermatology* in 2003 is described as a safety and efficacy study of tacrolimus therapy in patients younger than two years of age with atopic dermatitis. This study was a review of records for 12 patients. The second paper is a safety and efficacy study of non-steroid pimecrolimus cream 1% in the treatment of atopic

dermatitis in infants. Again, this study proposes that use of these products is safe in this population currently and off-label indication. And the final publication, a review study in a supplement in the *Journal of Allergy and Clinical Immunology* published in 2003 that is entitled, "The Current Management of Atopic Dermatitis: An Interruption of the Atopic March" this was a supplement that was funded by Norvatis Pharmaceuticals and that suggests that pimecrolimus cream and tacrolimus be used as first line therapy for atopic dermatitis rather than topical corticosteroids which are currently the first line agents.

That's the current landscape. Here's where we are today. We have unknown certainty about a serious cancer risk that we may never be able to accurately quantify. We have additional animal carcinogenicity signals and additional human reports cancer in individuals who have used these products. We have medical literature that is focusing on expanded use and off-label indications for these products and supports the concept of safety for them

and we have increasing use.

That's the current landscape and I hope I set the stage for you and look forward to your feedback. I want to thank you again for being here. Also I want to just thank Jan Johannessen for all the great work he's done for us.

Our next speaker is Dr. Jeffrey Cohen. Dr. Cohen is with the National Institute of Allergy and Infectious Diseases at NIH. He's the head of the Medical Virology Section in the lab of Clinical Infectious Diseases and is an expert on Epstein-Barr virus (EBV). We're very grateful to have him come and give us an overview on Epstein-Barr virus and its relationship to cancer.

I just want to mention that Dr. Cohen has limited time to be with us today because he's on service. So after his presentation, there will be some time for questions and answers. So please be sure you ask him one when we have him here with us. Thank you.

DR. COHEN: Okay. Thank you. Just as a preface for my talk, patients who are receiving

immunosuppressive medication particularly transplant recipients can occasionally develop Epstein-Barr virus related lymphomas. So in this setting, I was charged to give a talk about the relationship of Epstein-Barr virus with cancer particularly lymphomas in immunosuppressed patients and its relationship with immunosuppressive agents.

Epstein-Barr virus is a ubiquitous pathogen. Approximately 90 percent of adults are infected with Epstein-Barr virus. Most individuals are infected actually during childhood. The virus when it infects people is transmitted through infected saliva. Individuals are infected usually through the oropharynx in either the epithelial cells or the B lymphocytes which are trafficking through the oropharynx and become infected. These B lymphocytes then move through the lymphoid tissues in the peripheral blood and when they're in the peripheral blood the cell can either be latently infected and express only latency associated viral proteins or they can undergo a lytic infection in which case all the different viral proteins are made and the cell dies

and viruses are produced.

Initially during infection, the virus infected cells are kept under control by either cytotoxic T cells (CTLs) or natural killer (NK) cells. And then later on when people are persistently infected which 90 percent of the people in the room here are persistently infected with Epstein-Barr virus, the virus again latently infects about one in one million B cells but some of these cells can reactivate the virus and these reactivated cells are controlled primarily by cytotoxic T cells that are either CD8 cells or CD4 cells.

Now some of these latently infected cells traffic back to the oropharynx where the virus reactivates inside the cells. The virus is produced and then can spread to other individuals. So the real point of this slide is that Epstein-Barr virus which is associated with lymphomas is really controlled by predominantly cytotoxic T cells be they CD4 or CD8 cells during the chronic phase of the infection or during the initial phase of the infection by NK cells. So it's these cells that are going to be important

for controlling EBV and for prevention of lymphomas.

Again early on in infection, it's the natural killer cells and non-HLA specific cytotoxic T cells and later during infectious mononucleosis, HLA restrictive cytotoxic T cells that can recognize viral lytic epitopes and viral latent epitopes and then in healthy seropositive persons, the CTLs recognize predominantly latent epitopes of the virus but also proteins that are made during the lytic infection.

Epstein-Barr virus, the reason we're particularly concerned about this virus, is that it can transform B lymphocytes in vitro and these transformed B lymphocytes in vitro proliferate in vitro and are immortalized and can grow perpetually in cell culture. These transformed B cells expressed a limited number of the latency proteins, the Epstein-Barr virus nuclear antigens and latent membrane proteins and they also express certain cellular proteins on the surface particularly adhesion molecules, LFA-1 and ICAM-1 as well as a number of cell activation markers, CD23, CD30, etc. shown here.

Now how does the virus maintain a latent

infection and what's important for transformation? The virus encodes have protein called Epstein-Barr virus nuclear antigen-1 which is important for the viral genome to be maintained in B cells. It also encodes a number of other proteins, latent membrane protein-1, EBNA-2, EBNA-3 which are transactivating proteins. They help regulate B cell proteins and cause proliferation of the cells. And then latent membrane protein-2 is important to keep the virus in its latent state and to prevent reactivation.

So latent membrane protein-1 is the protein that we are most concerned with in terms of lymphomas. It's clearly the Epstein-Barr virus oncogene and if one expresses the protein in transgenic mice, the animals develop typical B cell lymphomas that have latent membrane protein-1 in them. If one expresses LMP-1 in fibroblasts, the fibroblasts become oncogenic and the animals develop tumors. This protein is transactivated, up-regulates a number of proteins. It activates NF-kappaB and it inhibits programmed cell death or inhibits apoptosis by up-regulating a number of proteins which are

important for inhibiting apoptosis.

So this is really the last basic science slide. Latent membrane protein-1 has been shown to activate a number of signaling pathways in the cell and it interacts with the tumor necrosis-associated factors which then interact with a number of signaling molecules, the STATS, jun N-terminal kinase, AP-1 and the net result is that NF-kappaB is activated. The cells undergo proliferation and growth. This is important for allowing these B cells to proliferate in the body and also is important in terms of lymphomas.

So here's a slide from a patient who has an EBV lymphoma shown in panel four. These are the lymphoma cells as well as some B cells that have been infected with EBV in vitro that express Epstein-Barr virus. What you can see is that NF-kappaB is activated both in the B cells in vitro as well as actually in the tumor cells themselves. NF-kappaB is not activated in tumor cells that do not have Epstein-Barr virus in them or B cells that don't have Epstein-Barr virus in them. So LMP-1 and NF-kappaB is very important for activation and for lymphoma genesis by

the virus.

In terms of diseases associated with Epstein-Barr virus, it's the cause of infectious mononucleosis that has EBV in it. It's associated with a number of other rare disease shown here. As we'll see about anywhere from 30 to 60 percent of Hodgkin's Disease lymphomas will have Epstein-Barr virus DNA in them. Burkitt's lymphomas frequently have Epstein-Barr virus DNA in the tumors.

And the disease I'm going to focus particularly today is lymphoproliferative disease which is associated with immunosuppressive medication. EBV however is also associated with other cancers, nasopharyngeal carcinoma, gastric carcinoma, other rare lymphomas and in transplant patients who are on immunosuppression, Epstein-Barr virus is also associated with smooth muscle tumors which I'll talk about as well.

So as I mentioned, there are a number of different diseases associated with Epstein-Barr virus and the ones on the top here are the ones in which most or all of the latency associated proteins are

expressed. We say that these diseases are really driven by Epstein-Barr virus. In contrast, Hodgkin's Disease and other lymphomas have varying degrees of Epstein-Barr virus gene expression and they often have other chromosomal changes and other mutations. So we think of Epstein-Barr virus as one of the hits involved in developing these tumors but that there are other changes that are also probably necessary for developing these tumors. EBV is not the sole thing that drives these tumors.

Now if we look at viral gene expression, this reiterates what I showed on the last slide, the different genes expressed during latency, we can that with lymphoproliferative disease and with mononucleosis all the latency genes are expressed and again Epstein-Barr virus is very important for driving lymphoproliferative disease. But in other tumors, Burkitt lymphoma or nasopharyngeal carcinoma or Hodgkin's Disease, we see expression of some, but not all of these proteins. Therefore EBV has a role, but we don't think it's the true necessarily cause of these tumors.

Just to survey the landscape a little bit before I really focus on lymphproliferative disease, Burkitt lymphoma is associated with EBV. About 90 percent of cases in developing countries, have Epstein-Barr virus in the Burkitt's lymphomas and these are generally jaw tumors particularly in sub-Sahara, Africa. Twenty percent of cases in the United States will have Epstein-Barr virus in them. These present with abdominal tumors. And AIDS patients can also develop Burkitt lymphomas.

As mentioned EBV is one of the hits, but all of these tumors have c-myc translocations, have chromosomal translocations and these chromosomal translocations result in abnormal regulation of the c-myc protein and as a result of this translocation, a tumor is formed. These tumors require chemotherapy for treatment.

Hodgkin's Disease is also strongly associated with Epstein-Barr virus. In developing countries, South America and Africa particularly, 60 to 70 percent of cases of Hodgkin's lymphoma will have Epstein-Barr virus in them. This just shows the

latent membrane protein shown in brown here in a Hodgkin's lymphoma tissue biopsy.

In the United States, 35 to 50 percent of cases of Hodgkin's lymphomas have EBV in them. The virus is present in the Reed-Sternberg B cells and again chemotherapy is usually used for therapy. There is some very recent preliminary reports that anti-Epstein-Barr virus specific cytotoxic T cells may have some role in therapy, but this is really a handful of patients at this point.

Then in terms of transplant patients who are getting immunosuppression, EBV has been relatively recently associated with smooth muscle tumors. These occur both in transplant patients who are on immunosuppressive agents, in AIDS patients and in patients with congenital immunodeficiencies. The pathology shows a leiomyosarcoma or leiomyomas that are in various organs as well as can be in the lymph nodes. Some of these tumors actually regress with reduced immunosuppression indicating that the immunosuppression is very important in terms of driving the tumors.

The real disease I want to talk about today is EVV lymphoproliferative disease which occurs with immunodeficiency, in patients with AIDS, in patients with congenital immunodeficiencies such as severe combined immunodeficiency, Wiscott-Aldrich disease, other immunodeficiencies or after transplantation in patients that are getting immunosuppressants like cyclosporine, tacrolimus, etc. at a systemic level and also has occurred in patients with rheumatoid arthritis on methotrexate therapy. These patients can present with symptoms of infectious mononucleosis or with mass lesions in organs and this is an unfortunate woman we saw at the NIH who had a congenital immunodeficiency and these are nodules in the brain which are tumor nodules and one sees an immunoblastic lymphoma that expresses EBV RNA, these dark blue areas, and contains EBV proteins.

Now the risk factors for lymphoproliferative disease as we'll talk about more are primary infection. So if one is a transplant recipient and develops an EBV infection after transplant that is a primary infection and you compare

those individuals who are already EBV seropositive and get transplant, there's a thirtyfold increase in lymphoproliferative disease if you're developing an EBV infection for the first time. Presumably this is due to the fact that particularly children don't have any memory cells or memory CTLs that already recognize EBV and they get very high replication of EBV initially and they don't have any prior memory to EBV in terms of their immune response.

In addition, patients with graft-versus-host disease who have increased immunosuppression are more likely to develop lymphoproliferative disease and individuals that receive a T cell-depleted bone marrow as opposed to just bone marrow that's not T cell-depleted. So the risk factors really are T cell immunodeficiencies that is immunosuppression that reduces T cells or primary infection with Epstein-Barr virus. Also individuals that are infected with cytomegalovirus (CMV) also are at higher risk for lymphoproliferative disease.

Again the risk factors are primary infection. These individuals get higher levels of

Epstein-Barr virus in their blood. They don't have any memory T cells to EBV at the time of infection. CMV. And there are some very recent small studies really at the abstract level showing that some individuals that have polymorphisms that is difference in the sequences of interferon-alpha (slide shows gamma), TNF-alpha or IL-10 are more likely to develop lymphoproliferative disease. This actually should be low level polymorphisms corresponding to low levels of gamma, TNF-alpha or low levels of IL-10.

These studies, I should just mention, are in studies of about 30 patients total. So these are very preliminary. As mentioned, the level of T cell immunosuppression correlates with the risk of lymphoproliferative disease.

This was a study done in the 1990s looking at transplant patients and if you look at the number of copies of Epstein-Barr virus per hundred thousand peripheral blood lymphocytes, you can see individuals that were seronegative at the time of transplant that became infected with Epstein-Barr virus. When you compare those that were seropositive and reactivated,

these seronegative individuals had higher EBV viral loads compared to individuals who are seropositive with reactivation.

In addition, individuals with post transplant lymphoproliferative disease tended to have higher viral loads than those without lymphoproliferative disease shown here. There is some overlap however and just measuring the serum viral load has been used in some cases to predict the onset of lymphoproliferative disease but this is not an absolute thing. So that if you just measure EBV loads in individuals who are immunosuppressed after transplant, although it's somewhat predictive, it's not absolute and we often see patients at the clinical center with very high EBV viral loads that never develop lymphoproliferative disease. So one can't simply measure the viral load and decide who's going to develop the disease and who is not.

There are studies done in Europe which suggest that in some centers when people have very high viral loads they'll give actually preemptive therapy with a monoclonal antibody to B cells,

something called rituximab which is an anti-CD20 antibody. So some individuals they get very high viral loads in Europe and some individuals in the United States are treated just with anti-CD20 antibody in an effort to reduce the number of infected B cells and possibly to reduce the risk of lymphoproliferative disease. Again these are still relatively small studies.

So how do we treat lymphomas in patients who are getting immunosuppressants? Well, we first reduce the immunosuppression and in individuals who develop lymphoproliferative disease early after transplant, these lesions are often polymorphic. They're more heterogenous when one looks under the microscope at the pathology and these lesions often respond solely to reducing immunosuppression. So you reduce the immunosuppression. The EBV specific cytotoxic T cells increase in number and they are able actually to kill the tumor cells and the tumor cells can go away in many cases.

Later lesions that occur, let's say, a year or more after transplantation are often more

homogenous under the microscope and they are so-called monomorphic lesions. These lesions can often have other chromosomal changes, will have mutations in c-myc, mutations in the P53 gene or in the Bcl6 gene and these lesions are much less responsive to immunosuppression. So you stop the immunosuppression and the tumors continue on and one has to be more aggressive in terms of the therapy.

Some individuals, some case reports describe removing localized lesions and reducing immunosuppression which is sometimes effective. Patients with central nervous system lesions require radiation therapy often or chemotherapy. I briefly mentioned anti-CD20 antibody which is a B cell antibody which the Epstein-Barr virus tumor cells are in B cells and this has some role in terms of treating lymphoproliferative disease. Interferon-alpha has been used and then donor lymphocyte infusions or autologous infusions of EBV specific cytotoxic T cells have been used. Again these T cells will kill the virus infected proliferating cells. So this is what the state-of-the-art is for treatment of

lymphoproliferative disease.

Now for today's session, one of the concerns we have about is cutaneous lymphomas in patients that might be getting topical immunosuppression. In terms of Epstein-Barr virus, there are two types of lymphomas that can occur, the lymphomas that can occur in non-immunosuppressed patients and in the Orient, particularly in Asia, there is a disease called hydroa vacciniforme which presents with vesiculopapular lesions on the face and hands and often can have fever. When one biopsies these lesions, they contain lots of Epstein-Barr virus. These can progress to T cell lymphomas.

We also occasionally see patients with NK/T cell lymphomas. Again these are pretty uncommon, that present with ulcers or nodules particularly on the face, the nose, the cheeks, the lips, extremities and these are often relatively difficult to treat. And then finally we sometimes see EBV subcutaneous T cell lymphomas which can present with plaques and fever and large spleen and lymph nodes, pancytopenia and hemophagocytosis.

Now perhaps more germane to today's talk is the types of lymphomas we see in patients that are immunosuppressed that are getting immunosuppressive agents. These include cutaneous ulcerated nodules which are B cell lymphomas that can occur after transplant or in patients with AIDS or cutaneous B cell lymphomas in patients with rheumatoid arthritis or polymyositis receiving methotrexate. Again these lymphomas have been reported to resolve in some, but not all cases after the methotrexate has been stopped.

Now who might get lymphoproliferative disease and one of the other risk factors for lymphoproliferative disease is that it sometimes occurs at sites of chronic inflammation. So the idea is that it's important that in terms of the lymphoproliferative disease or lymphomas both the immunosuppression reducing the T cell response to EBV but also there's a component of chronic inflammation that may be also be important for development of lymphomas.

If you look at transplant recipients who are immunosuppressed, the disease is much more

frequent or often occurs in the transplanted organ. These transplanted organs may have a higher frequency of EBV positive B cells, but also there's antigenic stimulation that occurs with B cell proliferation and cytokine activation in the organ. So it's thought that there is a stimulation of B cells in the organ. This can feed the process of EBV infected B cell proliferation and then in combination with reduced immunosuppression, there's more likelihood to develop a lymphoma or a lymphoproliferative lesion.

There are also reports of EBV positive pyothorax that is tumor cells in the pleural space around the lung, at sites of pleura inflammation after tuberculosis. So again you have a chronic inflammatory process due to tuberculosis resulting in B cell proliferation. This has been associated with some EBV lymphomas.

Then there are three reports of EBV lymphomas in patients with sites of chronic inflammation, two of them at sites of chronic osteomyelitis of the bone and one in a patient with chronic venous ulcers where the tumor occurred at the

site of the ulcer. Now the latency period for these tumors was in the range of about 20 years of chronic osteomyelitis before the tumor developed or about 10 years after the tumor developed at the site of the skin ulcer. So there's really a prolonged latency period.

In terms of immunosuppressive agents which we're talking about today that have been associated with EBV lymphomas, early on transplant recipients were often treated with steroids, azathioprine and some of them developed lymphomas. As I mentioned methothexate in patients who have rheumatoid arthritis and polymyositis has been associated with lymphomas. Antibodies to T cells, anti thymocyte globulin, anti-lymphocyte globulin, anti-CD3 monoclonal antibody has been associated with lymphomas and then the calcineurin inhibitors, cyclosporine and tacrolimus, as well as sirolimus have been associated with lymphomas.

So we did a small study in collaboration with a group at the University of North Carolina to look at what types of immunosuppressive medication

might be associated with increased viral replication and proliferation of EBV. We looked at azathioprine, cyclosporin, cyclophosphamide, mycophenolate mofetil, prednisone and methotrexate and found that of these agents only methotrexate resulted in lytic replication of Epstein-Barr virus. Here these B cells are treated for 72 hours with these agents and one can see that in Epstein-Barr virus, early protein BMRF 1 is made especially in the cells that are treated with methotrexate and these cells actually make infectious virus which can infect other cells. So in this regard, methotrexate might, in addition to causing immunosuppression, also reactivate EBV. Unfortunately in this study, we did not look at tacrolimus or sirolimus.

Calcineurin inhibitors, cyclosporin and tacrolimus, have been shown to inhibit generation of cytotoxic T cell activity. They induce expression of IL-6 and TGF-beta and IL-6 is a B cell growth factor supporting B cell activation of proliferation again which could potentially increase the risk of EBV lymphomas. Calcineurin inhibitors increase survival

of EBV transformed cells in vitro by protecting them from programmed cell death by Fas-mediated apoptosis.

These effects are clearly dose related. So lower doses of cyclosporin have been shown to allow more T cell immunity to EBV in vitro and have been associated with lower rates of lymphoma than higher doses. So in children in some studies, tacrolimus has been associated with higher levels or higher risks of lymphoproliferative disease than cyclosporin. But in more recent studies where tacrolimus was used as monotherapy which is shown on this slide, the risk of lymphoproliferative disease with tacrolimus was similar to cyclosporin.

This is a study from the University of Pittsburgh with about 130 patients who received liver transplants and of these 130 patients, about 13 developed an EBV lymphoma and their primary immunosuppressive therapy was tacrolimus. You can see that there's a increased risk for increased time after immunosuppressive therapy and after about two years, the risk levels off. But again the important factor is the duration of therapy here.

What about topical tacrolimus? The only study that I found in the literature where topical tacrolimus was associated with a viral related tumor was a 28 year old patient with AIDS who was on highly active antiretroviral therapy (HAART), had a low CD4 count under 500, who had psoriasis and seborrheic dermatitis. He was treated with topical tacrolimus ointment to the axilla (under the arm), the groin and the head for one month and came in the hospital about one week later with Kaposi's sarcoma lesions at the sites where the tacrolimus had been applied.

You can see here in the groin this purplish lesion and on the face a purplish lesion. So this patient certainly was infected with a virus that causes Kaposi's sarcoma which is human herpes virus A or Kaposi's sarcoma associated herpes virus but then developed lesions at the site where tacrolimus had been used and subsequently also had lesions actually in the lung as well. This is a single case report but suggested that perhaps tacrolimus might have possibly accelerated development of Kaposi's sarcoma or at least that the lesion occurred at the site where the

treatment occurred.

If you look at the literature for other evidence of lymphomas occurring at the site of topical immunosuppression, the only other cases that I found or that I'm aware of are lymphomas occurring at the sites where anti-thymocyte globulin or anti-lymphocyte globulin is injected. So there are four case reports in the literature which you have in your handout there of individuals who received kidney or heart transplants, received anti-thymocyte or anti-lymphocyte globulin and that developed lymphomas in the buttock at the site of injection or at the thigh in the site of injection and these are actually relatively rare sites for lymphomas to develop. It's strongly suggested that these lymphomas were related directly to the local high concentration of anti-thymocyte globulin (ATG) or anti-lymphocyte globulin (ALG).

If you look at these cases in a little but more detail, one was a 47 year old renal transplant patient who underwent thoracic duct cannulation to drain T cells to reduce the risk of rejection, also

received prednisone and azathioprine, got ALG for a year and then six months after the last injection which is now a year and a half after starting ALG developed a reticulum cell sarcoma.

No EBV studies were done back in the `70s. One year later developed, this is actually the same histology, it was just a different name back in the '80s, the same histology in draining lymph nodes and two years later died of bacteremia and was found to have more lymphoma in the liver. So again there was a long latency period here unlike the topical tacrolimus and the patient with Kaposi's sarcoma.

Another patient was a 32 year old renal transplant patient on azathioprine and prednisone, developed rejection, was treated with actinomycin and graft irradiation, got horse ALG in the buttock and then six weeks later which is a very short period of time developed a nodule at the site which enlarged over ten months and was found to be a lymphoma as well.

The two heart transplant patients were reported among seven patients who developed non-

Hodgkins lymphoma out of 182 heart transplant recipients. So it's really two out of 182 patients here who developed lymphoma at the site of ATG injections and there really wasn't much data in this report, but these individuals developed immunoblastic lymphomas or noncleaved cell lymphomas which are the typical lymphomas that one sees that are EBV associated with immunosuppression. This one went on to develop lymphoma in the brain and the lung. This one went on to develop lymphoma in the chest wall and the abdomen.

On the last slide here, the summary of lymphoproliferative disease and lymphomas that can occur in people who are receiving immunosuppression, the early lesions that individuals develop early on with immunosuppression are often heterogeneous polymorphic lesions that are clearly EBV driven. They generally don't have chromosomal changes and they may respond simply to reduction in immunosuppression.

The later lesions which are much more heterogenous often occurring let's say a year after immunosuppression may have chromosomal changes. They

usually require chemotherapy in addition to reducing immunosuppression. Lymphoproliferative disease is much more common in primary EBV infections. So children who may often be EBV seronegative who develop Epstein-Barr virus are much more likely to have higher viral loads, not have prior memory to EBV and are more likely to develop lymphoproliferative disease when they're receiving immunosuppression.

There may be a genetic component. This is very early data with a relatively small number of individuals who have differences in their cytokines that might be at a higher risk for developing lymphoproliferative disease. Disease is more common at the site of chronic inflammation. So if one has chronic inflammation at a site and has inflammation it's more likely to develop lymphoproliferative disease at the site.

Then there are some reports of lymphoproliferative disease developing at sites of local immunosuppression, again that one patient who developed Karosi's sarcoma after getting topical tacrolimus or patients getting ATG or anti-lymphocyte

globulin injections. Now these patients that I'm mentioning here all had other immunosuppression. So either they had HIV or they were getting systemic immunosuppression in addition to ATG or ALG.

To summarize, the people that I think would be at highest risk if they were getting a topical immunosuppressive agent would be individuals who have an acute EBV infection, that is, would have a higher EBV viral load, would not have a prior T lymphocyte response to EBV and also people that would be immunosuppressed for other reason. Let's say a child had HIV and it was not known that they had HIV or some congenital immunodeficiency. It was not known they had an congenital immunodeficiency and if they developed an acute EBV infection on top of that, they would have much more difficulty in regulating and controlling that EBV infection and then if one combines an immunosuppressive agent on top of that as well, it might also increase the risk.

But these are all theoretical and I'm just taking different risks things and combining them together. But those are the individuals I'd be most

concerned about. I think I'll stop there and take any questions.

CHAIRPERSON CHESNEY: Thank you very much, Dr. Cohen, for a superb and focused overview for exactly what we were looking for today. Are there questions for Dr. Cohen? Dr. Gorman and then Dr. Glode and Dr. Santana.

DR. GORMAN: Are there any models? You talk about when you reduce immunosuppression that these lesions in the early stages can remit. Are there models in animals that show the time course of this remission? And the drive for this question as these drugs are recommended to be used in intermittent therapy, is there a time between therapeutic regimes that we could feel, confident is the wrong word, but somewhat reassured that "-

DR. COHEN: Less worried.

DR. GORMAN: Less worried. Thank you. That the previous down regulation of immunosuppression could be reversed.

DR. COHEN: So in terms of the first question, animal models for Epstein-Barr virus, there

certainly are animal models where animals develop tumors associated with EBV. One can take an immunosuppressed mouse, inject it with EBV transformed B cells. The animals will develop lymphoma. One can treat the animals with different drugs. The lymphoma will resolve, but I'm not aware of animal models where one has an immunosuppressed animal and then one reverses the immunosuppression. There is that model with EBV.

There is a primate homologue of Epstein-Barr virus which is called the simian lymphocryptovirus which can infect rhesus monkeys. There have been some recent studies that those animals can develop EBV lymphomas if they are immunosuppressed. Again I'm not aware of reversing immunosuppression. And there are also some other primates that if one inoculates with very large amounts of EBV transformed B cells into them, they will develop lymphomas as well. Again, I'm not aware of reducing immunosuppression and reversing that.

Now your second question was about intermittent immunosuppression and unfortunately again

I'm not aware of any studies in terms of turning off and turning back on the immunosuppression in terms of this. Again, it's really the prolonged immunosuppression and also the level of immunosuppression. So potentially individuals that would have higher serum levels of immunosuppressive would be at higher risk for the disease.

DR. GORMAN: Thank you.

CHAIRPERSON CHESNEY: Dr. Glode.

DR. GLODE: I was just wondering if you could comment on what you believe to be the most sensitive measure of subtle systemic immunosuppression? So if you're receiving topical agents and you have very low or almost undetectable levels in the serum, is there a way beyond, perhaps even beyond numbers, to assess function of NK cytotoxic T cells? Is there a simple test you would do?

DR. COHEN: The short answer of that is no.

DR. GLODE: I was afraid of that.

DR. COHEN: The studies really currently

are ongoing are to look at EBV-specific immune responses because that's what's most important. One can look at the number of cytotoxic T cells as a surrogate, but what's most important are the EBV-specific T cells. So for transplant patients for instance currently people are looking at EBV-specific T cells by Elispot, by tetramer staining, etc.

These are actually fairly complicated ways of looking the things. There are not really simple tests to do and it's not clear how well that correlates at the present time with who develops lymphoproliferative disease. In the clinic what we generally do is look at EBV viral loads, again the level of EBV in peripheral blood in individuals who are getting immunosuppression and in some individuals, that level starts to rise and that rise is associated with a higher risk of developing lymphoproliferative disease, but not in all patients. So unfortunately there's no simple test to predict who would develop lymphoproliferative disease. Again, I would be worried if a patient had an underlying immunodeficiency of some sort, had HIV and again had a

primary infection because those are all the things that really are most important for increasing the risk of developing EBV lymphomas but there is no simple test unfortunately.

CHAIRPERSON CHESNEY: Dr. Santana.

DR. SANTANA: So, Jeff, when I think of lymphoproliferative disease, I usually think of it as severely immunosuppressed patients that tend to get B cell disorders, lymphomas. But we have a very limited dataset of what's been reported with these two topical agents and at least when I look at the pediatric cases, and granted it's very limited data, two of these cases are associated with T cell type lymphomas. If I remember correctly, I went in back and looked it up. One was a lymphoblastic lymphoma and one was a 16 year old that had something like a Sezary type syndrome which is a T cell kind of associative malignancy. So if the pattern is very different at least in a very limited dataset versus what you're presenting and talking about which is a very completely different animal if you want to use that word, can you try to reconcile the differences maybe

between what we're seeing versus what we should be seeing?

DR. COHEN: So the Epstein-Barr virus driven lymphoproliferative disease is nearly always B cell. There are rare cases of EBV associated T cell lymphomas, but these are in the vast, vast minority. From the cases that have been reported, most of the tumors as you mention are not tumors that would be particularly associated with EBV. Again, individuals that are immunosuppressed can develop other types of tumors and certainly skin cancers, they are at much higher risk for developing skin cancers than people who are not immunosuppressed.

But in terms of the EBV, many of the tumors that you're referring to are not the ones that are strongly associated with Epstein-Barr virus. So again, my expertise is really Epstein-Barr virus and infectious disease not really oncology.

CHAIRPERSON CHESNEY: Dr. Newman.

DR. NEWMAN: Could you comment on the potential for systemic, inhaled and topical steroids that cause the kind of immunosuppression that might to

lead to lymphoproliferative disease? This is important not only because there are alternatives to the drugs we're talking about today for treating eczema, but you mentioned that you would be most worried about children who are getting some other immunosuppression and many of these kids with eczema also have asthma and are getting a lot of inhaled steroids and even frequent courses of oral steroids. And is the immunosuppression that steroids cause less likely to cause this or just different or that is not known?

DR. COHEN: I think the cases of lymphoproliferative disease early on before the cyclosporine/tacrolimus era were more associated with a combination of steroids and azathioprine as opposed to steroid therapy alone. It's less likely for us to see lymphoproliferative disease in individuals getting high dose steroids really alone than in individuals getting the systemic cyclosporin/tacrolimus/sirolimus type of thing.

That being said, I think when one adds immunosuppressants on top of each other particularly

with different mechanisms of action that affect the T cell arm of the immune response, the additive effect or possibly even synergistic effect can increase the risk of lymphoproliferative disease. But I suspect that steroids have a lower risk than would things like tacrolimus would. Again the combination is a potential there.

CHAIRPERSON CHESNEY: If I could ask a question. Then Dr. Mattison. What is the mechanism of steroid-induced immunosuppression that's different than these agents and why don't we see more lymphoproliferative disease with patients on high dose steroids, EBV driven lymphoproliferative disease?

DR. COHEN: I'm not exactly certain a simple answer to your question. We generally don't see as severe T cell, reduction in T cell function in terms of patients on steroids that we do with these other drugs. But I want to be cautious about that statement and I'm not really certain as to why.

CHAIRPERSON CHESNEY: Thank you. Mr. Mattison.

DR. MATTISON: Two questions. The first

relates to a series that was asked earlier. Am I to understand that there isn't an easy biomarker that you could monitor in children treated with these drugs that would give some sense of either a local or systemic immune impact? Then the second question is related to systemic immunomodulation. Is it a result of systemic exposure to the drug or trafficking of cells through the treated areas?

DR. COHEN: So again, there's really no good biomarker that I can think of. If one had to pick a biomarker, one might look at viral load, EBV viral load, but you'd being doing an awful large number of viral loads on individuals that were, for instance, seronegative that hadn't been infected and you would start to see viral loads going up that might not be that predictive. So there really is no good biomarker. In terms of the immunosuppression, again I think it's a combination of both the systemic level of immunosuppression as well as what's going on locally and that's why I mention those cases of ATG injection where locally there is a higher immunodeficiency, let's say, and maybe there's also more proliferation

of cells going on at that local site.

But again my own opinion and again this is an opinion is that if you need both you would need a systemic immunosuppressant, systemic loss of T cell immunity like with a patient with HIV or a patient on systemic immunosuppression as well as something going on at the local site that's going to be stimulating these B cells to proliferate and it's probably a combination of both. The reason I say that is we see a lot of patients, transplant recipients, who don't develop lymphoproliferative disease that are on immunosuppression. So I think that there are other factors solely in addition to just the reduction in the immunity. There are clearly other facts that are involved there.

CHAIRPERSON CHESNEY: Dr. Gorman.

DR. GORMAN: Can you quantify in any way the relative risk of being EBV virus naive versus being exposed prior to the onset of immunosuppression?

DR. COHEN: So the studies that have been done looking at lymphoproliferative disease in individuals who are EBV-naive and then develop a

primary EBV infection versus people who have been infected with EBV and then reactivate the virus show approximately a thirtyfold greater risk of lymphoproliferative disease in the EBV-naive individuals compared to the people who had a prior infection with EBV. So about thirtyfold is what's in the literature.

CHAIRPERSON CHESNEY: Dr. Stern.

DR. STERN: You've mentioned that eventually about 90 percent of us are EBV infected. Could you tell us what are the peak years for acquiring the infection in the general population, particularly what proportion develop it in the first couple three years and then the first ten years of life?

DR. COHEN: I don't have those figures off the top of my head. I can tell you that in developing countries most individuals are infected with EBV by the age of ten. In the United States where there's "better hygiene," there's a much higher frequency of individuals who are unlucky enough not to get EBV infection until adolescence and young adulthood when

they can often develop mononucleosis. I know where to look and I could get back to easily and tell you what the curve looks like, but I don't have that in my head right now.

DR. STERN: But is primary EBV infection in the first couple three years of life quite frequent?

DR. COHEN: So it's going to be frequent in kids for instance who are going to be in day care settings where there's going to be lots of exposure to other children, to infected saliva, etc. I think most of the cases in the United States do occur prior to adolescence.

CHAIRPERSON CHESNEY: Other questions for Dr. Cohen who does have to leave? Dr. Wilkin.

DR. WILKIN: On your slide, I think it's 24, you're talking about calcineurin inhibitors and you mention enhanced survival of EBV transformed cells in vitro by protecting from Fas mediated apoptosis and then you go on and you give the Kaposi's sarcoma, the ATG story and if you go back to your original cartoon drawing, the one right after your title slide, if we

could just look at that.

DR. COHEN: Oh, yes. Next slide. That's it.

DR. WILKIN: Right. Down in the southeast quadrant if I look over at the left side, it's lymphoid tissue and peripheral blood. So you pointed out the importance of the cytotoxic T cell and this can occur in the lymph node. What my question is is it possible for these events to occur in the primary lymph node with the calcineurin inhibitors literally draining through the lymph vessels, coming from the skin, going to the regional lymph nodes in the setting where there really wouldn't be enough calcineurin inhibitors systemically for systemic immune suppression. Could these events lead to the lymphoproliferative disease in regional lymph nodes? And occasionally, there's lymph adenopathy and it's maybe from the inflammatory mediators that are coming from the skin as well.

DR. COHEN: I think that's possible. Certainly many of the cases of lymphoproliferative disease that we see are in lymph nodes and I can

mention that in children who are having primary EBV infections, often times the lymphoproliferative disease will present actually in the oropharnyx at the site actually up here where there's a lot of lymphoid tissue at the site of primary EBV infection.

Again, we sometimes will see children with very enlarged lymph nodes that can actually have tumors in the oropharnyx at the initial site of the infection and I guess it's also possible that one could also have tumors in the lymph nodes early on here as well. It's difficult to do studies in humans and it's really hard to be certain, but I suspect that that's a possibility.

CHAIRPERSON CHESNEY: I think we may have exhausted the questions for you.

DR. COHEN: Worn everyone down. Okay. Thank you.

CHAIRPERSON CHESNEY: Thank you very much for taking time to be with us today.

DR. MATHIS: It's my great pleasure to introduce Bindi Nikhar who is a Medical Officer in the Division of Dermatologic and Dental Drug Products.

She's a Board certified Pediatrician and is the primary reviewer for these products.

DR. NIKHAR: Thank you, Dr. Mathis. As Dr. Mathis mentioned, I'm Bindi Nikhar, the Division of Derm and Dental Products. My talk covers topical immunosuppressants from the FDA perspective.

Starting with an introduction, topical immunosuppressants are the newest class of drugs to be approved for atopic dermatitis. They belong to a class of drugs known as macrolactam immunosuppressants which were introduced in 1980s for prevention of graft rejection in transplant therapy. There are two currently FDA-approved products: tacrolimus (FK506), the trade name being Protopic and pimecrolimus (SDZ ASM 981) the trade name being Elidel.

The other group of drugs indicated for atopic dermatitis are topical corticosteroids. Currently, these are indicated for first-line therapy and have been around for more than 50 years. The mechanisms of action of topical corticosteroids include anti-inflammatory, anti-proliferative and atrophogenic effects.

The anti-inflammatory effects exerted by inhibiting nuclear factor kappa B which up regulates cytokines. This inhibition is done by increasing the production of NFkB inhibitor and also by directly binding and inactivating an NFkB. Topical corticosteroids also effect all cells involved with inflammation and in addition, they inhibit prostraglandins and leukotrienes and have vasoconstrictive and antipruritic properties.

Now going to tacrolimus, an Advisory Committee was held in November of 2000 prior to approve of tacrolimus. The salient features discussed at this meeting included that this drug be approved as second-line therapy in the treatment of the atopic dermatitis, that it not be approved in children less than two years of age and that only the low concentration be approved for children two to 15 years of age. This was because a 12-week study in pediatric patients showed equivalent efficacy for both strengths, i.e. 0.03 and the 0.1 percent strength and it was felt that a larger body surface area would lead to more absorption and that in view of the longer

exposure and the long-term safety being unknown, there was no justification for the higher strength.

Therefore, when the Protopic was approved in December of 2000, the 0.03 percent ointment was approved for children two to 15 years of age and the 0.1 percent ointment was approved adults. Prograf which is systemic tacrolimus was approved in April of 1994 and was first introduced for allograft rejection and is currently used mainly in kidney and liver transplants.

Now going on to pimecrolimus, Elidel which is pimecrolimus cream was approved in December of 2001 for patients two years of age and older. This was because clinical studies showed a higher incidence of adverse effects in the Elidel arm compared to the vehicle arm and these included respiratory, gastrointestinal infections and viral rashes. So it is currently available only for topical use although a literature report mentions that in oral formulation is under development for psoriasis and atopic dermatitis. This report is from the *Expert Opinion on Pharmacotherapy*.

So as mentioned, clinical studies of pimecrolimus showed a higher incidence of infections compared to the vehicular across all pediatric age groups. This information is in the label. In the two to 17 years age group, these adverse effects included pharyngitis, nasopharyngitis, influenza, cough, etc. while in the three to 23 months age groups both the short term, six week study as well as a long term one year study showed similar adverse effects and these included pyrexia, respiratory and gastro-intestinal infections and viral rashes.

Not going on to indications for use, tacrolimus is indicated for moderate to severe atopic dermatitis and pimecrolimus for mild to moderate atopic dermatitis and both are indicated for patients as indicated on the label 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." So neither drug is approved for children less than two years of age.

This brings us to recent concerns that we have with these drugs. The risk for cancer associated with these drugs is uncertain. However, we know that there is a biological plausibility between the use of topical immunosuppressants and the development of cancers. This is based on non-clinical data that will be covered by Dr. Hill next and clinical data that will be explored in this talk and that there's an emerging signal in the types of tumors being reported in the adverse event reporting system. The risk as such is difficult to study and the answers for example from a long term cancer registry would be late. In fact, even a negative study may not be exculpatory.

The information landscape suggests that these drugs are often being used as first-line although the label implies second-line. They are being promoted as steroid-free and therefore devoid of a lot of harmful side effects. Direct-to-consumer advertising often portrays an overall visual picture of safety.

Other indications are being sought for both drugs and peer and non-peer reviewed literature

portrays safety that is not entirely substantiated. For example, there is a report that was mentioned where there were only 12 patients involved. So overall the number of patients and the length of follow-up is not optimal in most of these studies and still an inference of long term safety is drawn and propagated.

Now the precise mechanisms of action of both drugs in atopic dermatitis are not known. These are the proposed mechanisms of action and as such, the clinical significance of these observations in atopic dermatitis are unknown. But both drugs are thought to bind to the same cellular receptor, the FK-binding protein. The drug, FK-binding protein complex, goes on to inhibit calcineurin and hence the name calcineurin inhibitors and this in turn inhibits T cell activation. Both drugs are also thought to inhibit the production of proinflammatory cytokines from mast cells and down regulate the production of Th1 and Th2 types cytokines.

Now going on to pharmacokinetics. Dr. Ghosh will explore this in detail but we know that

systemic absorption can take place in both adult and pediatric age groups from the topical application of both drugs. Some of the factors that lead to increased absorption include larger body surface areas, younger age groups especially the three to 23 month age groups due to the larger body surface area-to-mass ratio and reduced skin barrier function, for example Netherton's syndrome which is autosomal recessive condition characterized by generalized erythroderma, hair shaft abnormalities and atopic diathesis and other generalized erthrodermic skins conditions, an example of which is graft-versus-host disease (GVHD).

To illustrate the point, acute renal failure has been reported in a patient with Netherton's syndrome, secondary to topical absorption of tacrolimus. In this patient, the 0.1 percent ointment was used for one year. On admission, the tacrolimus level was 34.4 nanogram per ml and the BUN and creatinine were 54 and 3.4 respectively. On discharge, the tacrolimus had fallen to 2.3 nanogram per ml after discontinuation of treatment and the

creatinine was down to 1.9.

Recently, there was a report where tacrolimus 0.1 percent ointment was used in an 11 month old patient to treat graft-versus-host disease secondary to bone marrow transplant. This patient died. This patient's background probably contributed to the cause of death. However, the tacrolimus levels were 75 nanogram per ml at the time of death. To give you an idea, transplant patients generally maintain levels between five to 29 nanogram per ml.

Now here are a few other cases. The first one is from the *Journal of Pediatrics*. This was a patient with a bone marrow transplant secondary to severe combined immune deficiency syndrome (SCIDS). At age seven months, a single application of tacrolimus 0.1 percent on the scalp for chronic dermatitis resulted in a tacrolimus level of 29 nanogram per ml at 20 hours after application. The ointment was discontinued and after seven days, 0.03 percent ointment was used. The level at that point was seven nanogram per ml 20 hours after application together with a transient tremor of the upper limbs

and jaw and by the way, tremors in adverse event, that's included in the Prograf label.

The second report is from the *Archives of Dermatology*. Increased tacrolimus levels were reported in three pediatric patients with ichthyosis and Netherton's Syndrome after treatment with topical tacrolimus. This is still another case from the *Archives of Dermatology*. In a 28 month old patient with lamellar ichthyosis, 0.1 percent tacrolimus ointment was used over 100 percent of the body's surface area. Seven weeks later, the tacrolimus level was 19.3 nanogram per ml three hours after application. Two weeks later after decreased amount of use, the level was 7.4 nanogram per ml and another two weeks later after decreased frequency, the level was 5.8 nanogram per ml.

The point that I'm trying to make about all of these cases is that absorption of these drugs can take place and agree that these patients had conditions that predisposed them to higher levels but levels are routinely monitored upon use of topical immunosuppressants.

This brings us to adverse effects. The most common are local and these include pruritis, erthema, irritation, edema and urticaria. The systemic ones include respiratory and gastro-intestinal infections, viral skin rashes such as herpes simplex and zoster and eczema herpeticum and lymphadenopathy.

Strep and staph infections have been reported and these have included cellulitis, abscesses, necrotizing fascilits. A 12 year old patient was reported to have a leg amputation due to infection after use of pimecrolimus. Unfortunately no further information was available.

Cases of septicemia in children have been reported with tacrolimus. They've included Staph aureus, Strep pneumo, Pseudomonas and Neisseria meningitidis. The eight month old patient with Pneudomonas infection had a cardiac arrest and neurological changes and the tacrolimus levels were 3.5 nanogram per ml two weeks after discontinuation of treatment. A patient with Neisseria meningitidis infection, the tacrolimus levels were less than three

nanogram per ml and again unfortunately, there was no further information available. The three year old patient died from developing Strep pneumosepsis.

Septic arthritis has reported in a nine month old patient enrolled in a clinical trial for pimecrolimus five months after onset of treatment and pyogenic arthritis has been reported in another eight month old patient about seven weeks after onset of treatment. In addition, osteomyelitis and osteitis have also been reported in a nine month old patient with pimecrolimus.

Cases of acute renal failure have been reported in patients with and without epidermal barrier effects. As discussed before, there was a patient with Netherton's Syndrome and there have been three other cases with concomitant medical conditions such as diabetes, gout, preceding renal failure, histo-nephrotoxic drugs, etc.

This brings us to systemic immunosuppression and malignancies. Patients receiving Prograf are at an increased risk of developing Hodgkin's, non-Hodgkin's lymphomas,

Kaposi's sarcomas and in particular, skin cancers such as squamous and basal cell carcinomas and malignant melanomas. In such patients, literature reports suggest a correlation between tumor regression and reduction in immunosuppression.

This brings us to a case report from the *Journal of Transplantation*. Here a comparative incidence of de novo non-lymphoid malignancies after liver transplantation under tacrolimus protocols was done using Surveillance, Epidemiology and End Results (SEER) data. A thousand patients were followed. The median follow-up period was 6.5 years and 57 malignancies were noted. Now by and large, 33 percent were skin malignancies out of which 50 percent were squamous cell carcinomas, 41 percent basal cell carcinomas and nine percent melanomas.

Now it is important to note that SEER incident rates are not available for squamous and basal cell carcinomas and this is where long term cancer histories are useful because they can capture such data. In this study, malignant melanoma was seen at 1.94 times SEER rates and interestingly,

oropharyngeal cancers at 7.6 times SEER rates.

Now going on to systemic immunosuppression and skin cancers. This report is from the New England *Journal of Medicine*. Squamous and basal cell carinomas account for more than 90 percent of all skin cancers in transplant recipients. Melanomas account for 6.2 percent in adults and 15 percent in children. In such patients, cancers are more aggressive. The incident increases with duration of immunosuppressant therapy and tapering therapy usually decreases the rate.

Cancers affect 50 percent or more of white transplant patients and so a genetic difference is present. For example, Japanese patients do not have such high rates. In Australian study, the incidence was seven percent after one year of therapy and increased 22 percent after 20 years. In a Dutch study, the incidence was 0.2 percent after one year and the long term incidence was 41 percent. The higher incidence in the Australian was most likely due to increased sun exposure.

This brings us to systemic

immunosuppression and lymphoma. This was discussed by Dr. Cohen. A post transplant lymphoproliferative disorder in immunosuppressed patients related to Epstein-Barr virus infection is a well recognized complication. The risk of this disorder appears greatest in young children who were at risk for Epstein-Barr virus infection while immunosuppressed. This risk appears to be related to the intensity and duration of immunosuppression.

This brings us to possible mechanisms of topical immunosuppressants in causing malignancy-related events. Topical immunosuppressants may break local immune surveillance resulting in skin cancers. Tacrolimus and pimecrolimus, draining from atopic skin into regional lymph nodes may result in immunosuppression and it is also possible that systemic exposure to these drugs over a course of time could lead to the formation of lymphomas and skin cancers. What is also of concern is that in a patient who is predisposed for malignancy-related events the use of these drugs may increase the risk burden. In a nutshell, it is not clear if the effects are local or

they involve draining lymph nodes or indeed if there is systemic involvement as well.

This brings us to a recent case report from the *British Journal of Dermatology*. Here three children with severe atopic dermatitis who were in long term treatment with a 0.1 percent ointment were noted to have developed multiple lentigines especially over areas of therapy. In the four year old patient, the lesions were noted six months after start of treatment, in the seven year old patient, five months after start of treatment and in the 11 year old patient about three and a half years after onset of treatment.

What was interesting in these patients is that these lentigines also occurred at some protected sites becsause the lentigines usually occur in childhood in sun-exposed areas. Treatment was discontinued in all patients and the lesions persisted. Per the report, focal distribution of lentigines to sites of tacrolimus use and the temporal association between use of tacrolimus and the development of lesions suggests a direct etiology.

Now simple lentigines are small, pigmented macules that represent the simplest form of melanocytic neoplasia. While post inflammatory changes are documented in atopic dermatitis, discrete pigmented macules are not. Systemic immunosuppressants are known to cause an increase in melanocytic activity but this case report raises a question. Does topical tacrolimus have an effect that is yet undefined on melanocyte biology?

So the concerns that we have in the pediatric age groups are that the long term effects of topical immunosuppressants and their effects on the developing immune system in infants and children are unknown. But in the meantime, these medications will be used on an 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.

Literature reports suggest use of both drugs in the following conditions: contact dermatitis, chronic hand dermatitis, seborrheic dermatitis, rosacea, psoriasis, lichen planus, lichen

sclerosus et atrophicus, graft-versus-host disease, pyoderma gangrenosum, etc. In the case of pimecrolimus in patients three to eighteen months of age, there is currently a study being conducted called the Atopic March Study where it is hoped that earlier application of a topical immunosuppressant such as pimecrolimus would alter the course of atopic diseases such as atopic dermatitis, asthma and allergic rhinitis.

As mentioned before, IMS data indicate the use of both drugs is increasing in the U.S. The use is increasing in the pediatric age groups and a substantial proportion of use is in children less than two years of age. This leads one to think how often are these drugs being used first-line. So the concerns about long term use are that both drugs are being widely reported as safe and effective with some local side effects but being steroid-free and indeed being promoted as non-steroidal anti-inflammatory agents. In medical and nonmedical journals the need for long term safety information and larger patient numbers is often ignored.

As discussed by Dr. Cummins at the October 2003 Pediatric Advisory Committee meeting, there were five malignancy-related events associated with tacrolimus and two non-malignant tumors with pimecrolimus. Since then, newer maligancies-related events have been reported and these will be discussed by Dr. Marilyn Pitts. At that time, the logistics of cancer registry was to be discussed. However, it was felt that this would be difficult to initiate and that the answers may not be available for ten to 12 years and in the end, it was inconclusive.

Label revisions including the addition of black box and other risk management issues were also discussed. As I've mentioned since approval, there have been 21 malignancies related events reported for tacrolimus and nine for pimecrolimus.

Now there are confounding factors in these cases, but this is not entirely unusual for these types of events. It is also important to remember that as of yet although there are fewer cases reported with pimecrolimus, it was approved after tacrolimus and so this may simply represent a latency period

before such events present themselves. It is also possible that tacrolimus is being used more so in cases of moderate to severe atopic dermatitis resulting in increased exposure. However, both drugs belong to the same class, i.e. macrolactin immunosuppressants and as such their adverse event profile is expected to be similar.

Finally, this brings us back to recent concerns that we have with topical immunosuppressants. The risk for cancer associated with these drugs is uncertain. However, we know that there's biological plausibility between the use of topical immunosuppressants and the development of cancers and this is based on long clinical and clinical data.

There's an emerging signal in the types of tumors being reported in the adverse event reporting system. The risk as such is difficult to study and the answers for example from a long term cancer registry will be late and in the end even a negative study may not be exculpatory. The information landscape suggests that these drugs are being used first-line although the label implies second-line.

They are being promoted as steroid-free and therefore devoid of a lot of harmful side effects and the direct-to-consumer advertising often portrays an overall visual picture of safety.

The indications are being sought for both drugs and peer and non-peer review literature portrays safety that is not entirely substantiated. An addition to all of the above, overall use of both drugs is increasing and the use in the less-than-two-years-age group is also increasing. Next is Dr. Tapash Ghosh from the Division of Derm and Dental.

CHAIRPERSON CHESNEY: Dr. Nikhar, we are a little bit ahead of schedule. So I thought if you wouldn't mind, I would just see if there are any questions from the Committee for you. Dr. Mattison.

DR. MATTISON: You have fairly good data on cancers appearing in individuals, human populations, where higher doses of the drugs have been used and it's common in cancer risk assessment or at least it's not uncommon to use a linear extrapolation back from those observed dose response levels through zero dose assuming a non-threshold mechanism. Has

that extrapolation been done?

DR. NIKHAR: Not as I'm aware. No.

DR. MATTISON: And up until now, a lot of the focus of discussion has been on cancer as an endpoint, but there is data suggesting increased risk of infection. Is that going to be discussed a little bit later as an endpoint?

DR. NIKHAR: Well, not really. Not in this talk. We have the data that I have here and then I believe you have the reports from Office of Drug Safety that covered adverse events seen over the course of the last year for both drugs.

DR. MATTISON: Okay. Thank you.

CHAIRPERSON CHESNEY: Yes. Dr. Garofalo.

DR. GAROFALO: Yes, just along the same lines, on slide 15 you had the common adverse events and then more serious. Is that open label data? MedWatch? Is there a mixture of? I couldn't tell what the numerator and denominator were. There was a lot of discussion yesterday about numerators and denominators.

DR. NIKHAR: Up until lymphadenopathy,

that's in the label. After that, the cases that I've described are mostly post marketing events and then the process of updating are labels.

CHAIRPERSON CHESNEY: Dr. Newman.

DR. NEWMAN: Thank you for a very clear summary. I want to come back to the question about infections. On your slides six and seven, there were a number of those and I got the impression that the increase in infections in the three to 23 month olds was statistically significant and felt to be causally related to the medication, but I didn't see the P values and I couldn't tell how many different outcomes there were that were compared and how many of them were significant in this direction versus the other direction.

When I looked at some of the information from the manufacturers it seemed like sometimes there were things that were statistically significant in the opposite direction. So can you say how convinced you are that these associations that you have up here for the three to 23 month olds are causal? Because if these are convincing increases in infections, then we

know the answer to whether there is immunosuppression from these drugs. If less than two years olds get more infections, then presumably there is.

DR. NIKHAR: Right. You're right and in general, these infections were found to be clinically and in most cases even statistically more significant compared to the vehicle arm. Also the biopharm data in general and that will be covered by Dr. Ghosh next that the levels of the drug were generally higher in younger age groups, that even the proportion of higher levels we see in the younger age groups compared to the older age groups. So putting all that together, it was felt that the incidence of the infections I described was higher in these age groups indicating more systemic absorption.

CHAIRPERSON CHESNEY: Dr. Stern.

DR. STERN: I wanted to go back to your issue of infection and at least I could not find explicitly one part of a recently published article in the briefing materials. I found the companion article in one of the briefing documents from one of the sponsors but didn't find part of these explicitly and

that's this long term study published this month in the *JAAD*, *(Journal of the American Academy of Dermatology)*, where they followed 76 people in an open labeled study, second year age range whose is basically, I believe, the mean was around two, two and a half, years and they were almost all under four, so little kids. And in this 76 person-years of open label as use, they had two cases of eczema herpeticum and they had two cases of herpes zoster.

Now I happen to look at Platt's old article which was a population based study of the incidence of herpes zoster and the relative risk was 5,714 by my rough calculations. The lower limit of the 95 percent confidence interval the way I did it at least which was a Poisson model was about 600.

In fact, I brought up this issue because we had Journal Club yesterday and now everything was public because it was 24 hours. So I asked our residents who as part of the Harvard program all circulated and spend some of their time at Children's and the Mass General Children's Service. My hospital is all adults. I certainly don't see very many young

children and I asked them about two things.

One is prevalence of use among people referred into Children's from primary pediatricians of the agent and they say about 70 percent of kids they are seeing for referral in are already on topical calcineurin inhibitor and secondly, how often they see disseminated herpes simplex and do they think they see it more often in these people.

This is poll of 15 residents who all see multiple cases and when they think about it in atopics virtually all of them are on calcineurin inhibitors and at least historically when we didn't have these, it was a reasonably infrequent phenomena. I was quite frankly nonplussed by how many cases they reported and I was very specific, cases that you were the first resident to see not cases you were brought in to see because clearly in the teaching setting if that occurs, it's a rare enough event. You grab everybody you can find and their cousin and bring them in to illustrate the case. So with that one data from a prospective open label study published in the *Journal of the American Academy of Dermatology* and that

anecdotal data, I would say there's little doubt that at least in terms of cutaneous events that are immunologically related, there is to say the least a very strong signal.

DR. MURPHY: Dr. Newman, I think one of the other issues clearly is the population. Some of the differences is that though there are lots of studies that the company has provided the cut from many of them are the whole pediatric population. Some of them are in the very young group and I think that's maybe some answer to what you're asking.

CHAIRPERSON CHESNEY: Thank you very much. Our next speaker is Dr. Ghosh who is from the Office of Clinical Pharmacology and Biopharmaceutics with the FDA.

DR. GHOSH: Good morning. I am from the Office of Clinical Pharmacology and Biopharmaceutics and the topic of today's presentation is "Systemic Human Exposure of Pimecrolimus and Tacrolimus following Topical Application." My discussion on topical pimecrolimus cream is based on information included in the Approved NDA 21-302 for Elidel cream

one percent and I will discuss exposure in adults, exposure in children and exposure in infants. Similarly, my discussion on topical tacrolimus ointment is based on Approved NDA 50-777 for Protopic ointment, 0.03 percent and 0.1 percent and I will discuss exposure in adults, exposure in children and bio-availability.

First, I will start with pimecrolimus. In this slide, I have tabulated the salient features of three pivotal studies representing three different age groups. The first study, Study A, was done in adults. The second study was done in the children of population one to four years old. And the third study was done in the infant population of age 4.9 to 11 months. All these studies were done under twice-a-day settings and they were conducted for three weeks. The BSA involvement of the pivotal first study was 15 to 59 percent and for the second study it was 20 to 70 percent and in the third study, it was 25 to 58 percent.

The maximum concentration absorbed among all the patients during the inter-study period was

11.4 nanogram per ml on Day 17 in the adult study. The same maximum concentration absorbed in the second population among all the subjects during the inter-study period was 1.8 nanogram per ml and that was absorbed on Day 4. The maximum concentration observed in the infant population during the entire-study period was 2.6 nanogram per ml which was observed on Day 4.

Similarly, the maximum area under concentration, zero to 12 hours, was observed 11.4 nanogram per hour per ml. That was on Day 17. The same maximum AUC observed in the second population was 18.8 nanogram per ml on Day 4 and in the third population, AUC could not be calculated because of the study design. Now AUC could be calculated from two patients on more than two sampling days in the first adult population and AUC could be calculated from three patients on Day 4 in the children population.

Here is the concentration sampling time profile. This is the profile obtained of the systemic pimecrolimus given to adults, children and the infants on Day 4 for topical BID application of one percent

cream. Here the red square represents that adults data and the blue triangle represents the children data and the green diamond represents the infants data. The X axis is the sampling time, different sampling time on Day 4 whereas in the Y axis it is the concentration in nanogram per ml.

Now if we look at the distribution of the data, most of the adults data were contained within zero to one nanogram per ml. whereas the children data were above that. If we look at the infants data, even though it was a single time point it was even above that. So based upon this limited data on Day 4, it shows there is a trend that systemic exposure of pimecrolimus in children were above adults and infants was even above children. Basically, there is a trend showing that exposure in children and infants were more compared to adults based upon the Day 4 data.

In summary, we can say that pimecrolimus cream one percent to adult patients resulted in low which is less than 0.5 nanogram per ml blood concentrations of pimecrolimus. Second, the maximum systemic pimecrolimus concentration was observed

mostly between Day 2 and Day 4 and there was no evidence for high systemic blood concentrations of pimecrolimus with increasing body surface area treated.

The summary on the pediatric data is pimecrolimus cream one percent to pediatric patients largely resulted again in low which is less than 0.5 nanogram per ml blood concentration of pimecrolimus. Again in that population also, the maximum systemic pimecrolimus concentration were observed between Day 2 and 4. But interestingly in contrast to the adult population, relatively higher proportion of subjects which lies between 30 to 75 percent displayed blood concentration about 0.5 nanogram per ml.

Overall in summary of the pimecrolimus include that pimecrolimus cream one percent indicated consistently low systemic exposure in adults, less than children and infants with atopic dermatitis and infants under two years of age were found to have relatively higher blood concentrations of pimecrolimus compared to older children and adults.

Now I'm moving to my discussion on

tacrolimus. Again this is a summary table where I will describe the salient features from three different studies, again, representing three different populations. The first study that is Study One was conducted with 0.1 percent tacrolimus ointment and that was conducted in adults. The Study Two that was also conducted with 0.1 percent tacrolimus ointment and that was conducted in children with the age of six to 12 years. The third study was conducted with 0.03 percent tacrolimus ointment and that was conducted in children with the age group of two to five years.

The percent BSA involved in the first adult study was 11 to 60 percent. Whereas in the second study, the BSA was 17 to 83 percent and in the third study the BSA was 30 to 82 percent. All these studies were actually two weeks of duration. Excuse my slide. It shows it is three weeks, but actually it was two weeks of duration.

Again, maximum concentration absorbed during the entire study from all the adult patients was 9.9 nanogram per ml which was observed in Day 4. The maximum concentration observed from the second

study was 1.5 nanogram per ml. That was observed on Day 1. The maximum concentration in the third study was 14.8 nanogram per mil observed on Day 1 from one patient.

Maximum AUC (0-12 hours) was observed to be 31 nanogram per hour per ml observed on Day 4 in the first study. Maximum AUC observed in the second study was 13.2 nanogram per hour per ml again observed on Day 1. The maximum AUC observed in the third study was 103.3 nanogram per hour per ml and that was observed on Day 1.

In the first study, AUC could be calculated from almost all patients on each sampling day. That is the sampling days were Day 1, 4 and 14. In the second study also, AUC could be calculated from almost all patients on each sampling day which was Day 1 and Day 14. Similarly in the third study also, the AUC could be calculated from almost all patients on each sampling day. That is Day 1 and Day 14.

I would like to draw everybody's attention that the high Cmax and high AUC value obtained which

is shown in the third column was obtained from one patient who showed persistently high level of tacrolimus throughout the 14 day study period though the percent BSA involved reduced significantly from 82 percent on Day 1 to 22 percent on Day 14.

Here is again the profile of the concentration and maximum observed concentration. The X axis here represents the days of sampling and the Y axis represents the maximum observed concentration on each particular day from each patient. This is the time concentration profile from two studies and again the blue diamond represents the adult data and the pink square represents the pediatric data. There are three sampling days, Day 1, Day 4 and Day 14, involving these two studies.

This was a study done under twice-a-day application of 0.1 percent ointment in the adult and children of age six to 12 years old. If we look at the distribution of data, on Day 1 the data on adults and pediatrics are more or less superimposeable. Though there was one data which is higher in the adult population. In the second set of date on the Day 4,

we had data only from the adult. There was no data from children population, but the maximum data as I described on here was 9.9 nanogram per ml and in the third set of data, that is on Day 14, again the children data was pretty much low compared to the adults data but there was some adults which were in around the 6 nanogram per ml level.

This is again the time and maximum observed concentration profile from 0.03 percent tacrolimus in children. This data were obtained on Day 1 and Day 14. This is the data I was talking about, the highest data which I already described which is obtained from a single patient and the high value we obtained from the single patient on Day 1. From his data actually, the mean AUC and the Cmax data were driven. So what I want to mean is that data from a single patient drove the mean AUC value and mean Cmax value very much.

In this table, I summarized. It is a comparison of the systemic absorption after oral and topical administration of tacrolimus. Here there is data from the adults and data from the children six to

12 years old, data from the children two to five years old. Also this is in comparison to the liver transplant pediatric patients and kidney transplant adult patients.

So if we look at the mean AUC value and mean Cmax value, generally there is not much difference between the children and the adults data. But again here, I want to draw the attention of people on that there is a child who was in the 0.03 percent BID group for 14 days and who had initial BSA of 82 percent. His mean AUC on Day 1 was 206.7 and Cmax was 14.8 which is pretty close to the level which we obtained from the adult kidney transplant patient when that group was given oral tacrolimus at a dose of 0.2 milligram per kilogram per day.

In this slide, this is the assessment of bioavailability of tacrolimus. In comparison to the intravenous and oral administration of tacrolimus, the bioavailability of topical tacrolimus on Day 1 was measured to be 0.5 and 0.3 respectively on Day 1 and Day 8. When you compared it against IU dose what we called the relative bioavailability and in comparison

the relative bioavailability in comparison to the oral data was 2.7 percent on Day 1 and 1.8 percent on Day 8.

The overall summary on tacrolimus is that on average systemic exposure of tacrolimus from 0.1 percent tacrolimus ointment was lower relative to exposure generated from oral dosing. However occasionally, some patient showed relatively high exposure which we have observed with the 0.3 percent application of the ointment. There are no significant differences in systemic exposure between adult and pediatric age groups who are within two to 12 years of age. Systemic exposure tends to increase with increasing body surface area.

So in conclusion, in terms of systemic exposure, both pimecrolimus and tacrolimus show systemic exposure following topical applications. More patients had detectable blood levels following topical applications of tacrolimus in comparison to the pimecrolimus. Not much difference is noted in exposure between adult and children populations.

Now in terms of regional exposure, the

amount of pimecrolimus and tacrolimus that enters into the lymphatic system as well as its consequence following topical administration of these two agents is unknown at this point. Thank you.

CHAIRPERSON CHESNEY: Thank you very much. I wonder if there are any questions. If I could just start and maybe you or Dr. Nikhar could answer this. I noticed that one of the adverse events is reported to be renal failure and I wonder if there's any explanation. Well, I just looked up the metabolism. Apparently up to 80 percent is excreted in the feces and I wondered if you had any explanation for why that one child had such persistently high levels or if there are other examples of that and if it had anything to do with renal function or if there's any explanation for why one of the adverse events was renal failure.

DR. GHOSH: We also recognized the patient's deficiency and we also tried to find if there is any reasoning for that, but so far we couldn't find other than involvement of large body surface area. Even the sponsor's explanation was also

that they also basically tried to hypothesize that this is due to the involvement of larger body surface area. There was no other factor involved which we could identify from the patient history.

CHAIRPERSON CHESNEY: So the child you had had normal renal function.

DR. GHOSH: Yes, as far as we know.

CHAIRPERSON CHESNEY: Any other questions for Dr. Ghosh. Dr. Gorman and then Dr. Diaz.

DR. GORMAN: The model for pharmacokinetics that you used was probably a one compartment model. When you use the skin as a transfer agent, does it also act as a depot for this agent? So is there a terminal half-life effect that may in fact increase the area under the curve that was not measured in these studies?

DR. GHOSH: The measurement of concentration of the topical application is very sporadic. It's generally not like IV or oral that we get a consistent exposure. So basically the AUC was calculated as long as there were three measurable or evaluatable concentration on one particular sampling

day. That's how the AUC was calculated.

DR. GORMAN: Has there ever been an attempt to measure levels after the cessation of topical therapy?

DR. GHOSH: There were. Some of the studies even though after the cessation of the therapy, it went even sometimes up to three days and sometimes even went up to seven days. Most of the cases, the levels are not detectable.

CHAIRPERSON CHESNEY: Dr. Diaz.

DR. DIAZ: Can you clarify? The child that had the much higher concentration, was the body surface area different than the other children in that study group?

DR. GHOSH: Yes, I think that particular child had surface area involved was 82 percent. The second highest involvement into that particular group was 55 percent. So there was a difference.

CHAIRPERSON CHESNEY: Yes, Dr. Epps.

DR. EPPS: How did you determine the number of participants or how were they determined? I mean we're talking about millions of prescriptions and

patients and the numbers seem rather small.

DR. GHOSH: This was mostly a PK study. So generally the number of subjects involved in the PK study is much lower compared to the overall clinical study. That much I can tell.

CHAIRPERSON CHESNEY: Dr. Wilkin.

DR. WILKIN: In follow-up in part to Dr. Epps, but it's under maximal use conditions. In other words, the clinical pharmacology and biopharmaceutics team asks that it be under maximum use per labeling at the largest body surface area and this in case children and adults with involved skin.

Then I wanted to come back to Dr. Chesney's query on the patient with acute renal failure. There really was an additional factor in that patient. That patient had Netherton's Syndrome. That shows up in our labeling that you don't want to give these products to children with Netherton's Syndrome. They seem to have lack of a cutaneous barrier to these products. So we've seen higher levels in the circulation after exposure in children with Netherton's.

CHAIRPERSON CHESNEY: This is a trivial point but do you think the higher levels are causing the renal failure or does the renal failure result in higher levels or how are those two related?

DR. WILKIN: You know I think associated is about the best we can do with the information that we had. I don't think we can establish causality.

CHAIRPERSON CHESNEY: Thank you. Are there any other questions for Dr. Ghosh?

DR. GHOSH: Thank you and I would like to introduce our next speaker.

DR. MURPHY: Before you do that, just one sec. Okay? Before we go to monkeys, Dr. Roberts has an answer to the question that was asked earlier today about the incidence in EBV sero-conversion in the U.S. population. So Dr. Mathis is going to read it.

DR. MATHIS: She handed it to me. "In the U.S., EBV is not a reportable infection and the exact frequency of systematic primary infection is not known. By age five years, approximately 50 percent of the U.S. population is infected. During childhood, primary infection usually is asymptomatic or

associated with mild elevation of liver function tests and EBV infection acquired during adolescence is asymptomatic or associated with a syndrome of acute infectious mononucleosis.

Incidence of acute mononucleosis was approximately 45 cases per 100,000 population per year in the early 1970s with the highest incidence in individuals aged 15 to 24 years. However changes in economic status may have changed both the age of initial infection and the incidence of infectious mononucleosis since the large epidemiologic studies were completed. In lower socio-economic groups, EBV infection is more common, occurs at an earlier age and less likely to be associated with acute infectious mononucleosis.

Roommates of students with primary EBV infection develop sero-conversion at the same rate as a general population of college students and approximately 90 percent of the U.S. population is infected with EBV by age 25 years. EBV infection does not occur in epidemics and it is of relatively low transmitability."

DR. MURPHY: Thank you all.

CHAIRPERSON CHESNEY: Thank you, Dr. Roberts. Just before you introduce Dr. Hill, I wanted to bring on issue to the attention of the Committee and consultants. In your briefing materials, you received something like this that had yellow marking on it. Just to remind you that all of the yellow areas although we have them, they have been redacted by the FDA and in our questions, we should be vigilant that we don't refer specifically to this material. It was suggested that you be reminded about this before we hear Dr. Hill's presentation.

DR. GHOSH: Okay. So our next speaker is Dr. Barbara Hill who is of the Pharmacological/Toxicology Review Board and she joined FDA after being a postdoc at NCI for a number of years. Thank you.

DR. HILL: Good morning. I'm a pharmacology/toxicology reviewer in the Division of Dermatologic and Dental Drug Products. Today I'd like to summarize the animal toxicology data available for two topical immunosuppressants which are referred to

as calcineurin inhibitors that have been approved for the topical treatment of atopic dermatitis. The two drug products are Protopic (tacrolimus) ointment approved in December 2000 and Elidel (pimecrolimus) cream approved in December 2001.

I'd like to present the structures for both compounds and then describe the general toxicology, the genetic toxicology studies and the carcinogenicity studies conducted for both compounds and also present the results of a nine month oral monkey toxicology study conducted with pimecrolimus and conclude the talk with a summary of all the non-clinical tox information.

The structures for the two compounds is provided on this slide and even though they have different molecular formulas, you can see that their overall structures are similar indicating that they belong to the same class of drugs, in this case, calcineurin inhibitors.

The potential immune target organs of toxicity were indicated in chronic rodent and non-rodent toxicology studies and these include the

thymus, lymph nodes and spleen. The non-clinical toxicology study results indicate that both compounds are classic immunosuppressant agents.

An appropriate battery of in vitro and in vivo genotoxicity tests were conducted for both tacrolimus and pimecrolimus. Both compounds were non genotoxic in the standard battery of genotoxicity tests.

The carcinogenicity studies conducted for both compounds are summarized on this slide. For tacrolimus, an oral rat and mouse carcinogenicity study were conducted. In addition, a dermal mouse carcinogenicity study with a marketed formulation was conducted. For pimecrolimus, an oral rat and an oral mouse carcinogenicity studies were conducted and a dermal rat carcinogenicity study with a final marketed formulation was also conducted. In addition, special high dose studies were done after dermal administration to the mouse with pimecrolimus dissolved in ethanol. The duration of these studies was 13 weeks.

This slide summarizes the result from the

oral carcinogenicity studies, once again after oral administration of the compound. We're focusing specifically on the lymphoma signal. The first two rows of this table summarized results of the oral rat and oral mouse carcinogenicity studies were conducted to support Protopic.

The first row is for the rat study and at the highest dose tested of 3 milligram per kilogram per day which is equivalent to nine times the maximum recommended human dose which is based on comparison of AUC, the results of this study were negative. In the second row is the results from the oral mouse carcinogenicity study and at the highest dose tested of 5 milligram per kilogram per day which is equivalent to three times the maximum recommended human dose again the results were negative. But it's important to note that an adequate systemic exposure was obtained after oral administration. This may be the cause for seeing a negative response in these two oral studies.

Then the last two rows of this table summarize results from the oral mouse carcinogenicity

study conducted to support Elidel and at a dose of 48 milligram per kilogram per day equivalent to 258 to 340 times the maximum recommended human dose, a lymphoma signal was noted and the NOEL which is the dose at which no lymphoma was noted was identified in this study as 15 milligram per kilogram per day equivalent to 60 to 133 times the maximum recommended human dose.

This next slide summarizes the results from the dermal carcinogenicity studies conducted for both compounds, drug products and once again focusing just on the lymphoma signal. The first two rows of this table summarized the results from the dermal mouse carcinogenicity study conducted with the marketed formulation of Protopic ointment and at a dose of 3.5 milligram per kilogram per day equivalent to 26 times the maximum recommended human dose based on AUC comparisons, a lymphoma signal was noted. The NOEL for lymphoma was identified in this study as 1.1 milligram per kilogram per day which is equivalent to ten times the maximum recommended human dose.

The third row of this column summarizes

results from the dermal rat carcinogenicity study conducted the final marketed formulation of Elidel cream. At the highest dose possible in this study based on a maximum feasible concentration obtained in the final marketed formulation at a dose of 10 milligrams per kilogram per day which is equivalent to 3.3 times the maximum recommended human dose, the results of this study were negative.

However in the results of a special high dose study conducted after dermal administration in the mouse with pimecrolimus dissolved in ethanol, we were able to see a lymphoma signal. At a dose of 25 milligram per kilogram per day which is equivalent to 47 times the maximum recommended human dose, a lymphoma signal was seen after 13 weeks of administration. The NOEL for lymphoma was identified in this study as 10 milligrams per kilogram per day equivalent to 17 times the maximum recommended human dose. The last row of this table shows a higher dose at 100 milligram per kilogram per day equivalent to 179 to 217 times the maximum recommended human dose. Lymphoma was noted after eight weeks of treatment. So

in summary, the results of these last three rows of this table show that the formation of lymphoma is a dose-dependent and time-dependent expression.

This next table summarizes the result from carcinogenicity studies conducted to support Elidel focusing on other tumor signals besides lymphoma that were noted in these studies. The first four rows of this table summarize results in an oral carcinogenicity study conducted in the rat. At a dose of 10 milligram per kilogram per day equivalent to 40 times the maximum recommended human dose, benign thymoma was noted.

Benign thymoma was also noted at a dose of 5 milligram per kilogram per day in male rats equivalent to 32 times the maximum recommended human dose. The NOEL for benign thymoma was identified in female rats as 5 milligram per kilogram per day and in male rats as 1 milligram per kilogram per day. This last row of this table summarized results from the dermal rat carcinogenicity study conducted with the final marketed formulation and at the lowest dose tested in this study of 2 milligram per kilogram per

day equivalent to 1.5 times the maximum recommended human dose, follicular cell adenoma of the thyroid was noted.

The results of the rodent carcinogenicity studies indicate that systemic immunosuppression leads to lymphoma formation. It is not clear if the mechanism of lymphoma formation is the same for rodents and humans.

On the next few slides, I'd like to summarize results of an oral monkey toxicology study conducted with pimecrolimus. In this study, oral doses of 0, 15, 45 and 120 milligram per kilogram per day of pimecrolimus were administered for 39 weeks. The high dose group in this study was discontinued after 19 weeks of treatment due to a high morality rate. The immunosuppressive related lymphoproliferative disorder was noted in all dose groups tested in this study and immunosuppressive related lymphoproliferative disorder frequently progresses to lymphoma with increase duration of treatment.

This next slide summarizes the results in

the monkey study focusing on the immunosuppressive related lymphoproliferative disorder signal. In the low dose group of 15 milligram per kilogram per day, the incident rate was one out of eight monkeys and it was noted after 39 weeks of treatment. In the mid dose of 45 milligram per kilogram per day, the incident rate was five out of eight monkeys and it was seen in one monkey after seven weeks of treatment but noted mainly after 39 weeks of treatment in the mid dose group. And then the high dose group of 120 milligrams per kilogram per day, the incident rate was seven out of nine monkeys and was seen after 14 to 18 weeks of treatment.

Immunosuppressive related lymphoproliferative disorder was associated with lymphocryptovirus which is an Epstein-Barr related virus. Immunosuppressive related lymphoproliferative disorder exhibited a dose dependent expression in this study. In addition, opportunistic infections were noted in some animals in all dose groups and three of the high dose monkeys with immunosuppressive related lymphoproliferative disorder had concurrent leukemia.

A NOEL for immunosuppressive related lymphoproliferative disorder was not established in this study. The low dose is 31 times the maximum recommended human dose based on AUC comparisons and once again, this is 31 times the maximum AUC after topical administration of Elidel cream. The mechanism of lymphoma formation appears to be the same for monkeys and humans. It related to an Epstein-Barr virus. It is unknown if the mechanism of leukemia formation is the same for monkeys and humans.

The results from this study confirm that adequate systemic exposure to pimecrolimuscould elicit lymphoma formation via a similar mechanism that has been established for tacrolimus in humans.

In summary, Protopic ointment and Elidel cream are topical immunosuppressants. Neither compound exhibit a genotoxic signal. The tumorigenicity exhibited by tacrolimus and pimecrolimus appears to be mediated by a non-genotoxic mechanism (immunosuppression).

A lymphoma signal is evident in a dermal mouse carcinogenicity study conducted with tacrolimus

ointment. A lymphoma signal is evidence in a oral mouse carcinogenicity study conducted with pimecrolimus. A lymphoma signal is evident in the 13 week dermal mouse study conducted with pimecrolimus dissolved in ethanol.

Other tumor signals included benign thymoma noted in the oral rate carcinogenicity study conducted with pimecrolimus and follicular cell adenoma of the thyroid noted in the dermal rat carcinogenicity study conducted with pimecrolimus cream. Immunosuppressive related lymphoproliferative disorder was noted in a nine month oral monkey toxicology study conducted with pimecrolimus and the biologic plausibility of lymphoma formation in local lymph nodes cannot be ruled out at this time. Thank you for your attention.

CHAIRPERSON CHESNEY: Thank you very much. If you wouldn't mind being available for questions. I have a very simple one. Could you remind us of how you calculate the NOEL particularly for the rat studies?

DR. HILL: Well, what we did was we used a

very conservative approach where we compared the AUC in the animal studies versus the maximum AUC seen in the pharmacokinetic. So it would be the information that was presented by Dr. Ghosh earlier. We used a very conservative approach.

CHAIRPERSON CHESNEY: So you extrapolate from what's seen in humans to what the equivalent that would be seen as the area under the curve in the animal.

DR. HILL: It's the actual area under the curve measured in the animals at that dose divided by the maximum AUC seen in human pharmacokinetic studies after topical administration of each agent.

CHAIRPERSON CHESNEY: Thank you. Dr. Glode and Dr. Stern.

DR. GLODE: Could you just review briefly if you know from memory how this would compare to topical corticosteroids in animal models in terms of tumors?

DR. HILL: Unfortunately, topical corticosteroids have not been studied as extensively in animal models and the data is not as clear. So

it's difficult to make a direct comparison between the two.

CHAIRPERSON CHESNEY: Dr. Stern.

DR. STERN: Nearly five years ago when I chaired the committee that looked at Protopic, one of our concerns was cutaneous carcinogenesis and there was only one animal study that I recall that looked at it and it was not a very well designed study at least in some of our opinions and at that time, we proposed or strongly recommended as I recall and the consultant for Fujisawa, Dr. Forbes, seemed to agree that one avenue for learning a little bit more about cutaneous carcinogenic risk with these agents might be some better designed carcinogenic studies.

To my knowledge and trying to follow this literature, I've only been able to find one which was in fact not a photocarcinogenesis study, but a chemical carcinogenesis study in mice and a very classic DMBA followed by TPA or not where they showed in fact enhancement of cutaneous carcinogenesis in this mouse model when pimecrolimus was added to it. When I went through the briefing document, although

there was so much material I could have missed it, I didn't see any other materials. Are you aware of any other studies that have been done by the sponsors in the four and a half years photocarcinogenesis studies beyond the one where they didn't show enhancement because they got such a high tumor yield with the vehicle is pretty typical in photocarcinogenesis?

DR. HILL: You are correct. There have been no other additional animal models investigated for examining the question of cutaneous malignancies. The article that you mention is what I would consider a typical initiation promotion study. So in these animals, they would have received initiation by a carcinogen and have been treated with the immunosuppressant which would serve as a progression of the initiated cells.

One problem with animal models is that they have a different mechanism of DNA repair. So it's hard to extrapolate that. Rodents in particular are not exposed to the sun. So they wouldn't have the initiated cells you would expect, for example, in humans who are exposed to the sun on a daily basis.

It's difficult to get a grasp on skin carcinogenesis of topical immunosuppressants in an animal model in my opinion. The only way you could do it is with a literary reference that you mentioned which is to initiate the cells first and then treat with atopical immunosuppressants.

CHAIRPERSON CHESNEY: I have one question and then Dr. Mattison, Dr. Santana and Dr. Newman. Do you have serum levels, this is Slide 13, that correlate with your dose and lymphoma incidence?

DR. HILL: We'll get Slide 13 up so it will refresh my memory. Now could you repeat your question?

CHAIRPERSON CHESNEY: Do you have serum levels to add to that slide? Peak serum levels at those doses?

DR. HILL: Yes. We have the AUC levels for those doses. I don't have them memorized, but the information that I provided use those doses for the lowest dose in this study. On this slide it would show that at that lowest dose which is the 15 milligram per kilogram per day where you did see one

out of eight monkeys with a lymphoproliferative disorder was 31 times the maximum recommended human dose. Now once again this is taking the AUC from that low dose and dividing it by the maximum AUC seen in the pharmacokinetic study.

CHAIRPERSON CHESNEY: Thank you. Dr. Mattison, Dr. Santana and Dr. Newman.

DR. MATTISON: This was a good summary of carcinogenicity but to what extent have there been animal studies that have looked at response to infectious agents?

DR. HILL: We have not done any animal studies. You're talking like for example a host resistance assay and things of that nature.

DR. MATTISON: Yes.

DR. HILL: We haven't done that because those assays typically help you to identify if a compound is an immunosuppressant. We ask for those types of studies if we are concerned about that for a compound that we don't think would be immunosuppressant. But the general tox studies that were conducted for both of these compounds show that

the target organs were typical for immunosuppressants. So we had a very clean and strong signal that they were already immunosuppressants. So doing a host resistance assay wouldn't give you any additional information.

DR. MATTISON: And then as a follow-up and I probably missed it but how many of the carcinogenicity studies were started in immature animals?

DR. HILL: These studies are started in very young animals to try to represent a lifetime exposure, to try to extrapolate to humans if they had a lifetime exposure. So they were started in very young animals and go for a full two years which is equivalent to a life span of a rodent.

DR. MATTISON: And in the monkey studies?

DR. HILL: In the monkey studies, they weren't necessarily very young. They were probably adolescent type. We haven't asked for any pediatric monkey studies.

DR. MATTISON: And were there any other developmental endpoints evaluated in the animal

studies, functional endpoints?

DR. HILL: It's an excellent question and the answer is no and the reason is that developmental immunotoxicology is a complicated area and it's unclear at this point if you could extrapolate from effects that you would see in animals to effects that you would expect to see in humans. The toxicity is very clear. If you see renal toxicity, you would expect to see the same thing in humans. It's better to do those types of studies looking at developmental immuno-effects in humans and some of those studies have been initiated by the sponsors.

CHAIRPERSON CHESNEY: Dr. Santana.

DR. SANTANA: As a follow-up to that comment and an earlier comment we heard this morning that although there's been a lot of focus on this lymphoma signal, there may be other signals in data that would suggest that these patients are immunosuppressed. If you go back to Slide 14, one more, you very briefly mention that these monkeys also had opportunistic infections. Can you elaborate on that? What kind of profiles were you seeing? Was

that consistent with some of the things that have been reported in the clinical dataset for patients that develop infections?

DR. HILL: It actually mimics the types of infections that you see after systemic exposure to these types of immunosuppressive agents and that's the reason why I put it on this slide. It also is an indicator that these monkeys were immunosuppressed and they were able to express these opportunistic infections.

CHAIRPERSON CHESNEY: Dr. Newman.

DR. NEWMAN: Just to follow up on Dr. Chesney's question to make sure I understand it. When you say the maximum recommended human dose and you use the highest one, does that mean you use that one child that had the 200 nanogram hour per milliliter area under the curve that was sort of in the same range of what is seen in adult transplant patients as your maximum recommended human dose?

DR. HILL: That particular level was for tacrolimus. This is pimecrolimus.

DR. NEWMAN: Okay.

DR. HILL: So the highest level is about 38 nanograms per ml and that's the value that's used for these calcalutions.

DR. NEWMAN: Okay. And since I'm getting these two mixed up, how high is that in relation to, actually pimecrolimus isn't used in transplant patients I guess. Right? So you can't actually compare.

DR. HILL: That's correct.

DR. NEWMAN: Thank you.

CHAIRPERSON CHESNEY: Other questions for Dr. Hill? Thank you very much.

DR. HILL: Thank you.

DR. MURPHY: The only hint I have for trying not to confuse is that the "E" in pimecrolimus is the Elidel and the "P" for the Protopic.

CHAIRPERSON CHESNEY: We are, I think, actually ahead of time because we've done questions and answers after the speakers instead of our allotted ten minutes later, but let's try to keep ahead of time. So our break is scheduled for 15 minutes. If everybody could please be back here at 11:00 a.m. for

our next presentation which is actually scheduled for 11:20 a.m. Thank you.

(Whereupon, the foregoing matter went off the record at 10:47 a.m. and went back on the record at 11:05 a.m.)

CHAIRPERSON CHESNEY: Our next speaker will be Dr. Marilyn Pitts from the FDA. And while everybody is finding their seat, I wonder if I could just mention that if you have a cell phone although we're interested in the musical selection that you've chosen as a measure of your particular temperament, for the purpose of this meeting we would ask if you could turn it to the vibration mode or better yet turn it off. I didn't know if anybody from the FDA would like to introduce Dr. Pitts or maybe she could introduce herself.

DR. CUMMINS: Marilyn Pitts is a safety reviewer with the Office of Drug Safety and we're lucky to have her back. She reviewed the safety reports to you in October of 2003 and she'll report on an update of that again today.

DR. MURPHY: My only other hint for the

people presenting is that the buttons are the opposite of what you would think. The top one is not forward. It is backward. The second one is forward, not backwards.

CHAIRPERSON CHESNEY: It's the story of life. Don't you think?

DR. PITTS: Thank you. Good morning. My objective is to describe the post-marketing cases of tumor adverse events reported with the topical calcineurin inhibitors, pimecrolimus and tacrolimus. During my presentation, I will briefly review some aspects of AERS database system. I will provide a separate analysis of the post-marketing cases of tumor adverse events reported with pimecrolimus as well as provide a separate analysis of the post-marketing cases of tumors reported with topical tacrolimus. I will also provide some drug use information and a summary of my presentation. Finally, I will offer the Division of Drug Risk Evaluations recommendation.

Prior to reviewing the post-marketing tumor cases, I want to briefly review some aspects of the AERS database. The AERS database is a system of

voluntarily submitted adverse event reports. Spontaneous databases such as AERS are designed to collect adverse event reports that occur in association with marketed drug products for use as safety signal detection.

It is important to realize that AERS has strengths and limitations. I will not review the strengths of the system at this time, but I wanted to refresh your memory concerning some of the limitations of this tools. Limitations include, but are not limited to, under reporting of adverse events as well as the lack of clinical details in individually reported cases.

Consequently, this tool although valuable in post-marketing surveillance may not be the optimal surveillance tool for adverse events that have a long latency period between drug exposure and expression of the suspected adverse event such as occurs with tumors or malignancies. In addition, other exposures that may occur during long latency periods may further complicate analysis.

We include cases in our series that

describe benign or malignant tumors excluding cases specifically describing skin warts. We also included cases that specifically contained the term "tumor."

I'll start first with Elidel or pimecrolimus. We queried the AERS database for cases of tumor adverse events associated with pimecrolimus. We found nine cases. The majority of the reports were of U.S. origin with three reported from foreign sources. The cases were split between adults and children with children accounting for three of the nine cases and two of the three pediatric cases occurred in children less than six. There were no cases in children less than two.

The cases were almost evenly split between males and females who use pimecrolimus primarily to treat atopic dermatitis. The cases reported a median time to onset of 90 days with onset occurring in as short a time as seven days to as long a time of 300. There were no cases reporting death and the most serious outcome was hospitalization in an adult patient who developed a squamous cell carcinoma within three months of using pimecrolimus.

On this slide and on the next slide, we describe the type of tumor events reported, the age of the patient, the site of application of the product, the site of occurrence as well as onset information if provided in the report.

On this slide, we report three pediatric cases. The first case is a non-Hodgkin's lymphoma in a two year old that occurred ten months after starting pimecrolimus to treat atopic dermatitis over 20 percent body surface area. The second case was described as a tumor papilloma and occurred on the chin of a two year old after three months of use. The third was a facial tumor reported in a child of unreported age. It is important to note that significant clinical information such as risk factors and other details were unreported in these three pediatric cases as in many cases in our case series.

On this slide in adults, we describe six tumors which included four cutaneous tumors and two additional tumors that did not provide sufficient information to determine if they were cutaneous or non-cutaneous. The first case was a squamous cell

carcinoma that occurred at the site of pimecrolimus application in a patient who used pimecrolimus to treat lichen sclerosis of the vulva, a condition with an increased cancer risk. The second case was a T cell lymphoma at the site of application in a patient who used both pimecrolimus and topical tacrolimus. This patient is listed in both series. The next case was a basal cell carcinoma of a nose that occurred one to two weeks after starting pimecrolimus. The patient had a history of nose nodules prior to starting pimecrolimus and the next case was an intraductal papilloma that was determined to be benign. The last two cases of lymphoma provided very little clinical information.

I'm going to switch to topical tacrolimus. We also queried the AERS database concerning tumor adverse events associated with the use of topical tacrolimus. We found 21 cases of which eight were U.S. and 13 were foreign. In this series, there were three children and 18 adults, 15 males and five females. One case did not provide gender information. The patients primarily used topical tacrolimus to

treat atopic dermatitis.

There were also cases that used topical tacrolimus to treat balantiis, vitiligo, inverse psoriasis as well vulvular atrophicus sclerosus lichen. Overall, the cases reported a median time to onset of 240 days with onset occurring in as short a time as three weeks to as long a time as 940 days or two and a half years.

There were three deaths reported. All occurred in adults. One death occurred in a patient who developed a cutaneous Kaposi's sarcoma which was metastatic to the lung. The second death occurred in a patient with extensive atopic dermatitis who died from lymphoma complications. The third death occurred in a patient who developed metastatic esophageal cancer. There were also eight cases reporting hospitalization, two occurring in children.

On this slide and then on the next three slides, we will again describe the type of tumor events that were reported as well as the age of the patient, the site of application, the site of occurrence as well as onset information if provided in

the report.

On this slide, we report three pediatric cases. The first case was a metastatic angiosarcoma that suddenly worsened in a patient with previous disease. The second was a malignant lymphoma in a child with a seven year history of atopic dermatitis who may have had symptoms of Sezary's syndrome prior to starting topical tacrolimus. The third pediatric case was a five year old child who underwent a hepatectomy to treat a hepatoblastoma.

All of the remaining tumor cases reported with topical tacrolimus occurred in adults. On this slide, we describe five cutaneous tumors. All five tumors occurred at the site of topical tacrolimus application. The first was a squamous cell carcinoma that occurred on the face of a patient who was described as having a reasonable amount of sun exposure. The next was a recurrent squamous cell carcinoma of the vulva in a patient who used topical tacrolimus to treat vulvular atrophicus sclerosus lichen, a condition with increased cancer risk. The third was a squamous cell carcinoma of the penis in a

patient who had a history of balantis, a condition with an increased cancer risk.

The fourth tumor on this slide was a cutaneous Kaposi's sarcoma in a patient who was improving on highly active antiretroviral therapy prior to starting topical tacrolimus. The fifth tumor on this slide was an anaplastic large cell lymphoma occurring on the right hip of a patient who did not have a history of previous disease. The squamous cell carcinoma case of the penis and the Kaposi's sarcoma both have been recently published in the medical literature.

On this slide, we describe five additional cutaneous tumors. The first was a possible lymphoma that occurred at that site of application in a patient with a previous history of lymphoma. The second was a T cell lymphoma where the patient used both topical tacrolimus and pimecrolimus. The third was a sweat gland tumor that may have been malignant since the patient underwent chemotherapy after excision of the tumor.

The next case is a new onset of a

generalized metastatic melanoma in a patient with a previous history. The new onset occurred three to four weeks after topical tacrolimus. The last case on this slide was a lymphoma on the neck that occurred one and a half to two years after exposure.

There were eight additional tumor events reported. Only three provided sufficient information to determine the location of the tumors. The first was a squamous cell carcinoma of the mouth that occurred in a patient who had a long history of cigarette and pipe smoking. The second was a metastatic esophageal that occurred in a patient who was reported not to have a history of alcohol or cigarette abuse. The third was a B cell lymphoma of the kidney that was Epstein-Barr associated in a patient who later developed primary lung cancer. The patient had a history of working in a chemical plant. The five additional tumors of lymphoma cases did not provide sufficient information to categorize as cutaneous or noncutaneous.

I'm going to switch gears now and discuss drug use data. We obtained drug use data from IMS

Health. Prescription volume data is obtained from retail channels which include chain, independent and mail order pharmacies as well as discount houses, food stores and long term care facilities. For Elidel from approval in December 2001 to November 2004, there were slightly more than 8.7 million prescriptions dispensed in the U.S. For Protopic from approval in December 2000 to November 2004, there were almost 3.5 million prescriptions dispensed in the U.S.

We also obtained drug usage data stratified by age. Age information was obtained from IMS National Disease Therapeutic Index Audit or NDTI which is a survey of office based practitioners in the continental U.S. NDTI data shows that 14 percent of Elidel is used in children less than two and seven percent of Protopic is used in the same age group. Additionally, 44 percent of Elidel is used in children between the ages of two and sixteen and 34 percent of Protopic is used in the same age group. Overall, the pediatric population accounts for 58 percent of Elidel use and 41 percent of Protopic use in the U.S. with a substantial portion occurring on an off-label basis in

children less than two.

This slide demonstrates the number of prescriptions dispensed in the U.S. for Elidel and Protopic comparing two periods. The green bar represents drug use data from approval to December 2003 and the blue bar represents drug use data from approval to November 2004. The green bar for Elidel represents 24 months of data and the green bar for Protopic represents 36 months of data. The blue bar for both products represents an additional 11 months of data.

For Elidel at the end of 24 months, more than 4.9 million prescriptions had been dispensed. When you extend the period an additional 11 months to the end of November 2004, we see more than 8.7 million prescriptions dispensed. This represents 3,750,000 prescriptions dispensed in an 11-month period compared to 4.9 million in a 24-month period.

For Protopic, we see a less dramatic increase in the number of prescriptions dispensed in the U.S. At the end of 36 months, we see slightly more than 2.5 million prescriptions dispensed. When

the period is extended an additional 11 months, we see almost 3.9 million prescriptions dispensed representing almost one million additional prescriptions. This rising trend in overall prescriptions dispensed for both products is also seen in the pediatric population.

In summary, we queried the AERS database for post-marketing tumor adverse event reports for the topical calcineurin inhibitors. We found nine cases for pimecrolimus and 21 cases for topical tacrolimus. The tumors reported were a mixture of types and malignancy status. We analyzed IMS Health prescription volume data and IMS Health drug use data stratified by age. We saw an increase in the number of prescriptions for both products but a more dramatic increase in the number of prescriptions dispensed for pimecrolimus. Additionally, for both products, a significant amount of drug use occurs in children less than two, an age group that is not approved to use either product.

In evaluating these cases, the Division of Drug Risk Evaluation considered the following. A

spontaneous reporting system such as AERS is not the optimal tool to determine the role of the topical calcineurin inhibitor in tumor development in the cases we presented today. However, collectively, the reported cases generate a safety signal for a possible association between topical exposure of the calcineurin inhibitor and the development of tumors.

We know that systemic absorption occurs with these agents. However what is unknown in these particular cases is whether absorption occurred and if absorption occurred, the degree of absorption and the degree of possible systemic immunosuppression. We also know that there is increased development of lymphomas with Prograf, a systemic calcineurin inhibitor. However, there are differences in the latency period of the topical cases when compared to the cases of lymphomas with Prograf. These differences in latency may possibly be explained by possible differences in the mechanism of tumor promotion.

Therefore after taking all of the presented issues into consideration, the Division of

Drug Risk Evaluation recommends the additional of a boxed warning to enhance the labeling of each product. Thank you.

CHAIRPERSON CHESNEY: Dr. Pitts, if you could entertain questions.

DR. PITTS: Sure.

CHAIRPERSON CHESNEY: And I had two. At the October 2003 meeting, it was brought to our attention that there is a lot of individual or creative compounding that goes on by pharmacists and that in some cases these drugs are being compounded within a steroid base and I wondered if you have any information from your AERS reports if any of these individuals had received preparations that had been compounded with steroids and also if you had taken or were able to determine how many of those patients had previous steroid use or concomitant steroid use.

DR. PITTS: Okay. All of the AERS reports, only one case had a compounded preparation and it was actually a mixture Protopic 0.1 percent with Vaseline or a petrolatum to decrease the concentration to 0.75 percent, I believe. All of the

other cases reported the commercial preparation. There was no mention of any compounding. So I really don't know the extent of that particular practice. In terms of your second question, your second question was?

CHAIRPERSON CHESNEY: How many of these patients have been on steroids just prior to starting these drugs or were they also on it at the same time?

DR. PITTS: Many of the patients were on steroids and I can get that number for you later. I just don't have it off the top of my head. Some of them were newly start, but many of the patients had either been on steroid just before starting or I think there may have been one or two cases where it was concomitant.

CHAIRPERSON CHESNEY: I don't know what it means but is it a majority?

DR. PITTS: At the same time.

CHAIRPERSON CHESNEY: Would you say a majority were also on steroids or had been on steroids?

DR. PITTS: I would like to get the

information because I cannot remember.

CHAIRPERSON CHESNEY: Okay. Thank you very much. Dr. Andrews I know had a question.

DR. ANDREWS: Yes. I had several questions about the market research data that you showed. I assume that you weren't able to look at some longitudinal patterns. If you had, I'd be real interested and for that population, not just the spontaneously reported events what proportion of patients who had prior evidence of steroid exposure concomitant and whether they vary by age and also whether there was any information about duration of therapy or quantity dispensed over time. That would be really helpful I think in understanding the level of exposure and possible risks.

DR. PITTS: Right. I don't have that information. I don't know if the information is available because some OTC, corticosteroids, are available OTC. So that may or may not be reflected in those particular databases.

CHAIRPERSON CHESNEY: Thank you. Ms. Dokken.

MS. DOKKEN: Yes, your slide number 18, the bar graph which was the growth in numbers of prescriptions. To me, there's a significant difference between the two. Is this something that we'll discuss later maybe in the presentation on promotion or advertising. I mean I'm just curious whether you've hypothesized why Elidel has grown so much more than Protopic.

DR. PITTS: I don't personally have. I know that there's two different indications. Elidel is indicated for mild to moderate and Protopic is for moderate to severe. But in terms of other factors, I think they may come up.

MS. DOKKEN: Okay.

CHAIRPERSON CHESNEY: Other questions? Dr. Moore.

DR. MOORE: I wanted to ask you if you had reviewed the AERS database with respect to oral tacrolimus.

DR. PITTS: I did not for this particular analysis. However we know that oral is already labeled for increase of lymphoma or risk of lymphoma.

DR. MOORE: I realize that. I was just curious as to the magnitude of the adverse events that would have been reported with the oral administration vis-á-vis this sort of level of adverse events.

DR. PITTS: No, I don't have that information here.

CHAIRPERSON CHESNEY: No other questions? Thank you very much.

DR. PITTS: You're welcome.

CHAIRPERSON CHESNEY: Our next three speakers are from Novartis Pharmaceuticals Corporation and I believe Dr. Hukkelhoven will speak first and then maybe you can introduce the other speakers if you wouldn't mind.

DR. HUKKELHOVEN: Sure.

CHAIRPERSON CHESNEY: Thank you.

DR. HUKKELHOVEN: Thank you very much. Dr. Chesney, Dr. Murphy, Dr. Wilkin, Members of the FDA Advisory Committee, FDA and guests. Good morning. My name is Mat Hukkelhoven and I'm responsible for global drug regulative affairs at the Norvatis Pharmaceuticals Corporation. On behalf of Norvatis, I

would like to thank you for the opportunity to review the safety experience to date with Elidel.

Based on the results of randomized clinical trials enrolling more than 19,000 patients on Elidel and the review of the post-marketing safety database, we will present data today from which we conclude that so far there is no evidence for systemic immunosuppression associated with the use of Elidel cream. However we do agree that concluded monitoring of post-marketing safety events including malignancies is appropriate. Today we will also present to you a broad clinical program which will prospectively assess the risk associated with Elidel treatment in children and adults and will allow us to detect any potential safety signal on a real time basis.

I would like to introduce today's presenters. Dr. Thomas Hultsch from our Clinical Research Department who will review the safety data on Elidel and Dr. Larry Eichenfield from the University of California San Diego who will discuss the current treatment options for atopic dermatitis. In addition to the presenters, we also have a few advisors with us

who will be able to answer specific questions that you may have. These are Dr. Raf Geha, Immunologist from Harvard Medical School, Dr. Eva Guinan, a pediatric oncologist at Boston Children's Hospital and Dana Farber Cancer Institute, Dr. David Margolis, Epidemiologist from the University of Pennsylvania and Dr. Felix Arellano from Risk Management Resources. In addition, we have Dr. Carle Paul, Medical Director of Elidel with us for answering questions. I would now like to turn the podium to Dr. Thomas Hultsch from Novartis.

DR. HULTSCH: Dr. Chesney, Members of the Advisory Committee, I would like to thank you for the opportunity to discuss with you the concerns about the potential immunosuppression and the risk of malignancies of topical calcineurin inhibitors.

Norvatis carefully monitors safety in large clinical programs and post-marketing surveillance. An analysis of this large database demonstrates no clinical evidence for increased risk of malignancies, no evidence for systemic immunosuppression based on pharmacokinetics,

immunocompetence in children and infections rates in children. Following the review of the data, I will address the large clinical programs in place to monitor long-term safety with Elidel.

Getting to the fundamental question, "Is there clinical evidence for an increased risk of malignancies?" To address this question, we will first assess the usage of Elidel today and then the malignancies reported.

In clinical studies over 19,000 patients have been treated. More than half of them were infants or children and some treated for up to two years. In clinical practice, over five million patients have been treated with Elidel. More than half of them were below the age of ten. The average patient in clinical practice treats intermittently for 45 days a year and uses less two grams a day.

Now let's look at clinical trials which provide the highest level of evidence because factors like under-reporting or surveillance wise do not come into play. Seven cases of malignancies were reported from clinical studies with over 23,000 patients,

Elidel plus Control. From 19,000 patients on Elidel, two malignancies were reported, both in elderly patients, none of them a lymphoma.

Of the 4,000 control group, five malignancies have been observed, a rate about ten times the one in the Elidel group. They included a case of an acute lymphatic leukemia in a five month old infant as well as a malignant melanoma in one adult patient, both treated with topical steroids. Clearly, data from clinical studies do not support evidence for an increased risk of malignancies in Elidel treated patients.

Now turning to the spontaneous reporting from post-marketing surveillance, there's a total of six reports of malignancies from over five million patients also having used Elide, four cases of lymphoma and two skin tumors. The fourth lymphoma case here is an unconfirmed, poorly documented case from outside the U.S. It is listed for completeness.

Focusing on lymphoma cases, here are the details. Two cases have been reported from adults over 50 years old, one case in a child. The

characteristics of these cases in terms of histology and localization are not typical of the lymphoma cases seen in patients with immunosuppression. Normally, you would expect B cell lymphomas as explained this morning by Dr. Cohen.

The usage of Elidel in these patients was not excessive based on the small body surface area treated in case one and the intermittent usage in case two and three. Based on the data, four independent oncology experts assessed the causal relationship between the lymphomas and the usage of Elidel to be unlikely.

Now what can we say about epidemiology. It limited because the numbers are small, but the number of reported cases of lymphomas is below the number of accepted cases. This slide shows the total exposure in the U.S. conservatively assessed being 732,000 person-years of which the majority occurred in children. The number of expected cases for the general population, 46 for all ages and four if we focus on children, is shown below. The number of reported cases, three versus 46, all focusing on

children, one versus four, is below the number of expected cases. Therefore, data do not support epidemiological evidence for an increased risk of lymphoma on any age group and clinically, we believe that one pediatric case reported from 2.7 million children treated is not a signal especially if the type is not the one associated with immunosuppression.

Now that we've reviewed the clinical evidence, let us examine the clinical plausibility of immunosuppression with topical cream while looking at pharmacokinetics, objective measures of the immune response and infection rates. When Elidel is applied topically only 0.02 percent reach the dermas.

What are the resulting blood levels? In pediatric PK studies described earlier today 75 patients, 366 samples and those were moderate to severe AD patients so they had a severely impaired skin barrier function. Sixty-eight percent of the samples were below 0.5 nanograms. Ninety-nine percent of the samples were below 2 nanograms and only in 10 out of 74 patients could we measure AUCs. These data show that with Elidel cream very low to nonmeasurable

blood levels are achieved in most children.

By using the highest AUC ever measured in the pediatric population provides the 38 nanograms hours per ml reference for the toxicology study that Dr. Hill referred to earlier. In these toxicology studies, doses resulting in over 1,000 nanograms per millimeter which is 27 times the highest pediatric AUC, not 17, administered continuously over 104 weeks did not show malignancies. So there are no malignancies in mice even when exposed for lifetime, 104 weeks at 27 times the single highest AUC in pediatric patients.

But what happens if higher exposure is forced with oral administration? Most toxicology studies are performed on rodents where a margin of about 25 or more of the maximum human exposure is considered to represent an adequate margin of safety. In an oral pimecrolimus monkey toxicology study explained earlier undertaken to further explore the toxicity of the molecule for an oral development program. AUCs around 1200 nanograms were achieved continuously for 39 weeks.

In these studies, immunosuppression related lymphoproliferative disease was diagnosed histologically in one out of eight monkeys in one out of 12 lymph node stations at the end of 39 weeks. The results in monkeys confirm the potential for producing lymphoproliferative disease with prolonged exposure at high levels of the drug previously reported in rodents. However, these exposures are not attainable with topical Elidel cream.

Now let's examine the impact of topical Elidel cream on more objective measures of the immune system in children. Vaccination, the data show that treatment with Elidel does not affect the B cell dependent vaccination response. Antibody titers from Elidel treated patients, infants treated for two years, are comparable to the titers reported in the literature. The ability to mount a cutaneous T cell response in vivo is typically tested measuring the delayed type hypersensitivity response. Again, data show that Elidel treatment does not affect this response.

In this control study, children were

treated for one year with Elidel or vehicle. Elidel treated children demonstrated a comparable recall antigen response. In all studies conducted, no evidence was found for an impact of topical treatment with Elidel cream on objective measures of the immune system. These findings are further reinforced in clinical studies.

This slide shows no imbalance of systemic infections in children. Displayed here is the relative risk for the most commonly reported systemic infections from all pediatric Elidel studies. Now the numbers as you will notice are different from the ones reported in the label earlier for two reasons, larger databases of January 2005 than for submission and time-adjusted analysis taken into account the greater exposure of Elidel treated patients compared to controls. In the control groups, more patients dropped out earlier from these studies.

If the box here is to the right of the zero value, this represents an increased risk or if it's to the left, it's a decreased risk for patients on Elidel. This is the law. Only if the confidence

interval does not cross the zero line is the trend significant. To make it easy, there are 12 boxes on the left side, 12 boxes on the right side and one exactly in the middle. This pattern provides no evidence for an increased risk for systemic infections with Elidel cream.

With regard to local skin infections, the data shows a similar picture, no increased risk for most skin infections except for virus skin infections where the relative risk is 1.6. This increased relative risk of 1.6 over placebo treatment not conventional treatment is already addressed in the label.

So overall, there is no data driven signal for an increased risk of malignancies. There is also no clinical plausibility for immunosuppression with Elidel cream. Yet Norvatis is still closely monitoring the long-term safety of Elidel. We have three on-going studies, two long term safety studies enrolling 3500 infants, five and six years of duration and a ten year prospective registry to assess risk of malignancies in children two to 17 years. It started

last November. Furthermore to be started soon, a controlled safety and efficacy study in HIV-positive patients and two case controlled studies to assess the risk of non-melanoma and melanoma in adults.

Taken together, the clinical data do not show evidence for an increased risk of malignancies. Systemic immunosuppression with Elidel cream is clinically implausible based on pharmacokinetics, maintained immunocompetence and the absence of an increased risk for systemic infections. In addition to the safety update presented which we believe shows the profile of a safe drug, an extensive clinical program is in place to monitor safety consistent with the recommendation of the Office of Drug Safety.

I would now like to turn over to Dr. Lawrence Eichenfield to compliment this information.

CHAIRPERSON CHESNEY: Could I just add for the Committee's information? There will be five minutes to ask questions after the next presentation.

DR. EICHENFIELD: Thank you, Dr. Chesney. I thank the Committee for allowing me to participate in the session. I'm a pediatric dermatologist out in

San Diego. I did pediatrics training and chief residency at Children's Hospital of Philadelphia. Then went on to do dermatology training at University of Pennsylvania and moved out to San Diego 14 years ago to set up the pediatric dermatology unit and have been fortunate to have developed a great interest in atopic dermatitis.

My task for the few minutes that we have is to discuss atopic dermatitis and its impact on individuals and families and the change in therapy that's happened with the introduction of calcineurin inhibitors. First of all, atopic dermatitis is a very common condition. This study from John Hanifin's group in Oregon showed that in five to nine year old school children, the prevalence of atopic dermatitis was 17.2 percent. This data as well as other U.S. data and data from other industrialized countries show a very consistent number of around 17 to 20 percent of children in the first few years of life having atopic dermatitis.

Atopic dermatitis is a complex disease with a complex immunologic basis. Much of the

pathology and consequence can be seen in the skin of patients with eczema, the redness, the papullas and plaques show the inflammatory component of the disease. We also see barrier dysfunction of the skin with dryness and scale.

Pruritis is a hallmark feature of atopic dermatitis. A common scenario that happens in my office pretty much every day is as a parent takes off the clothes of a child air on the skin is enough of a stimulus for that child to start scratching away. Pruritis and scratching that happens is something that can exacerbate the inflammation as well as the disruption of the skin barrier. Examining the skin is commonly colonized by staphyloccal aureus which is a common trigger for skin flares as well as super antigen stimulant and is a common problem with secondary impetiginization and cellulitus.

Atopic dermatitis is an inflammatory disease with a disordered immune response. In atopic dermatitis skin, there's a set of these inflammatory cells both Langerhans cells and inflammatory dendritic epidermal cells that are overly efficient presenters

of antigens. So these abnormal cells allow the skin system to be stimulated and it amplifies the skin inflammatory response. There is disruptive skin barrier function. Dry skin is common in atopic dermatitis and is a driver of itching.

Atopic dermatitis is linked to other atopic phenomena including asthma and allergic rhinitis and is also generally the first of atopic conditions to present. It's theorized in fact that skin inflammation in early life may rev up the systemic immune system allowing what's been called the atopic march to go forward.

There's a tremendous impact of atopic dermatitis on individuals and families. There's objective data showing tremendous impact on quality of life. I don't have time to go through the details, but just a month or two ago in the journal *Pediatrics*, Sarah Chamin from Chicago related studies on the significant impact of quality of life of atopic dermatitis on families. There is sleep disturbance, psycho-socio cost, high societal cost in terms of lost work time as well as a decreased performance at the

workplace and school place and of course medical costs involved including ER visits.

There's also a human effect. When we have patients who aren't functional, who can't go to school or can't go to work. I've had patients who've been on oral cyclosporin because nothing else could get them functional enough to get back to school and into the workplace.

If we turn back the clock to the last century before the introduction of the calcineurin inhibitors, you know 1999, what we had was a situation where there was a lot of under treatment of atopic dermatitis and certainly a lot of concern about the side effects of topical corticosteroids and a limited set of medications to use for atopic dermatitis. The calcineurin inhibitors have had a great impact on atopic dermatitis therapy. Patients and physicians now have a choice in addition to emollients and topical corticosteroids. The TCIs have allowed the ability to mix and match medications and allowed tailoring of treatment to disease severity.

There are parallels of atopic dermatitis

and asthma. They are parallels both in terms of epidemiology and pathogenesis but also in the evolution of therapy. Just as inhalants, steroids and non-steroid agents have allowed the ability to treat asthma with something other than intermittent oral prednisone so do the TCIs enable us to control eczema with a larger set of medicines.

The TCIs in clinical studies and in practice have appeared to be tolerated well. They are used with medication "sparers" standardly generally emollients. They're used intermittently in almost all patients. They have anti-inflammatory effect and also improve skin barrier function. They also decrease staph colonization and infection. At the beginning of clinical trials, we were looking for problems with systemic immune effects. Now we're beyond the trials and with millions of prescriptions and we've seen little evidence of them.

I worry about the under-treatment of eczema. Under-treatment of eczema can cause problems not only with skin inflammation and the disruption skin barrier also with cutaneous infection. Right

now, we have outbreaks of methicillin-resistant Staph aureus. They are community outbreaks in San Diego as well as in much of the country. Staph aureus is part of atopic dermatitis. Sixty to 90 percent of skin is colonized with Staph. We've seen MRSA in atopic dermatitis patients.

I worry that if we have more inflammatory skin disease out there untreated that it may impact on meth-resistant Staph with secondary problems with cellulitis and hospitalization and realize that we don't use topical calcineurin inhibitors there are other medicines that will have be used. We're not going to go back to emollients alone. There has to be anti-inflammatory care and remember that many of our patients have been on combination or exposed to medicines including systemic and topical corticosteroids, phototherapy and cyclosporin.

So the question that you'll be wrestling with the topical calcineurin inhibitors is there enough worry to warrant warning, watch the risk of lymphoma. It's a very hard question. The data presented on pimecrolimus doesn't show a direct risk

of lymphoma. There are case reports, but remember the concept of coincident events.

For those of us who are pediatricians, we're going to go back to our home institutions and in the next six months, there are going to be children diagnosed with lymphoma. Twenty percent of those patients will probably have had a history of atopic dermatitis because we have a one in five prevalence of atopic dermatitis and they probably will have been treated with topical corticosteroids and/or topical calcineurin inhibitors.

We really have to figure out. Is there an attributable risk and not just a concurrent? I'm concerned that aggressive labeling may lead to under-treatment of atopic dermatitis due to true and perceived risks of alternative treatments and that we may see an impact on this on our atopic dermatitis families with more inflamed patients and more burden of skin disease.

I thank you for your time and also for the commitment for balancing the concerns and needs for safety also within these patients, families and

physicians to take care of atopic dermatitis and minimize its impact. Thank you.

CHAIRPERSON CHESNEY: Thank you. These presentations are open for questions and I wondered if I could ask the last speaker if you've seen the same perceived increase in incidence of eczema herpeticum and shingles that Dr. Stern has seen and some of the others, some of the rest of us, who do infectious diseases have a impression?

DR. EICHENFIELD: Actually have not truly. The last two cases we had, one had no exposure to topical calcineurin inhibitors. One did have an exposure, but there are also cases of strep that can mimic eczema herpeticum. Realize if you look at that data on prior to the introduction of topical calcineurin inhibitors, there is a risk of eczema herpeticum as well. There are some people around the country who believe that there is an increase in that and when it comes to cutaneous infections other than viral infections such as Staph aureus and impetiginization, we have not seen that. If anything, there's a decrease and there's some data to support

that as well.

CHAIRPERSON CHESNEY: Dr. Fost and then Dr. Stern.

DR. FOST: A question for, I guess, Dr. Hukkelhoven. What is Novartis doing to encourage or discourage off-label use of this produce?

DR. PAUL: The promotional activities with Elidel are done according to the label. We make sure that the way the products attribute are communicated according to its label.

DR. FOST: Are do you doing anything to discourage off-label use?

DR. PAUL: Of course. As we encourage label use, we discourage off-label use. At the same time, we are committed to assess the risk of Elidel in patient under the age of two and we are conducting a large clinical program to assess the safety of this drug. We have two large studies as presented by Dr. Hultsch with more than 3,000 patients in order to evaluate further the safety of Elidel in patients under two.

CHAIRPERSON CHESNEY: Dr. Stern and then

Dr. Newman and then Dr. Glode and Dr. Gorman.

DR. STERN: I guess I had a comment and an observation and a question. My comment is that with respect to the data presented on the issue of cutaneous carcinogenesis there hasn't been either sufficient exposure, sufficient surveillance or sufficient time passed for us to even have a possible signal and we could talk later about the deficiencies as I understand it in your design to document that. But that's an unknown going forward and any data presented, we have three-quarters of a million person-year of exposure over three million people which is entirely irrelevant to what we have here.

In terms of your statement about no evidence of immunosuppression, I'd like to go to page 45 of your briefing document and one of the things as I mentioned earlier, I found the study published with the senior author an employee of your corporation and the first author a CRO employee. In that, you noted that there were two cases of herpes zoster. Yet in the same study in table 5.13, there's no mention of herpes zoster. Rather it's presumably but perhaps

subsumed under the incidence of chicken pox and varicella which also in these days of immunizations seem like pretty high numbers to me, 14 percent and eight percent in the first and second years of use. So I think when one looks for signals, one should perhaps look more finely and not aggregate data, one can often undercover things.

One other point is you're right that as labeled there is for intermittent use and short-term use I have relatively little concern about the long-term safety. When you present data from a population that is overwhelmingly dominated by people who have it short-term and intermittently, you won't discover whether people who have longer and more consistent use in fact are at increased risk. All of your strategies give us very big denominators of people not at substantial risk. That doesn't let us interpret and I'm worried about those what we might call in statistical parlance the outliers with respect to either underlying risk characteristics or larger exposures with respect to a mountain time and none of the kind of information you're doing is doing that.

Those are my concerns. And then the other side of course is with benefit. When we went through these agents in terms of benefit, how well did they work. We just heard a talk that made me think, "Boy, am I a crummy dermatologist. I should use these more often. Then all my people with atopic dermatitis who I've been treating, some of them for the last 31 years, they must be silly. They come back to me even though they all shop around. But some of them come back. Why don't I have them better?"

And the answer is if you look at least the information I've been able to glean about on average how potent are these agents relative to topical steroids. They are about as potent as triamcinolone, an intermediate strength topical corticosteroid with respect to at least short term and intermediate term efficacy at least as I read the studies. Maybe a little more. Maybe a little less, but they are not, if you'll pardon my use of the colloquial, knock-your-socks-off products for the great majority of individuals treated with them. There are always with any new agent the miracles where "I've suffered for

years and I use this and now I'm completely better." But if you look at all the data, they work about as well as triamcinolone and I think that that part of the benefit should be put in there.

DR. PAUL: May I have the opportunity to respond to the herpes zoster question?

CHAIRPERSON CHESNEY: Could I make a suggestion? Since we have already gone over our time for questions and we have three more and potentially more, I wondered if they could ask their questions. I think it would take you a day or so to answer Dr. Stern. So maybe we could hear the other three and then maybe you could give us a global response. Then we'll have to move on. So Dr. Newman and then Glode and Gorman and I think we'll have to stop at that.

DR. NEWMAN: Yes. It's a question for Dr. Hultsch. I really appreciate your slide CS-15 that had all the different systemic infections in the children with the point estimates in the 95 confidence intervals. But when I asked Dr. Nikhar about the same issue, she said that if you look separately in the children under two that in fact this picture would be

very different. I looked through and maybe I didn't find it, but I didn't see in the materials you gave us. Is there something like this either a table or a picture for the children under two to address this question?

DR. PAUL: We have the same slide for the children under two and the picture is very similar. What you should know is that the crude rates that were presented by the FDA are rates which are not adjusted for difference in time on study and especially in the infant study, the vehicle patients discontinued much earlier. So they stay in the study for a shorter period. In order to have an accurate comparison of incidence of detection, we had adjust for time on study.

DR. NEWMAN: That would be true if the FDA presented the results in person-time as opposed to just absolute rates. If they just give you 17 percent, and it was an intention-to-treat analysis, that wouldn't explain that.

DR. PAUL: It's a proved analysis. The denominator is not the same because Elidel patients

stayed on study on average 20 percent longer as compared to vehicular patients. So you need to adjust for the time they actually are on study using incidence sensitivity of Kaplan-Meier which are the appropriate methods. And these are actually the infant data, no the infant data slide please, which shows that in infants you have exactly the same picture as in older children with some systemic infections for which the rate is increased and some of which for which is the rate is decreased and there is no statistical significance actually between groups in terms of the incidence of systemic infections.

CHAIRPERSON CHESNEY: I think we need to move on but I'm relieved to see that there was very low incidence of tooth abscesses in infants. Dr. Glode and then Dr. Gorman and then we do need to move ahead.

DR. GLODE: My question, I think, relates to the same issue and it relates to Slide 16 which shows in the control trial a statistically significant increased incidence of viral skin infection which as you mentioned is noted on the label. I guess my

question is what is thought by the company to be the mechanism for a statistically significant increased incidence of primarily herpes virus infections of the skin. Why is the biologic plausibility not topical immunosuppression if you will or local skin immunosuppression or is it?

DR. PAUL: I think you are perfectly right. There is an increased incidence of some skin viral infection, mainly herpes simplex, but also skin papilloma. The relative risk varies between 1.5 and 4.0 and we attribute this to atopical immunosuppressive effect.

But if you look at what you have with topical steroids and we have a slide on a comparative study we did with steroids in adults, that's IF-22, you can see that the incidence of viral skin infections in patients treated with steroid is actually similar to what you observe with Elidel. On this slide, you see it's a 600 patient study and if you look at skin papilloma, actually the incidence was higher in the steroid group, triamcinolone as compared to the vehicle. So both topical steroids and Elidel

has a topical immunosuppressive effect. They both inhibit T cell function to the same level actually and if you want more information on that, maybe Dr. Raif Geha could provide some insight into the comparative activity of steroids and topical calcineurin inhibitor on the immune system.

CHAIRPERSON CHESNEY: I'm really sorry we have such a short time, but, Dr. Gorman, you can have the question for 30 seconds.

DR. GORMAN: Dr. Newman asked my question.

CHAIRPERSON CHESNEY: Thank you very much for your presentation. Our next presentation is from Fujisawa Healthcare, Incorporated and I believe Dr. Amy Paller will be the first speaker. I'll let her introduce the second speaker.

DR. RICO: Actually, I'm Dr. Joy Rico. I'm a dermatologist. I'm the Senior Medical Director at Fujisawa Healthcare in Chicago and I work in research and development for this product. It's my pleasure to introduce Dr. Amy Paller, my dermatologic colleague who is the Professor and Chair at the Department of Dermatology at Northwestern and also

Professor of Pediatrics at that institution.

DR. PALLER: Thank you very much and I'd like to thank everyone again for inviting to give our viewpoint and so I'll address Dr. Chesney and the group in saying that I present the viewpoint of a pediatrician and a dermatologist. I'm also President of the Society for Pediatric Dermatology. I have been a participant in trials testing both tacrolimus and pimecrolimus that started a good nine years ago. So my experience reflects treatment of many patients over that period of time.

I'm afraid I'm going to say many of the same things the Dr. Eichenfield said and just remind you that atopic dermatitis first of all is not a benign disease. This is an intensely itchy, often bleeding, painful relapsing inflammatory skin disease of children that affects up to 20 percent primarily starting in the first five years of life. As Dr. Eichenfield mentioned this has a severe impact on the quality of life not only of the effected children but of family members, particularly impacting on the ability to sleep at night, on the function at school

or in older individuals at work and also on social impairment. So treatment of this condition is important.

We do know that patients particularly with poorly controlled atopic dermatitis have a higher risk of both bacterial and herpetic infections of the skin and as Dr. Eichenfield mentioned a higher risk of developing asthma as well. I do want to mention that inflammatory skin disease and most notably cutaneous T cell lymphoma (CTCL) can be misdiagnosed as atopic dermatitis and one can have treatment for years with potent topical corticosteroids or calcineurin inhibitors and the diagnosis of cutaneous T cell lymphoma is missed.

Now the calcineurin inhibitors, Protopic and Elidel, are the only non-steroid topical options that we use regularly for treating atopic dermatitis. Treatment options do vary with different patient populations. So clearly not every drug or treatment works for all patients and some treatments may be contraindicated or not well tolerated.

Now as Dr. Murphy noted, topical

medications are designed to work at the level of the skin and we use them to avoid having to use the stronger medications like the oral steroids, like the cyclosporin that we have to use in our severely effected individuals who just don't respond even to the topical medications that we use.

Now in atopic dermatitis, in contrast to Netherton's Syndrome, in contrast to the rodent skin, where we see systemic absorption as Dr. Ghosh told you, we have seen minimal absorption into the blood or in most patients, undetectable levels. So I think we have to take care in extrapolating what we all know to be potential side effects from systemic administration of these calcineurin inhibitors in thinking about our patients who are having topically-applied calcineurin inhibitors for treating atopic dermatitis.

We do know that with topical corticosteroids that range from very mild to most potent topical corticosteroids, these have been the mainstay of therapy. They continue to be the mainstay of therapy for this condition. But we know that there are side effects. I feel like every other month I see

a patient with moderate topical corticosteroids who has severe stretch marks that I'm sure are related to topical steroids because they are exactly where we're putting them or have other evidence of thinning of skin.

So we do know that there are local effects from these and when we have to use the most potent topical corticosteroids, we know that patients are getting systemic absorption that we're not seeing the vast majority of our patients who are treating with calcineurin inhibitors. We're seeing growth retardation in these individuals and other signs of having a systemic steroid level. We prefer to use Elidel and Protopic intermittently particularly on the face and neck, these areas that are particularly sensitive to local side effects of topical steroids.

So Protopic and Elidel differ in their vehicle and in their indicated patient populations, but they really do show a similar safety profile and, Dr. Stern, I absolutely agree with you that these have a really broad use. The majority of patients now that I see referred in with atopic dermatitis have already

been put on one calcineurin inhibitor.

But in my experience in Chicago as opposed to the anecdotal experience of your residents with about 3,000 patients with atopic dermatitis seen every year in our very large volume pediatric dermatology group in Chicago, we have not seen an increase in the incidence of eczema herpeticum as compared with our years before these agents became available.

So as a pediatrician and a dermatologist, I really do care deeply about my patients and I appreciate the efforts that this group is taking to try to warn and be very careful particularly about the long-term risks that we don't know about at this point. But I have to be concerned about the conjecture about the safety of a topical agent versus the well-known side effects of their use systemically. I'm concerned that increased warnings could have the unintended effect of discouraging my patients from using this treatment option that we have and that this could lead then to the use of medication that we know can have increased side effects. This then will translate into either control with these agents that

have increased side effects or poor control of atopic dermatitis which in itself will as we know lead to increased risk of infections and also to the discomfort of atopic dermatitis. I thank you very much for your time.

DR. RICO: Next slide please. In the next few minutes, I'd like to share with you two important points and to remind you that Protopic has been an important and effective treatment alternative for patients with moderate to severe atopic dermatitis. Based on the data we've seen, there is no evidence of systemic immune suppression or an increased risk of malignancies or other diseases such as one would expect to see if we were having systemic immune suppression.

Protopic is an important and safe therapeutic option for patients with moderate to severe AD and I anticipate we may hear from patients later in the public comments section. As a reminder, the therapeutic options for patients who have this disease are limited with topical steroids being the mainstay of therapy and carrying with them risks of

their own.

In extensive clinical trials, over 19,000 patients have been enrolled globally in Fujisawa sponsored trials. Seventy-six hundred of those are pediatric patients. Over 8,000 patients in the United States were followed in a clinical study that lasted for up to two years. Another additional study followed over 300 U.S. patients for another three years. So we have an extensive database from which to draw from.

In those clinical studies, there was no signal of an increased risk of the types of systemic infections that have been reported in patients who are transplant recipients. The current product label does describe that in those clinical studies there was an increase in herpes zoster. There was no increase in herpes simplex. There was no increase in warts which are important markers also for immunosuppression.

In those clinical studies, there was no increased risk of malignancy. Additional studies have been conducted by Fujisawa that document no effect of

Protopic after topical application in patients with atopic dermatitis in the systemic immune response. Those include vaccination studies demonstrating the ability to mount immune responses to new antigens, in this case Pneumovax, no defect apparent in DTH (delayed-type hypersensitivity) responses and also laboratory analyses looking at B cell and T cell function.

A component of the pharmacokinetic and development program were the PK studies as described. In answer to Dr. Epps' question, additionally approximately 1700 adults and children had blood levels that were assayed during the clinical trial program. Those studies demonstrate minimal absorption after topical application of Protopic. Most patients have blood levels below 0.5 nanograms per mL. In fact, 86 percent of pediatric patients have levels below 0.5. To put that in context, trough levels, that is the minimal levels, seen in transplant recipients are maintained between five and 20.

Additionally, the bioavailability as described earlier today is 0.5 percent after topical

application of Protopic. There is no evidence of systemic accumulation if blood levels are observed, they appear early. They are transient and the dips appear with continued use. The absence of continued exposure mitigates against the potential of developing long-term immunosuppression and based on this minimal systemic absorption, the likelihood of systemic infections or malignancies is remote.

The Office of Drug Safety presented data earlier today about adverse events including adverse events in children less than two. Ten adverse events have been reported in total since the product launch in 2000. All except septicemia are in our current label. Malignancy reported events were also reviewed. Globally, the product have been associated with 19 post-marketing events. I shouldn't say associated. I say there were about 19 reported events totally. A causal relationship was not established based on the ODS review. I believe the more important place of focus is what we know about the transplant population.

Let's talk specifically about where we know there are known risks and in transplant

recipients, we know there are two types of malignancy commonly reported. Those are lymphomas particularly post-transplant lymphoproliferative disorders, commonly B cell and associated with Epstein-Barr virus infection. We also know from the transplant experience that skin cancers are also increased with long-term exposure and use.

If one looks at the SEER data for the malignancy rates in the general population, the age adjusted rate approximately 22 per 100,000. The non-melanoma skin cancer rates in children are negligible. The place where you begin to see skin cancer increase is patients after the age of 40 where a physician health survey data indicates a rate of approximately 533 per 100,000.

The total number of malignancies reported in 1.7 million patients treated with Protopic since product launch in the United States includes 11 lymphomas and 16 non-melanoma skin cancers. The lymphomas reported specifically are not the type associated with transplant experience or PTLD. There have been five non-cutaneous malignancies reported in

total. That's in clinical trials and post-marketing safety and there have been six reports of cutaneous T cell lymphoma including the child that was described earlier.

Patients with cutaneous T cell lymphoma present with a recalcitrant, inflammatory dermatitis. The onset of symptoms to diagnosis averages 6.2 years in the studies by Epstein et al. And additional studies have suggested even longer. So it's very important to think about the context of these patients.

CTCL is not associated with immunosuppression. Non-melanoma skin cancer is also important because squamous cell carcinoma is known to be increased in patients who have lichen sclerosus et atropicus, balanitis xerotica obliterans which are essentially premalignant conditions. Important to note also is that within the global database there have been no reports of lymphomas or non-melanoma skin cancers developing in children under the age of 16. These data demonstrate no increased rate of malignancy for patients treated with Protopic compared with the

expected rates in the population.

The Protopic label currently contains significant information that is appropriate regarding precautionary use. The product is labeled for patients over the age of two. Additional statements are in there regarding the animal carcinogenesis and photocarcinogenesis data. The evidence that has been presented and discussed today does not indicate immune suppression or an increased risk of associated diseases including malignancy in treated patients. If changes to the label are recommended for this product class, it's important that the information reflect our current scientific knowledge and that the information must balance the risks and benefits for this important therapeutic class of agents.

In summary, atopic dermatitis is a serious, life-altering disease. Treatment options are important for physicians, parents and providers to determine appropriate therapy for their patients. The topical calcineurin inhibitors have been extensively studied in clinical and post-marketing studies and those data to date have indicated no evidence for an

increased risk of systemic infection or malignancies.

Fujisawa is committed to the safety of patients and appropriate communication with patients, parents and healthcare providers. We welcome the opportunity to be here in participating in this meeting, but we additionally have continued to try to further understand all of the safety issues associated with the use of this product.

As a component of that, we have asked a number of external experts with expertise in specific fields to review the reports and review the ODS data and review our internal data. Those consultants are here with us today so that if you have specific questions around these particular areas they may help to address them. They include Dr. Samuel Cohen from the University of Nebraska who have specific expertise in animal models of carcinogenesis, Dr. Michael Green from the Department of Pediatrics Infectious Disease Group who has expertise in PTLD and Epstein-Barr virus, Dr. Peter Heald, a dermatologist from Yale with expertise in cutaneous T cell lymphoma and Dr. Annette Stemhagen, a fellow for the International Society of

Pharmaco/epidemiology. I welcome your comments. I appreciate the opportunity to have addressed this group. We appreciate the opportunity to participate. Thank you.

CHAIRPERSON CHESNEY: Thank you, Dr. Rico. We have five minutes for questions. Dr. Stern, then Dr. Andrews.

DR. STERN: I have two questions. I think you brought up the key point as I understand these deliberations which is good information and balanced information for the prescriber and you indicated your company's commitment to this. I don't mean to single out your company out from the other company that's here. But in fact, yesterday just before I left, I got a mailing and I said, "Maybe this hearing has been canceled because the issue's been resolved." The mailing from Fujisawa was entitled, "Facial Atophic Dermatitis: Is there a Safe Effective Therapy for the Long Term?" And inside it turns out that I'm invited to participate in a web-based learning exercise with someone who would talk about severe facial atopic dermatitis, an adequate control and side effects with

topical steroid treatment.

Now I think that tends to put an emphasis as I read it on the safety of your product versus fear about the use of topical steroids. I think this is a lot about informational bias about the kinds of information that have made prescribers and patients think that this is as safe as Diet Coke. I'm not sure. We live in a PC world. Right? I'm not sure that's what's occurring. The question is how to resolve that. That's my comment.

My question to you is as a dermatologist if locally applied calcineurin inhibitors do not give local immunosuppression how do they act and does one not believe that prolonged local immunosuppression in areas of chronic sun exposure over a lifetime are likely to develop more cancers sooner.

DR. RICO: My answer as a dermatologist is that I do believe that there are local activity of this product class. There's clear data. If you go and look actually in our briefing document, we alluded to some of those studies. Thomas Bieber, others, have been working in this particular area to talk about the

fact that in patients who have atopic dermatitis there is disregulation with the expression of high affinity IgE receptors for example on Langerhans cells. One of the ways in which topical tacrolimus may be having an activity is it down regulates that aberrant expression.

Do I believe however that the ability to present antigens is impaired with the intermittent topical use of these products over time? Absolutely not. If that was true, I would have expected to have seen a greater increase signal for warts, for other viral infections and those have not been seen in the clinical studies or in the post-marketing data presented to date.

CHAIRPERSON CHESNEY: Thank you. Dr. Andrews, Dr. Epps and Dr. Gorman and then I think we'll have to move ahead.

DR. ANDREWS: Great. I have a comment and then a question. The comment relates to actually both sets of recent presentations and I think what we've seen is that there may be a lack of evidence from clinical trials and spontaneous reports about an

increased risk, but I would take issue with the comment that there is evidence from that experience of a lack of risk.

I say that relating to spontaneous reports because I think that there was a comparison of the observed spontaneous reports against those cases of cancer that might have been expected in the general population. That assumes that there would be complete reporting of cases of cancer. I think that when you have a long latency period which we have heard for both skin cancer and lymphoma and different physicians who treat these two conditions, then it is highly unlikely that these events will be identified associated with a prior topical exposure and reported. So I would not conclude that lack of evidence means that there is demonstration of lack of effect. There may be no lack of effect. I'm not questioning that.

And then regarding clinical trials, I didn't hear in either of the sets of presentation what the average duration of follow-up was on patients in the clinical trials, whether there was sufficient follow-up in order to detect increases in cancer risks

and could we stratify that information as I think Dr. Stern alluded to so that we could look at the risk of patients with high doses and exposed over long durations of treatment.

DR. RICO: To address those two issues, one Fujisawa has a long-term commitment or commitment for a long-term safety study. We received final comments from the FDA within the past ten days and that study will initiate very shortly with appropriate expertise and a number of people involved in the design of that study. That's a ten-year multi-national, 8,000 patient, registry type study where we will have that long-term follow-up.

I did comment that we have data on 8,000 patients in one study who were followed for out to two years, another study with 878 patients who were followed for up to three years. We have paper in press that evaluated looking at specifically the patients over the age of 40 looking at patient years exposure to demonstrate that in that cohort there was no increased signal for non-melanoma skin cancer which is the one that we were particularly focused on.

CHAIRPERSON CHESNEY: Thank you for your pointed and brief answers. Dr. Epps and Dr. Gorman and then we'll move on.

DR. EPPS: My question was about immunizations. I've always been a little bit concerned about immunizations at under age of five and certainly under two or one. Most children are immunized properly. You mentioned Pneumovax. Were other immunizations looked at such as HBV? People immunize with hepatitis B. Now also for varicella.

DR. RICO: The study that we conducted was done with Dr. Richard Stiehm at UCLA. He's a very well-known allergy immunology guru. That study involved taking children who had moderate to sever atopic dermatitis, putting them on therapy. After three weeks, they were then immunized and we looked for post-vaccination immune response. We chose Pneumovax because we were wanting to look at a new antigen as opposed to a potential vaccination that children had already been exposed to. In that study, all of the children who were immunized developed protective titers. That study has been accepted for

publication and should be in the blue journal, *Journal of American Academy of Dermatology*, very soon.

DR. EPPS: Will there be a long-term follow-up just to make sure there's no loss of immunity?

DR. RICO: We have not undertaken a long term follow-up on that study yet. I appreciate, but that is the result of the study. It was a short-term study.

DR. EPPS: Also briefly, when you had your trials, were patients admitted to the trials sequentially or did you exclude people with warts or exclude people with certain conditions?

DR. RICO: No, there were no exclusions for underlying skin conditions.

CHAIRPERSON CHESNEY: Dr. Gorman.

DR. GORMAN: I think all the careful clinicians in this room would be hopeful that their topical medications stayed topically. But sitting in this room in the Food and Drug Administration, I'm aware that there's a large number of therapeutic agents that are applied to the skin for systemic

absorption. Your own speaker spoke to the fact that, your own dermatologist, that topical steroids are expected to affect topical and yet they have systemic effects that we can measure very rapidly because growth in children goes on continuously. So you can measure an interruption pretty rapidly.

I'm trying to draw an analogy from my own deliberations as we go forward. What fraction of people who have topical steroids develop systemic effects so that we can try to understand size of population we're going to need to look at to look at a potential effect for these agents?

DR. RICO: I think one of the other issues that comes up with topical steroids is that there are varying classes. There are actually seven classes with Class 1 steroids the most potent being those most commonly associated with the immunosuppression or with the metabolic and other side effects. There are studies that have been published about that. That's not my area of expertise and in fact, I'm wondering if my derm colleagues might like to comment on what those studies show for those patients.

DR. WILKIN: We have two locally-applied corticosteroid groups of products, the inhalers and for those products we can actually get growth suppression kinds of studies because the same product can be used over a sufficiently long period of time that measurements can actually be made. For most skin diseases, the process waxes and wanes sufficiently that it probably would be unethical to demand that a child would stay on the same steroid clean at the same potency. There might be days when they would need something with lower potency or days with higher potency. Then it would be very difficult to go back and say "Whatever you saw gross suppression wise is related to a particular product."

The pulmonary group, I think, believe that the gross suppression is actually the most sensitive way of looking for systemic events. We have HPA access suppression. We typically look at that at three or four weeks, continuous therapy. We use Cortisen (PH) stimulation. We use slightly different criteria than in the Cortisen labeling. We use the 18 number.

Basically the higher potency

corticosteroids often it's half of the subjects will have suppressed at three weeks. Lower potency sometimes none of the patients will have suppressed at three or four weeks and we conduct these studies in patients that have involved skin, large body surface area. So for many of the lower potency there's not that much of a signal.

DR. RICO: But in the higher areas.

DR. WILKIN: In the higher potency, absolutely.

CHAIRPERSON CHESNEY: Thank you very much. We need to move on to the open public hearing and we do have seven speakers, each one of whom will receive five minutes to speak and two comments about that. First of all, for those of you in the room who didn't receive the materials for the open public hearing, they are available at the front desk outside. Secondly, Dr. Johannesen will be using an automatic timer. So when you see the orange light, that means you have one more minute and he will actually turn off the speaker at five minutes.

First, I need to read something for all

the public speakers. 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 session of this Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include a company's or a group's payment of your travel, lodging or other expenses in connection with your attendance at this meeting.

Likewise, the FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it

will not preclude you from speaking.

Our first speaker is Dr. Daniel Yarosh. I will let him disclose his relationship.

DR. YAROSH: Good afternoon and thank you very much for this opportunity to address you. My name is Dr. Daniel Yarosh. I am President of Applied Genetics Inc. Dermatics which is a biotechnology company in New York and our specialty is DNA repair. I'm going to be presenting data. None of the data has been the result of any outside funding from either industry or government and our company has no financial interest in the outcome or success or detriment of either of these drugs. What I want to focus on today is the effect of these topical immunosuppressants on DNA repair.

So we've already discussed that these drugs fall into the class of calcineurin inhibitors. There are two general types of drugs that we talk about here. One is cyclosporin which is used systemically and then there's a family of drugs. The main compound is called ascomycin and tacrolimus and pimecrolimus are derivatives but these all have very

similar structures and they differ from cyclosporin. They have different binding partners within the cell, but nevertheless their target is all the same, calcineurin.

We know from studies in transplant patients that when these drugs are used the rates of skin cancer rise dramatically beginning in the years after immune suppression and rising to almost 80 percent in Australia after 20 years. So our company began to ask the question "Do these drugs have an effect on DNA repair in addition to their effects on immune suppression?" And what we have found is that these drugs do in fact inhibit DNA repair.

The study that is presented here I will be describing, this first set is called dot-blots and here we take keratinocytes and I want to emphasize that these are keratinocytes. These are the cells of the skin. These are the first living cells to see the drug when it's applied topically. If you UV irradiate keratinocytes, purify the DNA and blot it to paper and then apply antibodies against DNA damage, clyclobutane pyrimidine dimers, you can light up

spots.

So this represents the amount of DNA damage introduces to these cells from 500 joules per metered squared of UVB. This is a dose of UV which is in the range of an MED or a sunburn. Many of use get much more than this when we go to the beach. If you wait 24 hours, you see the diminution of the signal.

This represents DNA repair which goes on in each one of our cells. However if you pre-incubate these cells with one microgram per mL of cyclosporin for even an hour or twenty-four hours prior to UV irradiation then removal of DNA damage is inhibited. These doses of both cyclosporin and ascomycin that I'll be talking about are one microgram per mL and the doses that are used topically are between 1,000 and 10,000 times higher.

Not only do these calcineurin inhibitors, cyclosporin, inhibit DNA repair, but this is also true of ascomycin. So this is now a summary of additional studies which show that there's a significant increase in DNA damage persisting after doses of ascomycin or

cyclosporin compared to untreated cells.

We are also concerned not only with the persistence of DNA damage, the inhibition of repair, but also the inhibition of apoptosis. Apoptosis plays an important role in prevention of skin cancer by eliminating cells from the skin that are irreparably damaged. Here apoptosis is measured by the widely used marker called caspase-3 and using 500 joules per metered square, again it's a physiological oops, a physiological dose. You can see increase in caspase which represents the induction of apoptosis but in cells treated with one microgram of mL of cyclosporin or ascomycin, apoptosis is inhibited.

Let me remind you then that the combination of persistent DNA damage and the inhibition of apoptosis are clearly established as the early steps of skin cancer. This has been summarized as long ago as the *Scientific American* article available to the general public in July of 1996. These are clear steps in the development of skin cancer.

Let's now turn to what's available to the

public as far as animal carcinogenesis studies. Cyclosporin has been strongly linked to animal carcinogenesis in many different studies, most recently published in January of this year. I call your attention to a publication 2003 in which tacrolimus accelerated skin carcinogenesis by DMBA, a different kind of carcinogen. So it's been established that topical tacrolimus can accelerate carcinogenesis.

Let's us now turn to the photo carcinogenesis studies. One study was submitted for each NDA of tacrolimus and pimecrolimus that's accessible to the public. Both studies were flawed because the vehicle alone accelerated carcinogenesis. It is impossible to judge the carcinogenic potential from these studies in which the background noise drowns out the signal. These are insufficient studies to conclude anything about safety from animal studies.

If we turn to what's available to the public for human safety studies, the published studies are underpowered to detect changes in skin cancer. The number of patients is irrelevant. It's the number

of patients in a protocol which is powered correctly to be able to detect skin cancer. There is no published studies that can eliminate the possibility of skin cancer being induced.

To give you some sort of background or point of reference, transplants became widespread through the world in about 1965. The first report of increased skin cancer in the medical literature appeared seven years later in 1972. So it took seven years for the medical community to recognize the dangers of systemic immune suppression in skin cancer.

Let me finally then point out the risk of childhood exposure is particularly important. The cumulative UV exposure over your lifetime is a risk factor for skin cancer and especially squamous cell carcinoma. When you inhibit DNA repair, it is equivalent to increasing the dose of UV that you give and of special importance in childhood, childhood UV exposure and the number of painful sunburns before the age of 15 are independent risk factors for basal cell carcinoma and melanoma. These are well established risk factors.

I remind you that we're not talking about people who get a sunburn and get a skin cancer when they're a child. We're talking about people who get a sunburn under the age of 15 and then have an increased risk of skin cancer when they're 40, 50 or 60. Thank you very much.

CHAIRPERSON CHESNEY: Thank you very much, Dr. Yarosh, and we gave you an extra few seconds because we had trouble with the slides in the beginning. Our next speaker is Dr. Robert Silverman from the American Academy of Dermatology Association.

DR. SILVERMAN: I have a quick question for Dr. Yarosh. Is erythromycin a macrolide and in this class of ascomycins?

CHAIRPERSON CHESNEY: It is a macrolide.

DR. SILVERMAN: It is a macrolide.

DR. YAROSH: I do not believe its target is calcineurin.

DR. SILVERMAN: No, I'm not saying that, but it's in the same chemical class.

DR. YAROSH: It's a broad class. Anything that is cyclical is a macrolide.

DR. SILVERMAN: Okay. Thank you because I was wondering if you could erythromycin as a control for all of these studies, an antibiotic that we've had for decades. I need help with the pharmacology. My name is Robert A. Silverman. I'm appearing on behalf of the American Academy of Dermatology Association. Thank you for giving me this opportunity to speak to you about the issue of a potential cancer risk among pediatric patients treated for atopic dermatitis with the class of drugs that I call topical immunomodulators, not immunosuppressants. It's like calling Rogaine, Dr. Stern, Rogaine an antihypertensive medication.

I'm a clinician who has been practicing in pediatric dermatology for nearly two decades. My office is in Fairfax, Virginia and I'm also on the clinical faculty at Georgetown and at the University of Virginia. Nearly twenty percent of my pediatric dermatology practice time is spent caring for patients with atopic dermatitis or its complications. Although I have participated in Phase 3B clinical trials in the past with one of the medications, I'm currently not

participating in any pharmaceutical research and no one has paid me to be here today. Until last year, I had been on one of the speakers forums for one of the companies, but I have not spoken for them this year.

Atopic dermatitis is not trivial. Poorly controlled atopic dermatitis is associated with significant morbidity and pain and suffering as you already have heard. When the epidermal barrier of the skin is broken by scratching, the resulting open wounds weaken the skins natural protective properties and lead to frequent cutaneous bacterial and viral infections. You've heard that.

This is particularly important now that we get these children in control because of the emergence of community-acquired methicillin-resistant Staph aureus infections which are prevalent in many cities around this country. It's the duty of this community to clarify the as-yet unproven potential malignancy risks and weigh it against the proven evidence-based outcomes for this class of drugs. To do otherwise would be a disservice to atopic dermatitis patients and their families and all of the healthcare providers

that take care of them.

I want to point out that the post-marketing surveillance of topical immunomodulators has uncovered only a handful of isolated specific adverse events that with the exception of a few were non life threatening. Unfortunately, the evidence that has been presented online as a synapses has been taken out of context by the press in an article published in The Post and perhaps other papers this last Saturday. This will no doubt create a period of unfounded hysterical fear among patients and families who rely on these medications every day to treat their skin disease.

The possible development of some of these adverse events was predictable and clearly stated in the product packaging inserts while others were unexpected. And unfortunately for the purpose of this hearing, these few unexpected cases were incompletely investigated and reported as possible or probable adverse events when other explanations unrelated to this class of drugs were equally as plausible.

If you haven't already done so, you should read every one of those adverse reaction reports that

prompted this meeting. There aren't that many. I hope that your decisions are based on solid facts and not fear and not anecdote and not incomplete information.

If the FDA requires a black boxed warning on the labeling for this class of drugs treatment options for young atopic dermatitis sufferers will undoubtedly be limited by fear. The black box also is a faulty educational tool when based on unproven and suspected risks, just suspected risks. All right. Indeed it would be nice to compare the relative risk of malignancies from topical immunomodulators to the adrenal suppression of topical corticosteroids, the only reasonable therapeutic alternative for treating atopic dermatitis.

Finally, physicians who treat children less than two years of age with atopic derm are in a Catch-22 position now. At least 80 percent of patients with atopic dermatitis have their disease onset before the age of two years. Yet the only proven therapy for these young infants is application of topical corticosteroids which are absorbed easier

perhaps and potentially have a higher risk benefit ration than topical immunomodulators that are not approved for this age group.

So in closing, let me say that the health, safety and well-being of millions of children with atopic dermatitis are at stake. I believe that a forum for continuing education about topical immunomodulators is warranted. There's no question. However, a black boxed warning about a presumed or inferred association of topical medications, immunomodulators, and cutaneous malignancies at this time without further documentation of true cause and effect I think would be a disservice to everyone involved.

I'm sure that members of the Society for Pediatric Dermatology, the American Academy of Dermatology and the section on Dermatology in the American Academy of Pediatrics would be willing to work with you to develop an appropriate action plan once the facts really known. With this in mind, I'd like to again urge the Committee to focus only on the proven facts. We might have to find some more facts

but focus on those and not suspected risks when deciding further regulatory actions if further regulatory actions are needed. Thank you.

CHAIRPERSON CHESNEY: Thank you very much, Dr. Silverman. Our next speaker LaDonna Williams from the Inflammatory Skin Disease Institute.

MS. WILLIAMS: Good afternoon. I'm speaking to you today because I'm a parent and I want to thank you for allowing me to address this Committee and no one has paid me to be here today. I graduated from nursing school and specialized in pediatric nursing. I did clinical pediatrics for almost seven years and then I began to have children of my own, three as a matter of fact. Two have full body eczema also known as atopic dermatitis. So I'm here today for two reasons and they are Shelly and Zack.

Nothing, absolutely nothing in nursing school or in the pediatric clinical arena prepared me for the disease atopic dermatitis. The pain, the rash, the chronic itching of the rash, the sleepless nights, it all took a toll on our family with Shelly and Zack only having to wake up the next morning and

face the same day with the same rash, the same itch and the same discomfort.

They also had to face the ridicule because they looked so bad. Their appearance was different from others. They heard names like "walking scab" and "disease girl." They were unable to be included in their peer social activities because of their appearance and they became withdrawn.

My children are older now and they still fight the every day constant battle of atopic dermatitis. As a parent, I am thankful for Elidel and Protopic. These drugs are the first treatment to offer my children an effective alternative to oral or topical steroids. We are all familiar with the adverse side effects of long-term steroid use. My children have a better quality of life because Elidel and Protopic provide effective relief from the constant itch and discomfort.

As a parent, I hope that other children will have this same opportunity. I urge this Committee to please weigh the evidence very carefully before making any decisions or taking any action.

Thank you.

CHAIRPERSON CHESNEY: Thank you very much. Our next speaker is RuthAnn Newton also from the Inflammatory Skin Disease Institute.

MS. NEWTON: Good afternoon and thank you for the opportunity to speak. I'm the Assistant Director of the Inflammatory Skin Disease Institute. ISDI is dedicated to improving the lives of people with inflammatory skin disorders. We're a not-for-profit organization and we're funded by private and corporate donations including Fujisawa and Novartis.

Inflammatory skin diseases affects men, women and children of all ages and races. As you know, one of these inflammatory skin diseases is atopic dermatitis and that's why I'm here today. Millions of Americans suffer from atopic dermatitis. Most people may think of AD as a little rash behind the knee or on the elbow when in fact it can be a devastating serious medical complication for some.

These are the people that I work with at ISDI. We provide education awareness and patient advocacy. Our support groups offer an opportunity to

communicate with others and it's through the support groups that I'm familiar with Elidel and Protopic.

Not only have I heard about the improvement in the patient's atopic dermatitis, I've seen it. Elidel and Protopic have not only provided relief and a better quality of life for patients, it's provided relief to the whole family. There's no cure for atopic dermatitis. At this point, Elidel and Protopic are the best treatment alternatives to the oral and topical steroids.

Please consider the value of these treatments. Consider the potential impact of a black boxed warning. It's my fear that this could set treatment back decades. A black boxed warning could take a successful treatment away from many patients. Elidel and Protopic are improving the lives of people with skin disease. Thank you.

CHAIRPERSON CHESNEY: Thank you very much. Our next speaker is James Hendricks from the National Eczema Association for Science and Education.

MR. HENDRICKS: Good afternoon. My name is Jim Hendricks and I'm here speaking on behalf of

myself and the National Eczema Association for Science and Education. I have no personal conflicts of interests with any of the products being discussed here today.

The National Eczema Association for Science and Education has received donations in the last five years from the following business entities: Beiersdorf Kinetics, Fujisawa Healthcare, Galderma, GlaxoSmithKline, Johnson & Johnson, Ligand, Novartis, Ortho-Neutrogena, Proctor & Gable and United Parcel Service. I am here as a volunteer and have paid my own way to participate.

The term eczema is used to describe all types of skin conditions. I am here to tell you about one of these conditions more specifically known as atopic dermatitis. This type of eczema is something that a person is genetically predisposed to. It can start and stop at various points in one's life. For many people, it begins shorting after birth and lasts their entire life.

The primary symptom is dry, itchy skin that can cover the majority of the body. The itching

is so severe and intense that it not only affects the person's every waking moment and every attempt to sleep. It can also lead to serious infections, disfigurement and emotional distress and in some cases premature death.

The worst part is the itching. The person with atopic dermatitis is tortured throughout the day and night and is thus handicapped in their efforts to lead any type of normal life. My daughter has this condition and from age two to age 15, her life and her family's life were dominated by dealing with her consistent itching and resulting condition of her skin. She took three baths a day to hydrate her skin. She tried various antihistamines, sedatives, antibiotics and homeopathic substances.

When she tried to sleep, she did so with gloves and socks pinned onto her pajamas in a futile attempt to keep her from getting at and tearing her itching skin. The entire family was awakened almost every night not only by concern for her situation but also by the sounds of her distress.

She had to be careful about what food she

ate, what clothes she wore, the places she went and what activities she participated in. She could never be sure of how her skin conditions would present itself from moment to moment. We visited or contacted almost every pediatrician, dermatologist and allergist in the area and spoke with several specialists throughout the United States and several other countries.

My daughter actually learned to lower her body temperature by several degrees through biofeedback. We went to Children's Hospital in Washington, D.C. and spent a week at Johns Hopkins. No matter where we went the doctors and specialists had no good answers.

To alleviate the stress of this condition and to reduce the itching, a person with atopic dermatitis can turn to oral or topical steroids for relief but the side effects run from bad to worse. Most doctors are hesitant to prescribe corticosteroids for that reason. If they do prescribe them, it is only for a very short duration, maybe a two week course when a patient is at the breaking point of

dealing with their condition.

Such was the struggle until a few years ago when Elidel and Protopic became available. These medications have given patients with atopic dermatitis some relief for a tortured existence that most people just can't imagine. I do hope that access to these medications will not be jeopardized in any way without full consideration of the relief that they have provided to millions of individuals with atopic dermatitis, their families and their loved ones. Thank you.

CHAIRPERSON CHESNEY: Thank you very much. Our next speaker is Dr. Vincent Beltrani from American College of Allergy, Asthma and Immunology. We'll move on then to our last speaker, Dr. Eva Guinan from the Dana Farver Institute, is Director of the Bone Marrow Transplant either unit or laboratory there and I will let her explain in more detail.

DR. GUINAN: Yes, I actually was not on your schedule. I was asked to come here by Novartis having been asked to look at some of their oncology cases and that is the context of my being here. The

reason that I asked Dr. Chesney if I could speak was that in listening to today's comment, I was just struck by two issues and asked if there was any opportunity to make a clarification of two things.

One is that Dr. Cohen in his excellent review this morning suggested that ATG injected locally would be a local topical immunosuppressant and tried by the analogy to focus on the issue of topical immunosuppressants as compared to the TCIs you've been thinking about. I wanted to make the point that in fact there is zero data that ATG is a topical immunosuppressants. I don't think that's an adequate parallel.

In fact, ATG is a local stimulant. It's an immunoadjuvant in a lot of ways and while it can clear T cells systemically, it actually is a B cell adjuvant. It's a B cell mitogen that is known to cause B cell non-Hodgkin lymphomas and the transplant literature is rife with the examples of this. It is contraindicated in circumstances where you have an increased risk of lymphoma and has been largely replaced in programs for that reason. I think

therefore that one has to think that data in a somewhat different context than it was presented.

The second point that I wanted to make is that you've hear some very stirring and concerning anecdotal case reports of a variety of things including drug levels. As someone who struggles with calcineurin inhibitors daily usually in oral or IV format in much larger doses, I just wanted to caution people that interpreting these cases in the absence of understanding concomitant medications and conditions is really fraught with danger.

I think Dr. Wilkin made the point excellently about the case where there was Netherton's for example that one needs to have all the information at hand before assuming truths about levels and so forth so that presence of steroids, the presence of azols, the presence of other drugs and conditions will have significant impact on drug levels and therefore the implication that can be drawn about the causality of those findings. Thank you.

CHAIRPERSON CHESNEY: Thank you very much. Obviously it's now time for lunch. I'm just trying

to weigh the five questions which we've been asked in addition to more presentations this afternoon with the potential need for some members of the Committee although we were warned to have late flights. I know that some of us have flights at 7:30 p.m.

If you don't mind, I think we should try to be back here at 1:30 p.m. as scheduled. Thank you. May I remind the Committee members that you should not talk to each other or to anybody else about the substance of the meeting over the lunch period. Thank you.

(Whereupon, at 12:57 p.m., the above-entitled matter recessed to reconvene at 1:34 p.m. the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:34 p.m.

CHAIRPERSON CHESNEY: I'd like to start with having Dr. Marilyn Pitts speak very briefly to one of the questions which was answered earlier and that has to do the cancer risk relative to topical steroids and apparently they have looked this in the AERS system since the 1960s. I think Dr. Pitts is coming to the podium to respond to that question and then we'll move ahead.

DR. PITTS: Thank you. Actually, what we did was we queried the AERS database for all of the cancer-related adverse events reported with all of the topical corticosteroids and that database goes back to 1969. We found two poorly documented cases. One was an adult that reported that her psoriasis turned to cancer and the second was seven month child.

CHAIRPERSON CHESNEY: Thank you very much. Also as we're waiting for our next speaker to come to the microphone, Dr. Glode just pointed out to me that the January 20, 2005 issue of the *New England Journal of Medicine* has an article entitled "Today's FDA" which has a subsection based on post-marketing surveillance which is an issue we addressed in some

detail yesterday. Our speaker is Dr. Anne Trontell and if you wouldn't mind reintroducing yourself to everybody please.

DR. TRONTELL: I'll be happy to. I don't have access yet to my slides. I'm Anne Trontell I'm the Deputy Director of the Office of Drug Safety in the Center for Drugs Evaluation Research at FDA.

CHAIRPERSON CHESNEY: We could read your slides to you if you'd like.

DR. TRONTELL: Thanks. Good afternoon. I'm going to be speaking and providing a framework many of you may have heard before in earlier versions about the (Pause for technical difficulties.) Thank you. I'm going to provide some framework for some of the discussion that you'll have at the end of the presentations today about considerations in the use of what FDA now terms "Risk Minimization Action Plans" and I'll be speaking out the context of what is currently a draft guidance from the Agency on these kinds of plans and also to FDA's experience in implementing them.

I'm going to start with some definitions

of risk management and risk minimization and then talk about what we term "Risk Minimization Action Plans," when they might be needed and what you might consider in designing, implementing and evaluating and then again, speak somewhat to our experience with these programs.

Risk management as the Agency considers it is an overall process of assessment of the benefit/risk balance for a drug product and then as necessary the use of some kind of tool to minimize the risks that might be associated with that product and to also preserve access to its benefits. This in turn necessitates some evaluation of those tools and whatever impacts they might have upon the risks and benefits of that product which then gets reassessed and feeds back to where you started from.

Risk management then is a two part process that entails the process of risk assessment and then efforts to minimize identified risks. These are clearly very interrelated concepts. They can occur with information derived from the pre-marketing and post-marketing arenas and ideally both are best done

with an evidence basis to them. Clearly, we are in much better position to talk about risk minimization efforts if we have a common foundation in the kinds of risks that we agree need to minimized.

There are now three guidances in draft form from the Agency in the general topic area of risk management. We hope to have them available in final form too. The one that I'll be speaking to mainly is the one on development and use of risk minimization action plans. It's two companion pieces on pre-marketing risk assessment and on good pharmaco-vigilance and pharmacoepidemiologic assessment again form the basis for many of the risk minimization efforts discussed in the risk minimization action plan draft guidance.

Now we came up with this term risk minimization action plan in the draft FDA guidance to make it clear what was risk management in the overall process from the actual interventions that you might undertake to minimize risks. The abbreviation that I'll use in my talk interchangeably for risk minimization action plan is a RiskMAP.

I think the key question is what turf are we on when we start to talk about invoking something that we would call a RiskMAP. Unfortunately, we don't have a strict criterion or criteria to guide us. We do have a number of considerations that we set forth. Those include the nature of the risks and their known rate and severity and how those might compare to the benefits of the product.

We also looked closely to see what the risks are and whether or not they might be preventable. Obviously, it's easier to minimize risks if you can have some mechanism to intervene, to avoid them or perhaps mitigate the extent to which they occur. Clearly, the benefit enters into the decision about how you bring upon such plans.

The comparison of risks and benefits is complex. I think many in this room already appreciate that. We have no ready formula. They're often measured in different units. So we to date largely make case-by-case decisions within the Agency about when some form of active risk minimization is necessary.

That actually reflects what the Agency suspects will be its general practice which is such plans would probably be used judiciously probably for a select number of products where we're talking about a close balance of risks and benefits. We expect that for most products risk minimization will be done in routine fashion as it currently is using the package insert or product labeling.

And as a reminder the package insert is a form of FDA-approved product labeling again used by many but chiefly targeted to health professionals which we have termed the cornerstone of risk minimization and risk communication. We are invested heavily along with the drug company sponsors in making sure the information is this labeling is complete up-to-date, to include new benefits as well as new risk concerns as well as some ongoing efforts to try and make this information particularly salient to healthcare practitioners so they can readily locate information and a personal plea to make the font bigger. However, for purpose of this discussion, we draw a distinction. The routine labeling activities

are not what we consider a RiskMAP.

We define a Risk Minimization Action Plan as a strategic safety program. It's designed to meet what we term goals through a series of component objectives and that's to minimize known risks of a product while preserving its benefits and that the action plans as I've described will use one or more tools.

Now let me just define these terms. The goal is really the end result of what you hope to achieve relative to a risk of a product. It's typically and ideally expressed in terms of one or more health outcomes, one that you might wish to achieve or one that you might in fact wish to avoid. The objective would then be some component step toward the goals, some intermediate step. I'll give an example in a minute. A tool would be some system or process that was put into place that would be used to achieve an objective or the overall goal.

Let's take an imaginary example just for illustration purposes. One goal might be to say that a dangerous drug/drug interaction should not occur.

Objectives, steps that you might employ to achieve that goal, would be to direct efforts to physicians so that they would not co-prescribe those two drugs.

Alternatively, you might have an objection to speak to pharmacists to try and minimize co-prescribing of those products or you might again try to speak to patient populations to enlist them in avoiding the concomitant use of those two products. Tools could take the form education or some alerts to pharmacists the time of prescribing or dispensing so that the products wouldn't be given out together or there might in fact be some felt need for some restriction on physicians or others, again back to what I said before about the nature and severity of risk. You might use more or less stringent tools depending upon the consequences of this drug/drug interaction.

Let me now talk some about how one might go about selecting risk minimization tools. They come in the broad category of what we would consider a form of specialized communication, again more than the labeling that FDA uses on a regular basis to tell

clinicians or patients to do something or to not do something and try to make it pertinent so that behavior is followed. But in some instances, risk minimization tools might actually involve some alteration of what the typical chain of prescribing, dispensing and use might be. That might be via some reminder system, a so-called "voluntary approach" or some restriction "involuntary."

In the draft guidance, FDA described three broad categories of tools. They are somewhat fluid in terms of whether you might put one particular tool in one or another. They include targeted education and outreach, reminder systems or performance-linked access systems which I'll define further.

Broadly, targeted education and outreach serve the purpose of informing individuals of risks or of activities they should do to avoid risks. The reminders systems really remind me in some ways of the light on your dashboard that reminds you to belt your seatbelt. It's a little reminder, a little nudge to do to what should be safe. The performance-linked access systems are really designed to try and put an

obstacle to unsafe use, a real block to that.

Now again, these definitions are little bit circular. When might you think about going to targeted education and outreach? The situations might be you actually have evidence that current labeling through the product has not been successful in communicating the risk measures. You may have experience with another or related product. So in those instances where conventional means don't appear to work, this is what we suggest people think about again with the goal to increase the knowledge of key stakeholders who have the capacity to intervene or prevent or mitigate product risks.

Examples again might make it a little clearer. These include such things as healthcare practitioner letters, professional or public notifications, sometimes specialized training programs for prescribers or for patients, these might take the form of continuing education. In some instances, product promotion may have a particular focus or might be limited largely to a certain professional of sub-speciality and we include in this category patient

labeling which includes medication guides and patient package inserts (PPI).

Just to briefly recapitulate, these are two forms of FDA-approved product labeling for patients. Medication guides have been under FDA's authority since 1999. Medication guides are distinctive in that they are required to be dispensed to patients with every prescription and they intended primarily for outpatient prescription drug products where there's deemed to be a serious and significant public health concern.

There are three criteria set forth in regulation. At least one of these must met in order for a medication guide to be considered. They include the possibility that patient labeling could help prevent the occurrence of a serious adverse event or they may serve the purpose of risk information where a person may need to know this information to make an informed decision about whether to initiate use or continue use of a product. A third criterion could be that instances of products used for life-threatening conditions where use of the product is critical to its

effectiveness that a medication guide might be set forth. There are actually specifications within FDA regulations about the content and format of these designed in a way to enhance comprehension and also the prominence of the important safety information.

The other form of patient labeling that FDA approves is the patient package insert. This is not covered by regulation other than for oral contraceptives and estrogen products. These are not required to be dispensed with each prescription but in practice these days, most patient package inserts closely adhere to the medication guide format in content. We found that generally well accepted and well understood. When products are packaged in unit-of-use packaging, the distinction is somewhat lost to the patients getting it with each dispensing.

Let me now turn to that second tier of tools what we call reminder systems. These are often used along with targeted education in those instances again where experience directly with that product or another appear to be insufficient to minimize risks. These again have the goal to prompt or remind or have

some double-check mechanism to guide healthcare practitioners and patients in using the product. I sometimes have said this is just really to make it hard for people to forget as we all recognize information overload in the short time frames of many physician/patient/pharmacists encounters these days.

Some examples of reminder systems include what we've called patient agreements or acknowledgments. Some have actually used the term informed consent where in fact the patient is informed about the risks of the product and may sign or initial. Other forms of reminder systems might include some mechanism where the prescribing clinician is required to attest that certain safe use conditions have been employed, that necessary screening, patient selection, whatever has been followed.

In some instances, the reminder systems may actually attach to the product or the conditions of dispensing it so that the packaging might be configured in some way to remind people to use the product appropriately. It might be limited in amount so that misuse is more difficult to happen. Supplies

actually of the product might be limited or refills might be limited or even banned. In some instances, systems of records have been established to remind the various components and the prescribing chain that appropriate safety measures have been taken. So there are two systems in place now involving stickers where there's an added station by the clinician that it's okay to dispense that product and the pharmacist looks for that sticker to assure that appropriate risk minimization is in place.

Now we've called the last broad category of tools performance-linked access systems. Some might think of these in a closely-related term which is restricted distribution. But we use the term performance-linked access systems to really describe the process whereby access to the product is tightly linked to some form of compliance with something we believe will be increasing the safe use of that product. These are used in the situation when other tools appear to be insufficient to minimize the risk. These are applied to a very small number of products currently and typically they're products where there

is some significant or unique benefit but there is also unusual risks associated with that product, those risks possibly being fatal or irreversible.

The drug product access is in fact as I said tightly linked so that there may be some requirement that documentation of patient conditions, of laboratory monitoring and so forth might be put in place. These systems are involuntary in the sense that they're supposed to be somewhat last step. The pharmacist needs to have a phone call, an authorization number.

In the case of clozapine, an example that I have here, there has to be documentation of an adequate white count before the pharmacist is supposed to dispense that product. Some of you may also be aware of the drug product, thalidomide, where there are programs in place to minimize pregnancy exposures and again that requires actually registration of all of the members of the prescribing chain, both clinicians, pharmacists and patients and inputs to assure all parties that appropriate pregnancy testing has been performed and negative. Dofetilide is yet

another product and anti-arrhythmic where are concerns about appropriate monitoring and renal function necessary for dosing.

Now I have taken this heuristic of tools, goals, objectives and put forth what I'll frankly admit are candidate RiskMAP goals that might considered for the calcineurin inhibitors. Please don't consider your further discussions in any way limited to what I put here, but again to give some framework.

If you're thinking about a goal of these products to communicate the risk and make sure that individuals using them have some level of acceptance related to their potential tumorogencity, one might state that goal as no one should prescribe these products or use them without full awareness and acceptance of their potential tumor risk. An alternative goal or a companion goal might be to say we want to minimize risk of this product. That might be by trying to minimize exposure with the goal that we decrease risk of calcineurin-associated tumors arising in patients who are being treated for atopic

dermatitis.

Now following in the parallel to how I've laid these out, you might articulate some objectives and these will also show how where you put a tool in one category versus another is open to some interpretation. If the principal goal is to alert individuals to the risk to make an informed choice, obviously activities with education and outreach would be one mechanism to do so, patient labeling speaking to prescribers, to pharmacists. There might also be reminder systems to individuals along with the product that would say "You really shouldn't be using this in a long-term situation unless you have reason to believe that the risks are warranted for the benefits you expect to achieve."

If we're looking more toward the overt minimization of risk, we might think of objectives that would somehow constrain prescribing or dispensing of use to those atopic dermatitis patients where there might be some agreement based upon your input that the benefits are likely to exceed the risks. It might just in fact be those individuals who have poor

responses to other therapy. Would there be some form of education or outreach that would be done to make individuals aware again of what are the best candidates for this therapy? Or might there in fact be some kind of reminder or restricted access system put in place?

This text is a little bit fine, but again in this area of talking about alerting individuals to risk you could conceive of doing a healthcare practitioner letter, a PHA would be public health advisor, some explicit education of physicians, a medication guide and so forth. There could be what again we call a reminder system. You might ask for some form patient agreement or informed consent where the patient would acknowledge that their use of the product is fully informed about its potential risks. There might be even perhaps some limitations placed upon the amount of product, the tube size or whatever or the refills to again prevent the chronicity of use where individuals might imagine there would be greater risks.

Now in the second category, again we're

trying to limit exposure to those individuals where benefits would be expected to exceed risks. There could be activities. This would not be strictly a RiskMAP, but speaking to the package insert, some change in the warnings, inclusion of a boxed warning or making an explicit second-line indication for atopic dermatitis would again be one way to try and constrain exposure and minimize risk by that means.

Reminder systems again as I said before could involve actually some greater difficulty to individuals using those products for a long period of time without close medical supervision. You could imagine as exists for some products there might need to some requirement for physicians to attest that in fact the severity of atopic dermatitis warrants their use.

When one were to think of restrictions that could be put in place, one might imagine ways to try and constrain use so that individuals only greater than a certain age were allowed to have access to the product or individuals with a certain level of disease severity. Perhaps individuals with specialty training

or its equivalent experience in the diagnosis of atopic dermatitis would be candidates for some kind of limited program such as that.

Now in thinking of tools, we have some broad principles because again our experience with these programs is limited. Clearly, our goal in all of this is really to maintain what access to this product is appropriate so that individuals can continue to achieve benefits from their use and that in talking about such programs or any efforts to seek to design them would actually speak to key stakeholder groups, individuals in fact such as yourselves who can speak to the examples of healthcare delivery, prescribing the nature of practice, how such programs or tools might be feasibly employed in a day-to-day basis. This is really to minimize burdens and increase compliance by whatever means so then in fact these operate relatively smoothly.

Other considerations would be to consider current technology. Certainly as information sharing or electronic prescribing becomes more widespread, there may be opportunities again to build into such

systems reminders or prompts as I've already described. Again we need to bear in mind that a substantial amount of healthcare occurs outside of urbanized settings. Individuals who have out-patient or in-patient access to these drugs really need to be considered.

Probably what's listed near the end of list, but clearly very important, we really would like as much as possible to use systems that we have some reasonable expectation of effectiveness either based upon experience with another drug product, in a related area, related to physician/practice/patient practice changing patient or physician behavior. Again wherever possible, in putting in a system, try and think of the larger ecosystem of healthcare in which these operate since the possibility of unintended consequences is there. A restrictive system can in fact prompt work-arounds and individuals may in fact get products without any form of sanctioned information or monitoring.

A plea in all of these is as these programs are developed certainly if anyone is going to

the effort to institute a risk minimization action plan, it's vital to collect information on how these programs and their tools are performing. First and most importantly, we would like to make sure that the health outcomes that we've agreed upon or our goals are being achieved and that we're putting in our energy into those tools that are effective. This could involve not only evaluation of health outcomes, sometimes process measures, but stakeholder acceptability even in those design phases are very important. This information, I think, is important to feed back to the Agency as we all become a learning community about how best to institute such programs. Clearly, we all eager to identify areas of improvement.

In terms of some of our experience and lessons learned, in the area of the targeted education and outreach, we've done a number of patient package inserts and medication guides. There are any number of products that have had "Dear Healthcare Practitioners" letters. There's limited evaluation that's been done at that particular category of tools.

Reminder systems are relatively infrequently employed as we might so designate them. They include Lotronex or alosetran, isotretinoin, lindane where product is to be dispenses in only one or two ounce aloquots to prevent overuse of product, abarelix where there's a patient agreement and other ways to try and constrain use to individuals only with advanced prostatic cancer.

The performance-linked access systems include bosentan for pulmonary hypertension, clozapine the antipsychotic associated with agranular cytososis, Dofetilide, mifepristone or RU-486, thalidomide or xyrem. The ones that have the asterisk there are ones in fact where some form of confirmatory laboratory testing or result is required for paretic access to take place.

When we look at the broad category of tools involving education and outreach, we can identify some broad advantages and disadvantages The advantages of education, it's clearly a well-accepted means of communicating with healthcare practitioners as well as to patients in this information age. So

clearly, acceptance runs high. It's also something that really has almost no or very limited effect on access to the product. So it's readily feasible and achievable. To do it right obviously requires some skill.

Disadvantages however in our mind really reflect the limited knowledge that we have about the effectiveness of these education/outreach tools in actually modifying behavior. Instances of their being evaluated are somewhat limited and those have been disappointing or mixed in their results in terms of actually changing prescriber or patient behavior. Certainly, in what is probably a very difficult aspect of human behavior to modify that involving pregnancy prevention, that's certainly shown less than stellar results in the previous program to the SMART program for isotretinoin. It's been documented in trying to enhance monitoring of liver functions for troglitazone that it was also met with limited change in the practicing community.

If we look at the reminder systems, you know we go up one tier in terms of being a little bit

more intrusive on the system. Individuals bump up against something they're supposed to do, a piece of paper to sign, what have you. There is still however an opportunity for autonomy on the part of the physician, the pharmacist and the patient and in fact, these reminder systems really do give you another opportunity to reeducate and remind individuals about why this program is in place. So it's more intrusive than education, but certainly much less intrusive than those programs that actually overtly restrict distribution.

There are increasing costs associated with putting in such systems. The evaluations that have been done to date have to my knowledge largely been limited to the two sticker programs that exist. We are facing somewhat unusual results as we look at those systems. The program called SMART for isotretinoin in fact and evaluated by many individuals here as part of the Dermatologic Advisory Committee just about a year ago showed in fact very high process compliance with the sticker system well in the 90 percent. However, in terms of outcome effectiveness

pregnancy exposures continued at approximately the same rate as prior to the implementation of that program.

In contrast for the drug product Lotronex or alosetran put in place to prevent complications of treating irritable bowel, there's been a satisfying low rate of complications of ischemic colitis and no deaths. However measurements of whether or not the stickers are being used on routine basis are actually much less than has been seen for the isotretinoin program, more in the 70s to 80s percent with some change every month, people prescribing that product less frequency.

The last category of tools that we talk about, the performance-linked access systems, again advantages to this is that it really does for those instances where you feel it's absolutely critical that a system be followed to assure safe use as in the case of blood monitoring for clozapine, access is in fact largely limited to those situations. The added benefit of having such systems is that they actually do give you better data on whether or not they're

working because they have a mandatory nature to their participation. To make sure that all the information is collected before someone receives a product, you typically have registration of the various components, the physician, the pharmacist and the patient, and we in fact have for these paradoxically some of the best evaluation information that we have.

However it's also important to recognize if the goal is to try and restrict use to a select population just by the administrative burden alone you're likely to inhibit use. That may however work to your disadvantage if there are individuals who might really benefit from this product who are unable to reach it. Clearly there are burdens on the healthcare in costs as well as time expended.

This gets to the issue of what I described earlier as unintended consequences. You may in fact prompt some form of illicit access to the product without the safety measures that you would wish to have employed particularly in this age of the Internet where people may attempt to obtain products through that mechanism or others. These programs have largely

been employed for just a select number of drugs and generally not in products that are widely used. So I think we'll be eager to see how well or how workable these are in our increasingly electronic environment as they might be applied to other products.

So in summary, the risk minimization action plans that you may wish to consider as part of your deliberations about these two drug products, RiskMAPs as the Agency has at least conceived of them and described them are likely to be used for a relatively small number of products. Again at least a starting point if not the endpoint for risk management and risk minimization remains the package insert.

In setting these up, I think it's probably easiest to talk about the goals and objectives before we get into the weeds of the particular tools that you might set about to achieve those. What do we really want to do in terms of what are the appropriate patient selection or other factors that you would like to establish. In setting these up, try as much as possible to employ tools that have a good evidence basis for their effectiveness, that would allow

continued product access that's appropriate and that in fact considers stakeholder input from the healthcare community as well as technological and other factors that are pertinent and to also seek those that are valuable and can be monitored for their impact.

These are references for anyone who wishes to look at what are currently still the draft guidances on risk management from the Agency. Let me know introduce Melissa Moncavage who is a group leader from the Division of Drug Marketing, Advertising and Communication with special expertise in the area of direct-to-consumer advertising.

MS. MONCAVAGE: Thank you, Anne. Good afternoon. I'm the Leader of the Direct-to-Consumer Review Group in that long-named division. We usually call it DDMAC just for short. I'm just going to give you a very quick overview of how we do business and hopefully I'll even be able dispel a few myths about prescription drug promotion.

First what exactly do we regulate? FDA regulates prescription drug promotional labeling and

prescription drug advertisements. Promotional labeling are the pieces that a company disseminates itself. So it includes a broad range of products or pieces of promotional material, everything from a monograph perhaps all the way down a pen that you might pick up in an exhibit hall and all materials in between, brochures, pamphlets, price lists, calendars, etc.

Then we also regulate advertisements which are specifically those ads you see in newspapers, magazines, journals, on TV and hear them on the radio and so forth. We regulate that promotion to both the healthcare professionals and to consumers.

So what tools do we have to do this? Well, first we have the Food, Drug and Cosmetic Act and Parts 201 and 202 of the Regulations. That's really the basis for our regulatory work and sets out the standards for how we look at promotion.

Then I should say the first and second items are our primary tools. The second tool is the approved product labeling for each specific product. We look at promotion in terms of what is in the

labeling to determine whether that promotion is indeed consistent with what is in the labeling.

If there are claims in promotion that outside the labeling they are generally references. We can look at those references and determine whether there's substantial evidence to support the claim in the promotional piece and then also to be sure that it is not inconsistent with what is in the approved labeling.

So what are the standards? Generally, you can only recommend or suggest the drug for an indication or use that is in the approved labeling. The promotion may not be false, misleading or lacking in fair balance of benefit and risk information and prescription drugs are unique in that there is a requirement to disclose the consequences of using the drug. That means that disclosing the risks about taking this product.

What's false or misleading? Actually the regulations specify about 33 different ways that an ad can be, is misleading or may be false or misleading. I'll simplify it for you. Does the ad present the

product in such a way that it makes it look like it's better or more effective than is actually indicated? For instance, if a product is approved for moderate to severe pain? Is the ad somehow implying that it's also used for mild pain when actually there is no evidence to support that?

Does it imply that the product can be used in a broader range of conditions or with a broader range of patients who are actually proved to use the product? For instance, if a product can only be used in certain population, then the promotion itself should state that. Does the product compare itself to other products in its class and indicate that it's better or safer than that product when there is no substantial evidence? Is there somehow a misleading presentation of data in the promotion or does the product just imply in general that it's safer than it actually is by minimizing the risks or downplaying the number of people who actually might develop some kind of side effect from taking the product?

These are some of the things I'd like to make clear today about how we regulate promotion and

what our jurisdiction is. First, there is really nothing to prohibit direct-to-consumer promotion. That's one question I'm often asked. Why is this allowed? There's no prohibition in general and there is no prohibition for specific product classes or specific drugs.

So if the product has a boxed warning which is very serious, that can promoted to consumers. If a product is a controlled substance, that can also be promoted to consumers. But of course, we would always want to ensure that that important information is conveyed in the promotion.

Second, there is no distinction between how we look at or the tools that we use to regulate promotion directed to healthcare professionals and promotion directed to consumers. We use the same laws and regulations and we use the same labeling. Now sometimes there is also patient labeling and that is also very helpful for us especially in terms of recommending or looking at how information is conveyed in language that's appropriate for consumers, but that is not always the case.

And third, there is no preclearance or preapproval of promotion. One thing our Division does is when companies request and send us proposals to look at and advise in advance before their promotion is in the public domain, we will provide comments. But that really is voluntary. There's no requirement except when that piece is disseminated to the public or when that ad is actually printed in a newspaper or magazine. There's no requirement before that time to submit promotion to us. So when you see an ad in the magazine or on TV or in your journal, medical journal, that may also be the first time and is likely the first time that we also see that ad because that is the time the company is obligated to send it to us at the time it's in the public domain. The onus then is on the Agency to review those ads and determine whether they are in compliance with the laws and regulations and the onus is on us then to take action if we think some kind of action is necessary.

I'm going to go over the three most common types of promotion that you might see. We have help seeking, reminder and full product ads. The help

seeking ads are ads that don't mention a product name or a specific drug. They just generally talk about a condition or a disease and they talk about what the symptoms are and then suggest that the viewer or the consumer go talk to their healthcare provider about treatment options. These are not drug ads. In fact, we do not have jurisdiction over these ads because they're not drug ads.

Second, there are reminder ads which mention the name of a product but they don't make representations about the product. They may talk about perhaps the administration and dosing forum and perhaps the price, but they're not supposed to give you any indication about the risks or benefits.

Because they don't make benefit claims, they're exempt from disclosing the risk information. The one exception is that products that have boxed warnings cannot promote through the use of reminder ads or reminder labeling because the risks are so serious that it's important to disclose those all the time.

Then we have full product ads where claims

or representations are made that trigger requirements to truthfully disclose the benefit and risk information about the product.

This is an example of a help seeking ad. The product name is not mentioned. The company name is on the ad but it talks about the condition and then going to seek help, "Talk to your doctor if you are feeling this way," in this case, depression.

This is an example of a reminder ad. The name of product is in the ad but there is no representation about the product. It does say, "Go talk to your doctor for more information." Just as an aside, we do always encourage kind of a call to action to have consumers go and talk to their doctors about prescription drugs. So this is fine.

The third example is the full product ad. In this case, it's the two page spread for Zocor and imagine those pages side-by-side. What you see here is quite a bit of text and generally on the left side, the left column, is the discussion about the benefits of the product. On the right side is discussion about the risks of the product and what side effects you

might have by taking the product.

So with the full product ad, what communication requirements are there? First, you must communicate the indication accurately and include limitations to the indicator or context for any claims make about the indiction. For instance, it may be that your product should be given in conjunction with diet and exercise and if that's an indication, that would also need to included in the promotion.

You must disclose important information, what we call "material facts." They may not be omitted from the promotion. That may include important risk information or in some instances for instance if a product is administered in an unusual way relative to taking a tablet or capsule, for instance you need to go in for an infusion for several hours, we might say that that is a material fact that would be important for somebody to know about taking this product.

Then you must disclose risks about your product and communicate the most important risks in a manner that is reasonably comparable to the benefit

information. That is done in the presentation, the actual presentation, and in the language.

I mean by presentation what we hope we really don't see is a little chicken scratch in the bottom left-hand side of the page or a print ad. It's hard to read. It doesn't have good contrast. We would expect that there's some kind of reasonable presentation of the risk information to draw attention to it to insure that consumers are able to find it easily and understand it.

In terms of language, I'm talking about especially direct-to-consumer promotion considering the audience and what the appropriate language would be to insure that consumers understand the risks that are being disclosed in a promotional piece or in an advertisement. So we do encourage consumer-friendly language. That is taking that technical language, medical language, and translating it into something that is consumer-friendly, but also truthful and overly broad or somehow misleading.

So what risks actually have to be disclosed in promotion. Generally, you will see the

most serious and common risks from the approved product labeling. Those are most likely to be disclosed. However, you probably know that promotion comes in an infinite number of shapes and sizes and so there is not really one size that fits all. Sometimes we'll need to look at the promotional piece itself, how large is the piece, how much benefit information is presented, to help us make the determination about whether there is actually comparable risk information being presented. If you have a multi-page brochure, you might expect something different than you would in a one-page print ad or in a 45 second TV ad.

We think about the audience and what's relevant information to the audience and whether it's a language that can be understood. There are some risks that are clearly directed only to the prescriber that probably would not be useful to a consumer especially in something like a broadcast ad where there is such limited time anyway to disclose the risk information. Then we look at the totality of the ad just to kind of the gestalt about whether there are underlying deems or so or just little hints of

repeated suggestions of implications that might somehow sway the comparability of the risk and benefit information. That's essentially what we've called DDMAC 101 presentation in a nutshell.

CHAIRPERSON CHESNEY: Thank you very much. You don't have any requirements about speed of presentation, do you? I love it in the ads. You make that headache or that brain tumor blah, blah, blah.

MS. MONCAVAGE: No, the regulations don't direct that. There is nothing specific about speed, but we certainly think it's important to be able to understand what is being said.

CHAIRPERSON CHESNEY: Thank you very much. Questions for Dr. Trontell and Ms. Moncavage? Dr. Fost.

DR. FOST: Ms. Moncavage, it's clear that the products we discussing today are being used on a wide scale outside of the package insert. Clearly they are being used on the zero to two age range and for many, many patients for whom they are not being used as a second-line drug. This is the story of the FDA. This is the SSRI story, the Vioxx story.

Approval is sought for a very narrow indication from which you really can't make very much money and then somehow a way is found to get it to be used on a very wide scale outside of the indication.

You've list ways in which it would be illegal to do that and my question is how did we get from A to B. How did these products get from a narrow set of indications to being used on a wide scale outside of those indications? Is it by violating rules that are not being enforced or is it because the rules are inadequate to stop that? I don't know any other alternative.

MS. MONCAVAGE: I don't know the answer to your question but I'd like to just say that we are not, just to be clear, we can't discuss promotion that is in the public domain unless we've taken enforcement action on it.

DR. FOST: Right. Do you have knowledge of ads for these products, CME presentations, that are funded by the company of direct-to-consumer ads? I don't have them in front of me. I didn't see them in the materials. Do they exist and are they as part of

your office's assignment to check such things and see if they are in compliance?

DR. MURPHY: I'd just like to step in for a second here and say that we ask them to present not because we found something that we're trying to tell you that we're not telling you. They were asked to present so that you would understand what the implication of doing anything to the label would do the marketing. Let me just make it clear. They can't talk about their interactions and we really did ask them to come to present for just that reason. We're going to be talking about changes to the label and what effect any of those changes might have.

DR. FOST: I understand that. Can you help me understand how these drugs come to used? I'm guessing the average pediatrician in his or her office doesn't read Archives of Dermatology. So how do these drugs get to be used on such a massive scale? What are the techniques that the company has used to promote or to enable or to encourage or to facilitate the widespread use off-label?

DR. MURPHY: I would say first of all just

again because I know not everybody was here yesterday where we stated it that we don't regulate the practice of medicine as you know and therefore the things that we as physicians are all familiar with in promotion go on. I have no knowledge as to how "- I've been away from pediatrics now for seven years so I can't tell you what the detailing is.

I think maybe somebody else would like to just talk about, in general, how we think off-label happens which is that a product gets approved as you said for a very narrow indication and people because of literature, because of other needs, will use the product as a physician in any way they think they have to. We've all done it.

CHAIRPERSON CHESNEY: Dr. Gorman. Dr. Newman. Mr. Wilkin first and then Dr. Gorman and Dr. Newman.

DR. WILKIN: I'm not sure about pediatrics and allergy, but I do know that it's well established in dermatology off-label use. If you have a product and you believe it's safe and effective for a condition other than for which it's labeled, it ends

up getting used. If you just look at all the dermatologic indications and then look at the drugs that are available for those indications, those are not congruent Venn circles.

Quite literally, I would say there's a need to practice off-label to practice good dermatology at least in some aspects. You can't take that and look at the contrapositive and if you're practicing off-label on every occasion, that is probably not the best practice.

But I do think dermatologists do feel somewhat comfortable in part because of the necessity. I would guess pediatricians may well. We know in the past there really has not been that kind of good quality information about drug products available to pediatrician. So my guess is that qualifies as a form of off-label use.

There are a lot of very enthusiastic publications which show up in the peer-reviewed literature and very often they'll talk about new indications that are not yet approved by FDA. There may be foreign articles which show up in our

literature which are not even studies that are under INDs that we've had a chance to look at. I'm not commenting about either of the two products. I'm just giving you an example of what I see, the overall view on this.

These particular products there are articles in the allergy literature. There are lots of articles in the pediatrics literature. There are certainly a lot of articles in the dermatologic literature that are very enthusiastic.

I think that it's very difficult ultimately to sit back and know what is in the heart of the investigator who's writing. Is this enthusiasm because they think they've found something new that's really needed for the public health or is this some form of premeditate, calculated, coordinated use of weapons of mass promotion.

One never is really going to know but what we can do at FDA and what the Committee can do is we can look at the content of those materials. We can make some estimations as to what impact it might be having on the practitioners. That's the context in

which we can view perhaps needed labeling changes.

CHAIRPERSON CHESNEY: So we have a new WMP, Weapons of Mass Promotion. Dr. Gorman and then Dr. Newman.

DR. GORMAN: I dread going after funny people. But I'm going to just step into a single advertising question. Certain symbols in our society become associated with certain objects. If I said "Golden Archs," I suspect most of you would think of a certain fast-food restaurant and a big "E" you'd think of a large energy company which is now defunked.

How would a little flying man with an E on his chest be regarded in the promotional world? Is that a help-seeking, a reminder or a product claim when this symbol in my pediatric practice has been associated where the children that come into the practice recognize that little person? I'm not sure if he has a name or not, but the flying guy with the E.

MS. MONCAVAGE: How would it be regarded? It depends on the context that it's in. I'm not quite sure what you mean. Will it be a help-seeking "-

DR. GORMAN: One of the two products under consideration today has a very mind-changing advertising program which is professional as well as direct-to-consumer where it has a little flying man with an E that the children in my practice recognize. So if you just had a balloon at a park with a flying man with an E and it was promotional, would it be help-seeking, a promotion or a product claim because they'll be able to say the name of the product?

MS. MONCAVAGE: I did say I can't talk about. That's a hypothetical about a real product.

DR. MURPHY: Melissa, basically I think he's asking, and just correct me if I'm wrong here, if it just has the logo and nothing else, it would come under a reminder, wouldn't it?

MS. MONCAVAGE: It depends. If there's no drug name. Generally, a reminder has a drug name.

DR. MURPHY: That's what I meant.

MS. MONCAVAGE: If there is no drug name.

DR. GORMAN: It would be to the reminder stage. It's like golden arches makes you think of McDonald's. This would make you think of the product.

DR. MURPHY: If the product name was on it. I think what she's trying to say is if it just has the little guy who looks like one of those new characters the "Incredible" or something.

CHAIRPERSON CHESNEY: He looks like a flying man.

DR. CUMMINS: Can I just add to that? In our discussions with DDMAC about this presentation, one thing I really came to appreciate, the nuance process they go through in evaluating drug marketing and it's not a simple "This is this and this is that." It's very nuanced and it's almost impossible to put Melissa in a position of opining on an opinion.

And I also want to mention that the reason we wanted her to present this overview is so that you all would be aware of how decisions and opinions and advice that you give us might affect the product label and how changes in the product label influence the way the product is marketed. That comes from the fact that at the last few meetings that we've had where we've discussed safety issues, the Committee themselves has spontaneous brought up issues about

marketing of products and so we thought it would be helpful for you to have some framework and have an understanding of how the Agency itself approaches the oversight of drug marketing.

CHAIRPERSON CHESNEY: I think that has been very helpful. Dr. Garfalo from the industry perspective and then I haven't forgotten Dr. Newman next, Dr. Diaz and Ms. Knudson.

DR. GAROFALO: So I'll just step in briefly, dangerously, from my perspective and that is that of course it is highly regulated and of course it's very nuanced having been on the other end of some of the ads and the scrutiny and rightly so, appropriately so. So I'd say in the end it's the practice of medicine and it's not the children that come into the practice that write the prescriptions. It's the physicians and the promotion is all based on labeling.

CHAIRPERSON CHESNEY: Dr. Newman.

DR. NEWMAN: Thanks. I want to come back to the point Dr. Fost brought up about the off-label use. Clearly, the use in children under two is off-

label and there is more than one million prescriptions of Elidel for kids under two.

But it's clear to me from reading the indications that this is meant to be a second-line drug. If you look at the Elidel indications and usage, it says it's indicated for "mild to moderate atopic dermatitis in non immunocompromised patients two years of age or older in whom the use of alternative conventional therapies is deemed inadvisable because of potential risks." It doesn't say people who have not responded to steroids. So this could be promoted on-label by promoting the dangers of topical steroids rather than the safety or superior efficacy of this medication. That would be a labeled indication.

One of the things as a pediatrician I'm still having trouble with is where is the evidence that this is of the safety of this as compared to topical steroids. Is it any safer? I haven't seen any data on comparable efficacy of this compared to topical steroids and yet we've been urged to consider risks and benefits. I haven't seen any data about

whether it's any more effective than 0.5 percent tac which I supposed I guess it isn't.

CHAIRPERSON CHESNEY: Dr. Diaz and then Ms. Knudson.

DR. DIAZ: In relation to the nontechnical language, is there a maximum reading level for consumers?

MS. MONCAVAGE: We have no set standard for that. I think we have two social scientists who have the expertise in the area of communication of health information and especially in broadcast ads when we review a final ad or review proposals they will be involved in the discussion about the ads. We have a group review and generally, we will defer to their opinion about whether this is something they know based on their research and their knowledge of the literature whether this is something that would be understood.

CHAIRPERSON CHESNEY: Ms. Knudson.

MS. KNUDSON: I just wanted to comment on Dr. Trontell's presentation about the RiskMAP tools that are available and the fact that it's very

discouraging to think that so few of them have been thoroughly studied. We really don't know what works. I think the Agency really has to do more to find out what does work. There must be studies that can be done that perhaps have not been done.

CHAIRPERSON CHESNEY: Dr. Trontell.

DR. TRONTELL: The evolution of this term and this concept has really come as some programs have already been in place and certainly it's the Agency's effort as well as, I think in the interest of sponsors as well, to make some form of evaluation or requirement of putting such programs into place. We're just starting to reap that harvest.

CHAIRPERSON CHESNEY: I have two more people on the list and then I think we'll go on to Dr. Wilkin for summary comments unless somebody is insistent on taking a break. I have Dr. Santana and then Dr. Day.

DR. SANTANA: Mine is a follow-up of what Paula was asking. There was a previous recommendation from one of the FDA presenters that maybe there should be a boxed warning to enhance information related to

this product. I've heard that said at least two times I think during the day.

So do you have any data that when a product is already out there and then there is a requirement that a black box label is put in, what impact that really has in terms of risk management? Do you have any experience with other products where you can assure me that that would be good tool to apply in this situation if that's the way we ultimately decide that we should do? Because if not, then I'm very doubtful that that particular recommendation would be of any help to the consumers.

DR. TRONTELL: We don't have information to be frank on its impact. We might be able to look at impact on the sales through some of the databases that have been described here. I'm not really aware of any systematic evaluation that's been done of that.

As Melissa described however, there are aspects of a black boxed warning that do make some effective constraints on the use of reminder ads. We can speak to feedback that we received, individuals who perceive it as onerous or not or likely to

discourage appropriate use, but in terms of actual data on outcomes, we don't have that. I think we would be happy to receive it and to seek it.

DR. SANTANA: And just as a brief follow-up, that doesn't occur in a vacuum. Usually when there is a product that you go back and put a black box label, there's additional things that are given to consumers either letters or things like that. Am I correct? I've heard this discussion before about a year ago. This doesn't occur in a vacuum when you put a black box. There's additional information that's provided to consumers, to practitioners, to physicians. Am I correct?

DR. TRONTELL: Right. Again in a world where many things might happen, the appearance of a black boxed warning not uncommonly is accompanied by some letter to clinicians alerting them to the change and again the media itself may make that information more or less obviously in individuals. Again, teasing out what the black box did versus the article in a major newspaper would be very difficult to do.

DR. MURPHY: I think that's the point. It

doesn't always. You can get a black box actually and not have all that happen, but it frequently does. So it's very hard to dissect the impact. One other thing, the med guides, there is a level of reading that they aim for. Is that correct, Anne?

DR. TRONTELL: I think the previous question asked if there was an educational level that people sought for advertising. Certainly for important safety information to patients, the medication guides aim for really the sixth to eighth grade reading level, if at all possible, again trying to communicate the important scientific terms in a way that's appropriate.

CHAIRPERSON CHESNEY: Dr. Day will have the final question.

DR. DAY: My comment is about the reading level of a variety of different communications. We've conducted studies of the readability level of medication guides and mandatory patient package inserts and they're just above the eighth grade level. For Accutane and for Premarin, they're about 8.0 something but below 9.0. So that's non promotional

material.

If you look at TV ads, they are much lower. They tend to be around six grade. The only one we had that's relevant to this meeting I guess is the Elidel ad and that's 5.6. So it's right at a lower level of readability. Now it's not being presented as visual writing. A little guy is speaking and then there's a background person as well. But when you do an readability analysis on that, that's between the fifth and sixth grade level.

I am very interested in the label. There is a little section for both products which is information for the patient the physician is supposed to give and I want to talk about that later when we talk about recommendations. That doesn't always match then the handout which is patient information which evidently is packaged and the same content isn't always there.

The patient information is at a nice reading level and it is very accessible. However, some of the communication is very encouraging that you can use these products everywhere, on your hands and

your neck and use and use and use. It does say "to the effected areas" but that might encourage overuse. So we can consider something that would just make that language a little stronger. Say "Use on the effected."

I wanted to bring this back to Dr. Trontell's point that we can say "Do" and "Don't do" and it just seems to me that all the information about these products be it from the label to the patient information to the TV ads and other kinds of things is a "Do" and "Now you can use it on your face" etc. and "Even when your skin clears up and you feel better, continue to use" etc.

I think that our initial discussion of what things to look at might be whether that is appropriate or if some other cautions might be in. The first level is only "If" and the second level is "And do not do" something as well. That to me is a minimum place for start.

CHAIRPERSON CHESNEY: I think that we probably need to move ahead. I told the Committee that we couldn't have any more questions. I apologize

but I think we need to be fair to everybody. I'd like to keep our momentum going here in terms of having Dr. Wilkin give us his summary of the issues and evidence. Then we do have one more point of information that Dr. Mathis and her group have come up with respect to adverse events for combined steroid and calcineurin inhibitor use.

DR. WILKIN: Okay. We actually had part of the wrap-up I think just in this last go around. We touched on a lot of the key issues. So I think I can move pretty rapidly over this. This is a copy of the slide from Dr. Bindi Nikhar's presentation. We have the three key areas. First is biological plausibility and what is driving a lot of this is our knowledge about the pharmacology about these macrolide immunosuppressants. While a lot of what we understand is from the patients who have had immune suppression in the transplant setting, just simply to know that we don't have much in the way of systemic immune suppression in the patients that we're talking about today doesn't really make us feel all that calm. There are still other potential mechanisms in the skin

and I think Dr. Cohen allowed possibly also in the lymph node where these macrolide inhibitors might be making it through broken skin into the lymph vessels and travel to the regional nodes. So the biological plausibility is there.

Then something that was new to us. I was able to find only an abstract, and we at FDA have not really reviewed Dr. Yarosh's work. It just went below the radar for us, but clearly the comments that he made today are very provocative. We're going to be looking at what he's written in the past. We'll be very excited to read what is in his new publication, not just his conclusion, but look at the materials and methods and find out what other experts also believe about his information.

The emerging signal in the post-marketing database, I think we've heard comments go both ways on this. I can look at those same patients and agree in part with the experts that come from industry that it's really not definitive. It's not telling us one way or the other. We know that a lot of patients with cutaneous lymphomas have an atopic dermatitis like

presentation and they have that years before you get the positive biopsy that tells you that lymphoma is there.

Some of these case reports, it's so brief a time between the application of the medication and the finding of the cancer. The plausibility is stretched, but there are other cases that could be explained this way. We just don't simply have enough information.

This is a very difficult-to-study kind of question. We have routine set of animal studies that we get for all of our topical products. When we're looking for carcinogenicity in those studies, we're typically looking for genotoxic carcinogenicity. We're looking complete carcinogens. Those are the ones that we can most readily detect.

We're talking today about two chemicals that are closely related that are probably not complete carcinogens. They're not initiators. They need to be there in the presence of some other event that is initiating or perhaps even have a promoter on top of that before their effect can be elicited. We

know that 90 percent of the skin cancers in human beings come from ultraviolet light. We did ask for photocarcinogenicity studies and as was pointed, we didn't see a signal that was different from the vehicle and the active product.

When a photocarcinogenicity test in animals is positive, we think there might be some meaningfulness to that. But especially in the setting where the chemical is not absorbing ultraviolet light and is not a complete carcinogen itself, it's very difficult to know if the model is really adequate.

Think about the model for the animal studies. They are rodents typically. Rodents have a lot of hair on their skin. It's a good neutral density filter, protects against ultraviolet light. In addition to that, they're typically nocturnal animals. So they don't have all these mechanisms built into their skin that human beings require to really surveil and pick up the earliest groups of cells that have been altered by ultraviolet B especially.

I'm not convinced that we really have the

best models. The fact that we didn't find things in the skin, but simply found things systemically when there was evidence of systemic immune suppression, I don't believe is very reassuring. Again that's just a very difficult model to make much out of.

The next, the informational landscape, we spent a fair amount of time talking about what is out there for physicians to read. I do believe physicians read labels from time to time, but they are exposed to a lot more information in a lot more consistent manner. Certainly, there are a lot of other sources that will affect prescribing habits.

Just to remind, for two years of age and above, it has been pointed out quite eloquently. The attempt was to have implicitly second-line use, but it's really not all that clear when one reads that part. The other was to emphasize that it could be used acutely and then intermittently, but not continuously. We didn't say not continuously. We said intermittently.

There are lot of publications. They show up in the allergy literature, the pediatric

literature, the dermatology literature and they talk about all different kinds of uses of these products. It's very hard to find anywhere in those articles where at least they come back and talk about what we intended in labeling.

What they do talk about very often is the off-label. We know that there is use in children under two years of age from the IMS dataset. We infer that there are uses first-line therapy because in fact, you read the literature. There are recommendations for that and we believe physicians are reading that and then use as continuous and chronic which is another aspect of that we believe is part of off-label use.

Now I will describe one label here. Actually I'll look at two. This is the Elidel label. It says "Elidel should be used twice daily at the earliest signs of symptoms and for as long as they persist." Then there is a little footnote that takes one down into this area. I don't know if you can read that. I actually can't read it but I can tell you that what it says is the patient needs to be

reevaluated. I think it's at six weeks.

The other piece that it says is that if the dermatitis goes away, you should stop using it. But neither of those two little nuggets in the footnote say anything about intermittent use. This to me seems to imply that continuous use is a reasonable approach.

Now the other item of why I originally selected this is it has "steroid-free" and then we see "steroid-free" down here. I think that really does affect how physicians frame their use of these products. I'll go on to show you some more examples.

Now this is actually something that came out in *Family Circle*. This is not in a physicians's journal. Here it says, "Steroid-free Protopic" and here it is "Steroid-free Protopic" and in case you forgot, it also says as you're reading it several times, "Ask your doctor about steroid-free Protopic today." I think that was another piece that when we originally wrote labeling, we didn't realize the enormous cachet that goes with "steroid-free."

We scanned this paper in that Dr. Stern

referred to. I'm impressed that at Harvard, they've already had their *Journal Club* on this. I just got my journal three days ago. So I don't know how that happens.

DR. STERN: We're online.

DR. WILKIN: You're online. That's how you do it. This is that "long-term in infants and young children." It's just an example of something that shows up in the *Journal of the American Academy of Dermatology* that again dermatologists get to read.

The interesting piece that I really didn't lift all of this out of the article is that on page one and on page two there's a lot of discussion about corticosteroid side effects. If you went away and answered the phone for a minute, you'd think you were reading about corticosteroids and not pimecrolimus.

Then if you go back to the discussion section, once again the side effects are framed in the context of corticosteroids. So I do think this was something that we didn't think about when we were working on labeling at the beginning and obviously has an enormous impact on how physicians use these

products.

Now I would just like to capture this with Dr. Chesney said I get one quote per meeting. Ulysses Grant says, "I know only two tunes. One of them is `Yankee Doodle' and the other isn't." I submit that if you look at the literature on these products you get the Ulysses Grant factor and that's the two major topical drug classes for atopic dermatitis have side effects. One of them has steroids side effects and the other doesn't.

This is a skin therapy letter readily available to anyone. "Tacrolimus Ointment for Atopic Dermatitis" is the title. I don't know if you can see that from where you sit. I wanted to point out the table that is in this. This is just one of many recent examples "- You have to have an advanced degree to work this.

DR. MURPHY: We're going to get another one next time.

DR. WILKIN: "Topical corticosteroids, high, medium, low potency." So they've grouped all of them together and look at the side effect profile.

"Permanent skin atrophy. Systemic effects." I mean those are major. Under "Topical Calcineurin Inhibitors, transient." All of these are going to be short-lived, skin burning, stinging prutitis and at the application sites. So I think this is the kind of information base that is helping guide clinicians in their choice.

Now it is true. All of us have seen very young patients and it's a heartbreak when you see the atrocity and the telangiectasia and you know that some of the changes are truly going to be permanent. We've heard Dr. Eichenfield and Dr. Paller speak this. It's very sad. Sometimes you even feel a little anger with the physician out there who may have prescribed way too much.

If you do a history, often you find out that it's not the low and medium strength corticosteroids. I still think there is a place for the low strength corticosteroids in atopic dermatitis although it doesn't seem to get that much discussion. But the history is usually that of using higher potency corticosteroids. It may have been an access

potency steroid was what was prescribed. The problem may have been that the patient had lots prescribed. They may have been able to go back and get large amounts frequently. So it was a chronic kind of event.

Then there is the more surreptitious variety where I had one patient who her mother was able to get three different physicians to write for the favorite steroid that worked for her and they were very close in prescribing time. That's another source for how these sad events can happen.

I don't mean to minimize the problems with the medium to high potency corticosteroids. But I do think Dr. Williams and his colleagues have a point that there is a topical corticosteroid phobia in patients with atopic eczema. Let's see if I can read this. "Although skin thinning and systemic effects can develop very occasionally in people using topical corticosteroids, the concern expressed by people using them seems out of proportion in relation to the evidence of harm." That's their view.

Coming back to what we have today, we have

uncertainty. I realize there are some people in this room that have already come to the conclusion these calcineurin inhibitors are problematic. That over time, we're very likely to see skin cancer arise.

I think we have the other group that believes that there's very little harm. There's not much systemic absorption. There's not systemic immunosuppression and it allows physicians to use a product that's not going to lead to corticosteroid side effects and please do not label this in a manner where you're actually going to deprive the use for the patients who can really benefit from this. I mean this attention that is what we face when we do labeling. I think both groups have a point and we need to figure out what labeling actually balances best the overall values.

I guess the key question that we somehow need to get an answer to labeling is what are the consequences of long-term, continuous calcineurin inhibition in the skin, possibly the regional lymph nodes and even at low concentrations systemically in children especially those under two years of age. We

know it's being used in that population. Our safety database, this extends beyond the safety database that we really have.

So the answer to this question, the answer on February 15th, today, it's uncertain. That is the answer we have. I look forward to hearing how the Committee will work with that. The goal of labeling is to give information and also its level of uncertainty to the physician and to the patient. Thanks.

CHAIRPERSON CHESNEY: Thank you, Dr. Wilkin. Before tackling Question 1, Dr. Mathis, if you could provide the information that you have for us in a minute or two.

DR. MATHIS: Yes, I'll do it quickly. Thanks to Dr. Jean Temek who went back and looked at Marilyn Pitts' review. Dr. Santana had actually asked how many of the post-marketing tumor-related events were associated with concomitant steroid use and the answer if you want to reference the page is on slide nine in Marilyn Pitts' review. There was one 53 year old male with the T cell lymphoma who concomitantly

used Protopic, Elidel and topical steroids. The if you go to Slide 12 of her review, there's a 16 year old female with lymphoma Sezary's Syndrome who used Protopic with Vaseline and concomitantly used oral prednisolone, a 54 year old male with non-Hodgkin's lymphoma who used oral steroids and a 50 year old female with nodular follicular lymphoma who used steroids with an unknown amount of administration.

DR. TEMEK: (Off microphone.) So it was one of the nine Elidel cases and three of 21 with Protopic.

DR. MATHIS: That's Dr. Temek.

CHAIRPERSON CHESNEY: So the majority actually did not have concomitant steroid use.

DR. TEMEK: Correct.

CHAIRPERSON CHESNEY: Dr. Fost. Question for Dr. Wilkin.

DR. FOST: Dr. Wilkin, I'm still a little confused on what the intent of that original section of the label was that Tom Newman read before that you commented on. That is as Dr. Newman pointed out, the phrase "All you have to do is deem steroids

inadvisable" and that's the subjective criterion that any doctor could pass. Is that what was intended or was it intended that this should be used only as a second-line drug when either steroids failed or there was some contraindication to steroids?

DR. WILKIN: I think the intent was actually to be second-line to corticosteroids and we just didn't end up saying it exactly that way.

DR. FOST: So at least with regard to the intent, any use of it as a primary drug in a patient without some other justification is off-label.

DR. WILKIN: No, intent is one thing. The way we actually wrote is actually very different. I think our view was that there were, and I can remember back to some of the discussion we had internally. We thought do we say lower strength corticosteroids, low to medium potency. We ended up with what we had.

DR. FOST: So one of the options available to the Committee in terms of recommendations is to at least clarify that section of the existing label so that it says what it was intended to say.

DR. WILKIN: Exactly so. We can make it

much more explicit.

CHAIRPERSON CHESNEY: Dr. Santana had a question.

DR. SANTANA: Can I follow up on that? So the data that was presented to support those NADs were in studies in which the patient populations were second-line therapy patients. Do you recall that? I don't have those studies. I don't remember.

DR. WILKIN: My recollection is no, but I think we can follow up on that and give you the answer to that. First of all, I should point out that neither corticosteroids nor the topical calcineurin inhibitors cure atopic dermatitis. So if the definition is that they didn't have an enduring response, that really pretty much allows most patients with atopic dermatitis to participate. But my recollection is that they didn't have to fail to respond to corticosteroids to participate in the trial. But someone in industry may have exactly what the inclusion criteria were.

DR. PAUL: Sorry. Carle Paul from Novartis. The clinical registration studies were

performed in patients with atopic dermatitis without the requirement for prior failure to topical corticosteroids. That's why the label varies actually from country to country.

CHAIRPERSON CHESNEY: Thank you. I think we will go on to the questions. I'm actually giving Dr. Wilkin the opportunity to have two quotes. Where's my other quote? We need to do A-V instructions at the 5.6 grade level. So this is actually from Dr. Wilkin, but I actually after many years don't have to remind myself so often that straightforward issues are not brought to this Committee. Issues of uncertainty are brought to this and other advisory committees. This is from a *Lancet* editorial. "We take the view that the public should be told about uncertainty when data with public-health implications are preliminary or inconclusive."

The first question which everybody has in front of them has two parts to it and the first part I will read first. A. Based on the presentations today and the background materials provided, do you find that additional information about the potential

carcinogenicity of these products in humans should be communicated to physicians, patients and consumers?

I would like to start by doing what the foreman of the jury I ever made it to started by doing which is to ask for a show of hands as to those who do not feel that we need to transmit evidence of potential carcinogenicity to physicians, patients and consumers?

(Show of hands.)

I would take that as a "- I'm sorry. Dr. Bier. I apologize. You had asked for a question earlier and I crossed it out. So we have one person that does not feel that we need to pass this information on to physicians, patients and consumers. Dr. Bier, would you like to tell us why not.

DR. BIER: I think that the human data presented don't convince me that there's a clear risk. I take the fact that the data have not been collected for a sufficient period of time, but I'm weighing that against the argument that in fact it could cause a lot of grief in the people who have to make the decision, the patients, to use these medications. I think that

potential level of grief at this time is unwarranted given the data.

One of the remarks I wanted to make earlier was that we heard very briefly from the two manufacturers about ten-year registry studies to collect the data which were given to us in a tantalizing, right-off-the-slide way and we didn't hear anything about those studies which in fact may allow us to determine the data. I don't know how they're powered, what they're powered to detect, those sort of things. One of the options is to actually get some of the data to allow us to make a decision in the next year or two or three or four.

CHAIRPERSON CHESNEY: Ms. Dokken.

MS. DOKKEN: Actually, I wanted to make this comment before we specifically discussed any of the questions because for me, it's sort of a backdrop for all of them. But it follows right on what Dr. Bier just said. I hope that as we're talking about the various questions and the tools that are available to us as a committee and the FDA that we do not underestimate the role and the potential of families

and parents and in cases of older children their ability if given information to participate in some of this.

I would like us to think with each of the questions whether it's the messages or the tools to very much include patients and families, but also to not feel that we cannot communicate uncertainty. We've heard at least twice now that parents or families will be hysterical. I think we have some precedence that families do make difficult decisions about their children, certainly in clinical research now.

We talked a lot about the landscape and these same families are hearing other messages. They are apparently understanding those based on some of the bar graphs we saw. I think we have to trust that they can hear other messages too and that at the bottom line also that if there is a good relationship with a care provider that they will come back and try to make that decision together. I just hope that we don't leave out families and patients in our strategies.

CHAIRPERSON CHESNEY: Thank you. I think in Section A they have included consumer. Thank you for emphasizing that. If I could just give you an overview, the five questions we're being asked about and we're on the first one, have to do with what message we want to give about risk and the consensus is that we do want to give a message. The second will be what the FDA is asking us how we think they should manage the risk. How we should communicate the risk is point three. How we should minimize the risk is point four and how to monitor outcomes.

Again the question we're on now and with the consensus that we do need to communicate risk, Part B is "What messages about these products should be communicated?" What I understand they're looking for in this question is very specific not wording but specifically what issues should appear in whatever we decide, in other words, how to communicate it if it happens to be a boxed warning.

But what are the issues that the Committee would like to be very clear should be communicated to physicians, patients and consumers? I've made a long

list of issues that could be communicated, but as we all know if we try to communicate too much, we'll end up communicating nothing. The FDA is very much looking forward to our highest priorities in what you would like to communicate about risk to physicians, patients and consumers. Dr. Epps, Dr. Fost and Dr. Stern.

DR. EPPS: Let me first say as a pediatric dermatologist who treats people every day in little and old with atopic dermatitis, yes, I agree it can be serious and life altering. I think the question we're working with or wrestling with is whether lymphoma which is malignant and life-threatening is an issue.

One issue that I have, I guess part of this pediatric, is the mechanism of action in atopic dermatitis isn't really specifically known. That makes it extremely difficult. Yes, it's a calcineurin inhibitor, but I can't give any anticipatory guidance which is a big pediatric thing because I don't know what to anticipate.

Now looking through some of the reports, they say something "Well, there may be some

synergistic things or some promoters smoking. Smoking has a black box. People do it every day." Okay. Parental steroids seem to be an issue. EBV, we talked about. HBV may be an issue. Ultraviolet light may be an issue.

Something Dr. Wilkin said earlier today has been coming through my mind over and over. Just because it has systemic immunosuppressives, suppression is clinically implausible because it's not in the blood does not mean it's not in the lymphatics. I was also struck that in reading in one area that they said it was secreted in breast milk but there were no blood levels. So something is getting through.

I think a lot of the adverse events reported is just the tip-of-the-iceberg phenomenon. A lot of things that go on whether it's infections or other side effect, they just aren't reported and maybe people are fearful of litigation. Maybe they aren't aware of MedWatch. Maybe people don't know the steps to take, but they aren't reported necessarily.

Also as children get older or become older

in the pediatric level, initially visits are every two months. Then when they get to be four or five, it's every year. Now if you're not plugged into a dermatologist who may see you regularly if you're severely-effected atopic dermatitis, who is going to follow you? Who's going to pick up those signals? Who's going to pick that up? Will the first person be the oncologist? Do they know what to ask for?

People give the three months supply from the supply and give me the free refills so I can get 90 day supply and they come back a year later. Who knows? Who picks that up? Who's going to look for those signals?

Absolutely, I picked on the steroid-free. That's clear. Marketing too worked very, very well. I won't say non-dermatologists. I'm not going to pick on any particular specialty, but I have talked to many people over the telephone who don't understand a mean modulator. I said, "Did you know that's a mean modulator?" "Oh, I didn't know."

Also people don't necessarily know what they're treating. They're putting it on molluscum.

They're putting it on subderm. They're putting it on a lot of things which would bring to mind that there are some syndromes where it should not be used and one of them was alluded to earlier, Wiscott-Aldridge, ataxia telangectasia. These are immuno-deficiencies or symptoms with eczema, increased infections and an increased incidence in malignancy. They go together. They aren't common, but they happen.

A lot of time they're picked up whether it's by the oncologist or someone who's suspicious. The infection disease person. This kid still have infections, a little bit of eczema. It's a little bit different. Doesn't respond. Acrodermatitis enteropathica. Other syndromes where people might say let's put this on there because it's steroid-free or they've already put the steroids on and it's not working.

Some people don't think before they treat. Sometimes they'll say "Here's some samples. Try it out. Let's see what happens" because they aren't sure. You want to help your patients. You want to do what's right. But you want to do something and that's

how sometimes things happen which can be very unfortunate.

I do believe in conveying uncertainty. I think it's okay to say you don't know. I agree. More information is better. Lay it out on the table. You don't have to, as they like to say in Washington, you don't have to give different spin. If you don't know say you don't know. But if it's known, give that information to and I think most parents appreciate that. "I want to go into it with my eyes open. I want to know what I'm doing." I think that's all I have to say now.

CHAIRPERSON CHESNEY: Thank you. I think I've captured five points that you think would be important to communicated. One is that topical application doesn't rule out systemic effects, doesn't necessarily rule out systemic effects. There is a risk to long-term use. better information about the mechanism of action and perhaps loss of T cell cancer surveillance if you will. The fourth being accurate diagnosis, don't use it for unapproved diagnostic indications and fifth uncertainty. Would that be a

summary of your talk?

DR. EPPS: I guess that's what I said.

CHAIRPERSON CHESNEY: Dr. Fost and then Dr. Stern.

DR. FOST: I had a question first before I comment on some of these bullets. Dr. Hultsch presented some data on background incidence of lymphomas and related malignancies and said that the small number of cases so far in patients treated with the calcineurin inhibitors is no greater than would be expected.

Realizing all the difficulties of making interpretations from minuscule data, I haven't heard any response to that from the FDA or the epidemiologists on the Committee. Is it your or our view that we can't draw any conclusions? We worry about this because there's theoretical reason to worry about it from the oral history, from the history of transplant patients, from the animal studies and so on, but whether there are in fact any increased signals in human treated populations is unknown. Is that a fair statement?

DR. NEWMAN: Am I allowed to answer that?

DR. FOST: Yes. I would like to hear Tom and the other epidemiologists comment. Dr. Andrews.

DR. NEWMAN: I think that we know that there's such under reporting that in order to say that this is smaller than the number that would be reported in this population would presume that we are catching all of them which is completely absurd. We know that we're not.

The main way that I think these individual adverse event reports might convince you about causality or the situation where the tumor is right in the place where they were applying the drug or there`s a very unusual circumstance that seems happening. They're not really worrisome, but they are absolutely not reassuring these comparisons of rates between adverse events reports and what would be expected in the population.

DR. FOST: So would you say that we don't know is the current situation.

DR. NEWMAN: But my understanding is that when the drugs are given orally we know they cause

cancer.

DR. FOST: Absolutely, but that's not my question.

DR. NEWMAN: We know that the medications if you have enough of a systemic level would lead to cancer and to me that would be the concern.

DR. FOST: No, I'm convinced there's more than enough reason to say that there's a potential concern and I'll go on to say in a minute why I think that should be communicated. But with regard to the empirical question about whether there's any evidence now.

PARTICIPANT: There are no data, I think, is the best way.

DR. NEWMAN: I don't think we can say that we know of cases where topical therapy.

DR. FOST: Right. To prove or disprove the data.

PARTICIPANT: There is no data.

DR. FOST: So I have to say the pictures were the KS and the other things happened right at the place where it's applied are hard to quantify that

with numerator and denominator and say "Oh, this is too high a rate" because it's in this particular part of the body where the cream was applied. That would be more convincing to me.

CHAIRPERSON CHESNEY: Dr. Andrews, an epidemiologist.

DR. ANDREWS: I think spontaneous adverse experience reports are good for some things and not good for others. The example of whether there's a clear effect at the site of application may be a case where they are particularly good. For delayed reactions, our events of long latency, they are particularly poor and I would not expect them especially if the physician treating the cancer is not the same person that was treating the dermatitis. I think it's very unlikely that there would be the association and also the reporting. So I really would not rely on those data to detect or refute a signal.

CHAIRPERSON CHESNEY: I think Dr. Santana wanted to respond to your point also and then we'll come back to you.

DR. SANTANA: Yes. I wanted to say

something about oncology. The situations that we're most convinced that there are strong associations between an intervention and development of lymphomas are the EBV and lymphoproliferative disorders we heard this morning. I think we all agree that does happen and it happens in a period of time that's fairly well defined for that patient population too. That's how we recognized it.

We recognize it very early on when many patients were being transplanted. There was a mini burst of children and young adults diagnosed with EBV and lymphoproliferative syndromes and B cell lymphomas. We were able to capture that. It was a very unique population, transplant patients, who developed a very unique syndrome. Very characteristic. They were all B-cell associated lymphomas.

One of the concerns I have about the lack of data or the data that we have is that these don't appear to fall in that same category. I said that earlier this morning. The cases that I was able to discern from the dataset are the common lymphomas we

see in kids, T cell lymphomas, things of that nature, that are going to have longer latency periods and so we get into the problem that if we are going to be observing lymphomas in this patient population it's not going to be that spurt of B cell lymphomas that we see in the transplants. There's going to be a longer period of observation that we need in order to conclusively say that we are going to see an increase incidence rate.

I was making a calculation earlier this morning with Dr. O'Fallon and said, "There's 1,000 cases of pediatric lymphomas in the U.S. a year. I'm making the number up and all of a sudden these drugs cause a 10 percent incidence rate increase. It's going to take us three or four years to really see a change that the oncologist would say something is happening out there that we don't know what it is that's changing the trend.

I'm a little bit concerned about latency and how long we really need to wait before we can say there is no association. But on the other hand, I'm not really so convinced yet that these drugs really

are going to dramatically increase that rate. I'm more worried about the preclinical data which I think is a little bit more convincing. I don't think the clinical data exists yet.

CHAIRPERSON CHESNEY: Thank you. Dr. Fost, can I just make a point which I probably didn't make clearly enough before which is that I think in this question the FDA is specifically asking us how we want to transmit information about potential carcinogenicity. Dr. Fost.

DR. FOST: Okay. Well, that actually laps over to Question 2 and 3. Do you want me to comment on that now or just on 1?

CHAIRPERSON CHESNEY: Sure. You can go right through to Question 5 if you want.

DR. FOST: Okay. These things are all connected. Let me make my mini speech. It seems to me that whatever the problem is here, it's greatly aggravated by the enormous off-label use. That is it would be wrong to prescribe it to even one patient if it's not indicated in that patient and if there's a safer effective drug. But that would be of little

consequence where at its worst that would be an uncommon phenomenon. So it's only when millions of prescriptions are written, that it really becomes of consequential concern.

But that is happening and I'm hearing my colleagues at the FDA tell me that there's nothing they can do about that. That the existing rules and tools that you have in your toolbox at least in terms of "- Let me go back a step. Dr. Wilkin said that the FDA can't control peer reviewed and non peer-reviewed journals. That's true, but we know from many, many studies that 90 percent of doctors get 90 percent of their information not from journals. It comes from pharmaceutical companies. That is pretty much the source of information for doctors on drugs in general, through CME, through drug industry-sponsored CME, through sampling, through direct-to-consumer ads. Those are the three major ways.

This phenomenal growth in the use of these compounds outside of what is clearly intended by the label has to be the result of pharmaceutical company efforts. Just exactly how they're doing it, I don't

know because I haven't seen enough examples but we've gotten a clue from some of the ads.

If it's the case that the tools, that you can't regulate that because it's not clearly illegal, off-label advertising, then we have to use the tools that are available to us that Dr. Trontell mentioned. And while a black box or a boxed warning may be excessive, may be overshoot, may be unduly inhibiting as we've heard alleged with the SSRI story, it may that if that's the only tool left to stop millions of prescriptions that are inappropriate as I hear it at least when considering the intent of the original label that may be the only way to do it. Now there's other tools in between and we can talk about them.

I will say to repeat my comment I made a few minutes ago. It's clear to me now that the original label was intended for this to be a second-line drug. Dr. Wilkin confirmed that. It's at least ambiguous to put it generously and that should be clarified. It should be stated explicitly "This should be a second-line drug in children and low to moderate concentrated steroids should be the first

line of defense."

I don't really accept this argument that parents will freak out and not use steroids because of false fears that their kids will turn in to Jose Conseco or whatever it is that they're afraid of. All drugs have side effects. Most drugs have serious side effects even from mild trivial conditions. So it's part of a doctor's job to tell parents "I think for your child the steroids are reasonably safe and effective and I recommend them."

If it turns out that the calcineurin inhibitors indicate it even though there's a theoretical chance that they may cause cancer, "I think in your child given the disability that he or she has and so on I think it's appropriate to do." That's inherent in the practice of medicine. That part doesn't bother me.

In summary, I think there's clearly evidence of potential. There's more than plausible reason to be concerned about this and doctors and patients ought to know about that. They can come later to which of the tools in the toolbox to use.

Secondly, though to say that there is present, bullet two, evidence of human carcinogenesis, I think Victor summed up my views as well. I wouldn't call it evidence. I would say reason to be concerned and we need more data and we need more long-term follow-up and we'll come back in half an hour or so as to what the best way to do that is.

Bullet one for sure. Bullet two I don't think so. Bullet three about use of the product only as second line therapy. Yes, that was intended from the beginning. So that isn't a new recommendation. That is just clarifying what was the original recommendation even before these risks had more data. And younger than two, I wouldn't say "should not be used," but again "should be a last resort." There may very well obviously be children under two who have severe eczema or for whom steroids are not appropriate or they may even be worried about steroid absorption. So I wouldn't exclude them, but they should be strongly discouraged except for last resort situations. Bullet five, I'll defer to my dermatology and immunology friends as to whether that should

prohibited in immunocompromised folks. I don't have any view on that one.

CHAIRPERSON CHESNEY: You left us in the dark about bullet three which is dose duration risk.

DR. FOST: I don't know. That's with bullet two there.

DR. SANTANA: I think that goes with bullet one. The data that I saw for this point was supported by the nonhuman primates. I didn't see any clinical data that supports this bullet. So if you can tie that bullet to the first bullet I think that's reasonable.

DR. FOST: Yes.

DR. SANTANA;: That's where the data exists, but it's not in the human application.

DR. FOST: I agree.

CHAIRPERSON CHESNEY: Thank you. Dr. Stern and then Dr. Bier.

DR. STERN: Along with Dr. Wilkin, I like history and precedence and the discussions about this drug make me think about another drug, allopurinol, which in fact has a boxed warning because of a rare

hypersensitivity syndrome that is unpredictable and also has within that same box a warning that the use of, I'm sorry I don't remember the exact words, this drug for asymptomatic hyperuricemia which was at one time widely promoted is essentially a bad thing to do. So there is both a warning about a potential rare adverse effect, in this case, well documented occurring in the association with the drug and a warning about restricting its use and not using it in a population where people are unlikely to get substantial benefit.

It seems to me in looking at these six bullets that the one of the things we can say is Bullet No. 4 that in fact you really need to think about benefit/risk. At this time, the available information tells us that you should probably think about other things first because of potential risk and that in fact to me Bullets 1 and 3 are the key. I guess I would disagree about the order. To me, Bullet 1 supports Bullet 3 and everything we know about skin cancer which is different than post-transplant immunoproliferative disease suggests that dose

duration, location and of course, the underlying characteristics of the individual with respect to risk all are factors in skin cancer which is my biggest concern about this. So I think we're hearing a little bit different paradigms of what are the risk factors for developing each of our cancers of interest or perhaps expertise.

CHAIRPERSON CHESNEY: Thank you. Dr. Bier.

DR. BIER: Yes. First, don't interpret my earlier vote that I don't think it's plausible that there is a risk. It's plausible. What I have trouble waiting is whether the hypothesis that these drugs can cause lymphomas of a different cell type than the ones expected is any more or less plausible than the null hypothesis which I don't.

As a pediatric endocrinologist by training, I can weight the known effects of steroids side effects against the unknown effects here and I find I can't reject that null hypothesis either. And whether or not parents are going to understand and become worried or not, I'm sure some will understand

and some won't just like they will or won't understand the risks of steroids.

So it's harder for me to decide I want to reject the hypothesis that there isn't an effect. I think that all of these concerns are equally plausible. I also think it's going to be very hard to write any sort of a reg that says this is a second-line drug when you have side effects of steroids. Steroids have all kinds of side effects. I would find it very easy as a physician to get out of that one real quick. It would take me about probably six weeks or something to get on to a second-line drug. So I'm not sure that's going to help us at all.

We were talking about promotions here and there was certainly a lot of implied promotion today about the advertising issues. So either these ads are illegal and if that's true, then someone has a means to address those or if they're legal and I'm not sure why we're talking about them. So if they're illegal, then isn't there some way to address that independent of us? Not the package insert, but the promotions. There was a lot of implied issues about the

promotions. I don't think they're very balanced, but if they are illegal, then someone has a mechanism to address them.

CHAIRPERSON CHESNEY: Could I just summarize at this point and then Dr. Mattison. Again reminding myself what information the FDA is looking at is the message we want to convey and then we'll talk about how and when and so on. But the message we would like to convey with respect to potential carcinogenicity from Dr. Stern's point of view is most importantly that there is increased potential risk of cancer with an increase in the dose or duration of exposure and I wonder if we couldn't add in there some comment about latency that implies you may not see anything for a number of years and with Bullet No. 1 being a subcategory that this is based on animal studies including nonhuman primates.

Our second point is that there should be more emphasis on use of the product only as second-line therapy because of this uncertainty. Third, that is should be used in children under two years of age as a last resort because of this uncertainty and for

other reasons and fourth, I haven't heard specific comments about non-use in immunosuppressed patients or those with increased risk or cancer, but I feel like that's given.

But that is still a message we would like to convey and again remembering that we want to put a limited amount of information in the boxed warning if that's what we end up doing and making our points emphatically. That's what I'm thinking and the Agency has asked me to summarize periodically to be sure we're all on the same track. So let me know if I'm not. Dr. Mattison, you had a comment.

DR. MATTISON: You said it.

CHAIRPERSON CHESNEY: Thank you. Dr. Gorman, Dr. Fant and then Dr. Newman.

DR. FANT: I really liked your summary and I would just like to put in that statement that you're suggesting as wording that there is no human data to date.

CHAIRPERSON CHESNEY: Thank you. Dr. Fant.

DR. FANT: Yes. Just one point that if

possible in this format if I could get some clarification on it. It doesn't speak to carcinogenicity directly but it does speak to the issue of immunosuppression in kids and it didn't have time in the Novartis presentation earlier, but they presented some data with the confidence intervals of a bunch of infections where the point was made that there was not an imbalance in immunosuppression.

But when you actually look at the individual bars, it appeared that viral infections or conditions that are predominantly caused by viruses tended to be clearly shifted to the right suggesting that there was an effect on the body's ability to fight off viral infections. Does that constitute a signal? Is that something that would rise to the level of human signal from the data that we have that would suggest some systemic effect on immunosuppression? I would welcome any comments from anyone around the table or the Novartis people.

CHAIRPERSON CHESNEY: I think you've emphasized an important point that Dr. Epps also brought up that I think, my own personal feeling, that

it should be transmitted to consumers the concept that these are immunosuppressive agents because I've seen a number of patients who also happen to have eczema herpeticum which is why I saw them and the parents had absolutely no concept that these were immunosuppressant in action. So I would like to add that as a fifth bullet point. Let's see. Now we're on to Dr. Newman.

DR. NEWMAN: One thing that isn't up there but that we've talked a whole lot about and I'm not sure how to handle is the issue of skin cancer and treating sun-exposed areas versus not exposed areas and how much one should limited exposure to sun if one were going to use these. The existing product information does say patients should minimize or avoid exposure to natural or artificial sunlight, but it doesn't actually say the reason for that is the concern of increased risk of skin cancer or that these drugs might increase the risk of sun cancer.

I think compared to the other things all of which we worry more about systemic absorption or at lease lymphatic. That was one of the ones that worry

me. So I'm just wondering whether there should be a caution, a stronger caution, about sun exposure or a caution about sun-exposed areas of the body or something like that.

CHAIRPERSON CHESNEY: Let me ask for Committee input on that because it is there already and I don't know that I've heard enough evidence that we need to put it in a boxed label, but Dr. Stern may have other information.

DR. STERN: That's one of my areas of interest and to me it's all about benefit and risk. If you look at the areas of the body where topical steroids are most problematic, they are basically the face and the underwear area. So therefore the benefit relative to the competing agents is greater with respect to -- I'm sorry, the risks with respect to the acute side effects and steroid side effects are superior for Protopic and Elidel on those two difficult areas. So they have a relative advantage in those areas and they have the disadvantage that you speak about.

To me, I don't think we have the data to

go beyond what we've said to think do you really need to use them in a sun-exposed area or in fact in the genitals in a papilloma virus exposed area. So I think it's one of these funny things where when I first thought about it, "Oh, yeah, don't use them there" but then I'd say, "So why do you need them so much?" In fact what you need them so much for is particularly facial and intertriginous areas which are areas of special risk when you immunosuppress them.

I won't change beyond what we've done. I think the Agency did a pretty good job of balancing under the face of great uncertainty. Are they doing more for skin cancer in these areas where they are particularly helpful therapeutically relative to other agents or visa versa? I don't think we'll ever know that answer.

CHAIRPERSON CHESNEY: You would not include extra "-

DR. STERN: I would not further emphasize the existing warnings. They call people's attention to it. To go beyond that, we may end up cutting off the best benefit.

CHAIRPERSON CHESNEY: Thank you. Dr. Day and then Dr. Epps.

DR. DAY: I just wanted to comment on the behavioral component in the use of these products or any products where the patient or the caregiver puts the product on the skin. We don't really know how much they put on. It says to put on a thin layer on the affected areas.

You can go to many airports as you're waiting and you'll see an affected child and the mother takes out a tube of something and goes "Oh, that little boo-boo" and starting gently massaging around and that calms the child by talking and massaging and they massage a little wider and a little bit wider and so on. It may be that more is being given to infants than to older children or more to older children than to adults, etc. So that's why I very much support something like number 3 that talks about the potential things that can happen with increases in dose and duration of exposure so that patients will be cautious and caregivers in the amount of exposure that they have and that physicians will

caution the patients about this as well.

CHAIRPERSON CHESNEY: I think that's an excellent point. I thank you for raising it. I can say this with impunity since I have ancestors from England, but it said that for the English if a little bit is good, a little bit more is better. That's certainly what I've seen my patients use and probably what I would do myself. You put a little bit on the tip of your finger. Well, I think I'd use a thumbnail. How does the rest of the group feel about that? Is that something worth putting in?

DR. SANTANA: I'm concerned because we're supposed to be dealing with information and we're supposed to processing that information to make a recommendation. I did not see any clinical data today that would support a dose response or a dose duration effect for the development of the tumors that we were discussing. I saw in the preclinical model. I did see it in the lymphoma model. I think it's there, but to extrapolate that to say that it's happening in patients I think is a step that I'm not willing to take.

DR. DAY: We are not saying it's happening in patients because Bullet No. 1 has been limited that it has not been observed in humans but there is some concern because of animal and immunosuppressed patients. Therefore on the side of caution consider the amount that you were applying would be the communication I would support.

CHAIRPERSON CHESNEY: If we accept Bullet 3 which says an increased potential risk with an increase in the dose or duration based on animal studies, is that enough or should we emphasize that by saying it should be used only as indicated in the label? Dr. Glode.

DR. GLODE: I think the only hard information is in the animals and that's what you should stick with and you should not even imply that the increased potential risk might be related to dose or duration in humans. You can say it was related to dose and duration in the animals.

It would be very helpful to me, and I again I think I heard this was not available right now, if the mid potency and high potency steroids were

applied topically to the rats and the mice in the lymphoma model so that I could be sure that they were not dangerous in the animal model than these agents. So just repeat the experiment now in 2005 the exact same way you did and then we'd at least have that comparative information. I hate to be referring people back to a drug that might be more dangerous. It would just help me to know that.

CHAIRPERSON CHESNEY: If I could summarize once again where we're at and then see if there's anything else that anybody wants to add to this because we still four more questions to go. Our first point is make it clear to consumers, patients and physicians that there is an increased potential risk of cancer with an increase in dose and duration of exposure based on animal studies including nonhuman primates. We wouldn't say there wasn't human data. Leave it at that.

The second point is that there should be increased emphasis on use of the product only as second-line therapy because of the potential risk.

Thirdly, use in children under two years

of age should be minimized again because of unknown risk.

Fourth, it should not be used in immunosuppressed patients or those with an increased risk for cancer and we would include some wording that had to do with the fact that the mechanism of action was that of immunosuppression which in some cases may result in cancer.

DR. SANTANA: Can I comment on that last point? I would reword that differently because there really is no data on that either. We're making the assumptions that patients with eczema as part of precancerous conditions like AT or Wiscott-Aldridge, etc. may be at increased risk, but we really have no data. It's a plausible reason to say that but I don't think there's any data.

Maybe the message there is that there may be other conditions in which further caution is warranted like patients who are immunosuppressed from other medications or from other conditions. Something like that, I think to me would be just as informative without a true statement based on data that we don't

have.

CHAIRPERSON CHESNEY: Would it not be fair to say that this is known to be the case in oral use of these agents?

DR. SANTANA: I think like you said. The more complicated you make it less the message gets through.

CHAIRPERSON CHESNEY: Mr. O'Fallon. So now what we're looking for is anything else that you would like to be sure to give a message, about what you would like to give a message. Dr. O'Fallon.

DR. O'FALLON: I'm following up on this. Did they do studies in immunocompromised patients? Were those original studies in that population? I've forgotten by now.

CHAIRPERSON CHESNEY: They were probably excluded, were they?

DR. O'FALLON: If they were, then that's what we have to say. Given that the immunosuppression aspect of this and the lack of any data in that group of people, you would have caution about applying them to those people.

DR. HULTSCH: That's one of the six studies we are planning to do.

DR. O'FALLON: Planning, but we don't have the data yet. Okay. That's fair.

DR. SANTANA;: So I go back that I think that phrase should indicate that there may be other conditions in which patients are immunosuppressed either from a primary diagnosis of a primary immunodeficiency type syndrome like AT or Wiscott-Aldridge or immunosuppression from other conditions that would warrant further caution with the use of these agents in those populations. That's where the data is. There's no data. That's it.

CHAIRPERSON CHESNEY: Thank you and I was warned that they don't us to wordsmith and get precise wording. Although, Victor, yours is much more to the point. Is there anything else anybody wants to put in the label about potential carcinogenicity? If not, we can move on to Question 2. Dr. Cummins, can we move on to Question 2?

DR. CUMMINS: Yes. Sure.

DR. FOST: Shouldn't three precede two? I

mean the box is the nuclear weapon. Three is milder forms of communication.

CHAIRPERSON CHESNEY: Dr. Fost would like us to go to Question 3 next which is Mechanisms for Risk Communication. Could you put up three, Jan, please? Does the Committee recommend any of these, or any other approaches, to communicating and minimizing risk for these products? We're given a number of options: prescriber targeted, a healthcare provider letter, a professional organization letter and electronic alerts, CME courses for whom and by whom; for patients, a patient package insert, a medication guide which as I recall hearing earlier is required, if we suggest that it's something that must be done, an FDA public health advisory and information page; and government sponsored symposia or anything else.

So let me just be sure, Norm. I have me confused now. The boxed warning would come "- We're discussing the boxed warning at this point. How do we want to communicate this information?

DR. FOST: For openers, is there any reason not to include all of them?

CHAIRPERSON CHESNEY: I guess I would ask Dr. Trontell or somebody from the Agency. Is there a reason to exempt any of these?

DR. TRONTELL: I'd actually ask the Committee and particularly Dr. Day. I think repeated communication can reinforce but excessive communication can turn off. I'm not sure what the best balance is.

CHAIRPERSON CHESNEY: Dr. Day.

DR. DAY: I absolutely agree with that and from my experience with committees on Lotronex and Accutane, etc., I don't think this rises to the level of that. I don't think it needs a medication guide. I would have to be talked into their needing a communication guide for this, but I would strongly urge on the patient side that the patient package insert describe this information that we've already discussed but in patient-friendly terms and with then, saying something about "Therefore be cautious in your use of this cream or ointment and put it only on the affected areas, etc. as instructed by your physician or your doctor."

CHAIRPERSON CHESNEY: Could I just be reminded? The patient package insert goes into the box and so it's easy for people to pull it out and throw it away.

DR. DAY: I would like the companies to tell us that because there are tabs in our briefing books or in just the briefing document from Fujisawa where it says the label and you get the real label, the PI, and then right after that is the patient information. Is that package with the product? Could someone tell us from both companies please?

DR. HUKKELHOVEN: Mat Hukkelhoven from Novartis. The patient package inserts as well as the professional package insert are packed in every unit of the product. So there is 100 percent guarantee that every patient that gets a dispensed product will receive the patient package insert.

DR. DAY: But sometimes those are taken out by the pharmacist and it's up to the pharmacist to then provide some of the information. Is it actually in the box?

DR. HUKKELHOVEN: Yes, in the box. The

pharmacist delivers the box, the intact box, which is opened by the patient.

DR. DAY: All right. That's great. Thanks.

CHAIRPERSON CHESNEY: Dr. Fost, Dr. Diaz and Dr. Gorman.

DR. FOST: Is it appropriate for the patient package insert to inform the patient that the FDA recommends that this drug be a second-line drug and obviously in some light language to give the parents some idea that the FDA recommends that you use the preferred drug which are steroids.

DR. TRONTELL: Is that question "- Yes, that can certainly be put on the patient label.

DR. FOST: Since that's what the FDA thinks, I think it would help a lot if parents understood that.

CHAIRPERSON CHESNEY: Dr. Diaz.

DR. DIAZ: I think, in addition, to the patient, it would be important to also inform the healthcare providers.

CHAIRPERSON CHESNEY: Could somebody from

the FDA remind us of what is a Dear Healthcare Provider letter as opposed to the FDA public health advisory and information page?

DR. TRONTELL: There may be others at the table from FDA who know the enabling legislature. But the Dear Healthcare Provider letter is often negotiated with the sponsor. There are several categories that I think are important, prescribing information, certain colors on the envelope to alert the physician not to simply throw it away, putting something on the website.

DR. MURPHY: It comes from the sponsor. That's the point.

DR. TRONTELL: Thank you. So that is something that is sent out by the sponsor not by the Agency. It's an active form of communication that may or may not be regarded. Putting something up on a website unless someone knows to check that website or has some alerting mechanism to new posting on that website might go undetected.

CHAIRPERSON CHESNEY: And the public health advisory and information page?

DR. TRONTELL: The public health advisory has been used by the Agency in a variety of formats. Sometimes they are more or less ballyhooed in the press or may have accompanying press releases or talk papers. In my own experience in the last six years or so, they have varying degrees of impact. When phenylpropanolamine was effectively withdrawn from the market, that was done by a public health advisory. There are public advisories on SSRIs that some felt weren't given adequate recognition. So it runs the gamut.

CHAIRPERSON CHESNEY: In your experience, what is the best way to alert physicians and other caregivers, nurse practitioners, physicians assistant to this being a new and important issue to pay to?

DR. TRONTELL: I'll ask the Committee to give us their own experience in terms of what's most salient way to communicate because I've heard a variety of experiences and we don't have data to tell us which is the best.

CHAIRPERSON CHESNEY: Dr. Santana.

DR. SANTANA;: Maybe Dr. (microphone goes

off) on this subject because one of the things I was struck was that the prescribing rates are by pediatricians now, also by dermatologists, but clearly to big groups of which the pediatricians probably represent the "first line of attack." So how do pediatricians, I come from academic centers so it's a little bit different, in the community, how do they react to these informations and which do you think is the best tool if you were the one getting the letter or the information?

DR. GORMAN: We actually have a little bit of data of this from the Academy which is that the vast majority of pediatricians get most of their information from the pharmaceutical representatives. The second largest source of information is from Academy-sponsored CME and the third largest and the most important, maybe I shouldn't say this in front of this particular group, but the way that they change their prescribing patterns is the roadside consult which is you have a specific patient in mind, you have a specific clinical problem and you ask your good friend and trusted colleague, "What would you do in

this situation" and they suggest X and that actually changes your prescribing process.

So there's a where you get your information and then there's a secondary issue of what actually changes your behavior. Information from the pharmaceutical reps and Academy CME, but the thing that seems to change your behavior the most is the roadside consult with the trusted colleague.

CHAIRPERSON CHESNEY: Could I comment, Dick? I must confess, and this is probably embarrassing for all of us, but when I get letters from the FDA unfortunately often toss them. But if I get an email from the Academy saying "Alert. Wake up. Watch out" I read it. I think that's been a very effective tool for some of us that have to do specifically with pediatric issues.

DR. GORMAN: The Academy uses its, and it has some name, email system to alert Academy members very judicially and only in areas where they feel it has widespread and broad-reaching implications across all Academy members. So influenza vaccine this year got up to the broadcast level.

Certain Academy policies that they felt were going to have widespread press ramifications so that the Academy members would not be caught unaware also reach the broadcast level. The SSRI issue, for instance, which we debated in this Committee did not make it to that level. They were not announced over the Academy broadcast method.

CHAIRPERSON CHESNEY: That may be an Academy problem, not our problem, but I would think for atopic dermatitis with as high an incidence as it has in children. But what you're saying is we have no control over that. That's going to be up to the Board of the Academy.

DR. GORMAN: Actually, it is up to the Executive Committee of the Academy. If you can convince the five members of the Executive Committee and I'll be glad to give you their names and addresses to see if you can get to use that.

CHAIRPERSON CHESNEY: I don't want them. Dr. Andrews and Dr. Epps both had comments to make.

DR. ANDREWS: I was going to make two points I guess. In terms of what is effective, I

think there's not a lot of literature about the effectiveness of different types of communication and changing behavior. Probably the most literature suggests that the academic detailing model which is consistent with your point about the one-on-one consult is the most effective. But I think we're in an era where we need a lot more information on what does work and what doesn't.

The other point I was going to make about the question of does this rise to the level of warranting a medication guide, I think from everything that I've heard about medication guide plus Question 4 suggests that those mechanisms are intended for drugs that have evidence suggesting a particular risk that's over and above the expected risk for the type of treatment and there's a difference in the risk/benefit balance that suggests something additional is warranted and what we have here is a theoretical risk with no human evidence. My view is that the lack of data and the theoretical risk do not rise to the level that would warrant extreme measures like a medication guide which is reserved for only a few products per

year or risk minimization activities, but should stay at the level of targeted communication.

CHAIRPERSON CHESNEY: Somehow I have the feeling we're not making any progress or it seems frustrating. How are we going to get this message out other than in the package insert and the sponsors not being allowed to use reminder TV ads. Other than that and we do have the option of the healthcare provider letter. Dr. Gorman, Dr. Epps.

DR. GORMAN: I think that we talked about what message we wanted to get out but I'm not sure we've talked about what message we want to get out to reduce that risk. If we go back to the animal data that was shown this morning, the thing that reduced the risk of progression to disease was removal of the agent.

In the labeling already, it talks about acute, intermittent therapy. It would strike me that we're going to talk to practitioners about something they can do that's non-onus and may theoretically reduce the theoretical risk we've now postulated is we should emphasize the intermittent use of these

products so that there'll be time for the immune modulation or suppression to be reversed and hopefully allow the body to reach a homeostasis before it's reexposed.

I think that would be the message. Because if we tell people there's a theoretical risk, we might as least give them a theoretical intervention. We're doing that with skin cancer in other ways. We tell them there's a theoretical risk from sunburn. I know it's an association, but then we're promoting sunblocks with some what scanty data in terms that it prevents sunburn, but I'm not sure it prevents skin cancer yet. Twenty years from now, I'll be convinced about that too.

But that is the message that we could get out that it needs to be used in an intermittent fashion. I think that's the message to minimize risk that would be palatable inside the labeling and inside the animal data that we have up to the moment.

CHAIRPERSON CHESNEY: But that's part of Question 1. That's still part of the message and if we're now on Question 3, how are we going to transmit

that message? We already know that physicians don't read labels. I think if we went around the room, we could do all we want to the label and that's not going to get the message out.

So the question is how do we get the message? As I understand it, and anybody correct me, the Dear Healthcare Provider letter could be negotiated with the FDA and the sponsor but it comes from the sponsor. The FDA could alert professional organizations. We can add a patient package insert, but again we're dependent on patients recognizing that it's in there and taking a note and reading it. We've had some suggestion that we not look at the med guide and that the public health advisory may be over used. Dr. Epps and then Dr. Mattison and Dr. Andrews.

DR. EPPS: Thanks. One comment regarding something earlier about the second-line issue, I think you need to a little or some wiggle room for the physician to make a clinical judgment. Obviously, if second-line is preferred, but there are some people who cannot use topical steroids or whatever. So I think you need to do that.

There is an *AAP News*. There's *Skin and Allergy News*. There are other nonsubscription free journals that are out there and I think that's a way to get information out there. People do look at them before they are in the File 13 and certainly that can be very helpful.

I agree with a previous statement. I don't know that a med guide is indicated at this time unless we have more hard data. Letters, I look at them the FDA letters, even if they aren't on medications that I particularly use. I do like to look at them. So I think all those things would be helpful.

This is an aside regarding the number of prescriptions. One thing that hasn't been discussed is an influence in the managed care organizations, the managed care companies, and getting on their panels. There are some panels, particularly in the medical assistance patients, they have four steroids: hydrocortisone, triamcinolone, fluocinonide and clobetasol, and then they'll have an immune modulator.

Once you get past hydrocortisone if you're

treating the face or whatever, then the other areas are inappropriate. Or they're at the point where you don't have to make phone calls and get permission. They say "You can just write for it. You see you can get it." So I think that has influenced. If you're wondering about the difference, I think that has made a huge difference in the number of prescriptions as well.

CHAIRPERSON CHESNEY: Dr. Mattison and then Dr. Andrews.

DR. MATTISON: From public health, it's been demonstrated that risk communication is most effective when it's continuous, when the message is received multiple times. A Dear Healthcare Provider letter or an organization letters are singular as I understand them. That is to say they would be sent once.

So there are a group of providers who are just now entering practice who wouldn't have received them. There are patients who a year from now or two years from now won't be alerted the issue based on that kind of approach. Given the uncertainty but the

substantial animal and at least human data that suggests risks of carcinogenicity, there has to be a way of continuously reminding providers and parents of this uncertainty until the data is gathered that addresses that uncertainty.

So I don't think that the letters either to providers or organizations will help and some way of building that communication of uncertainty around this substantial health endpoint needs to be built in. So that leaves us with two approaches, one in the patient package insert and then the second in the label, the material that the provider reads. And the difficulty is or the challenge is that communicating an endpoint which is substantially uncertain but carries with it if it occurs substantial health consequence is not easy. But the health consequence is potentially so severe that I think we almost need to think about this black boxed warning approach that draws the provider's attention to the uncertainty and the consequence if that uncertainty is resolved in the direction of the adverse health endpoint.

I think healthcare providers can

communicate this complicated issue to their patients. I've heard that mentioned around the table. I don't see that as a barrier to appropriate use. What I see it as is perhaps an assistance to appropriate use. So I guess I would argue that because of the uncertainty, because of the consequence and because of what we know about effective health communication, it needs to be permanently attached to the product until the uncertainty is resolved.

CHAIRPERSON CHESNEY: I think we'll be getting to the boxed warning next. Dr. Day and then Dr. Andrew and then maybe we can summarize what we've done thus far so we can move on.

DR. DAY: About the repetition effect, you do a laboratory study where you give information to people. It can be on anything. The more times you repeat it, the more likely it is going to be recalled. That is true. We've only talked about it just now across different types of messages, but within a given if you put it in twice, it's going to work, pardon the expression, more better.

So if we put it in a warning place

whether it just says warning in the body or in a boxed warning up top, it should also be in potential adverse reactions as well. We've done studies where we only put it one place or the other place and you'd be shocked at how little people remember those things. So the repetition effect can work within a document.

CHAIRPERSON CHESNEY: Thank you. Dr. Andrews and then I'll try to summarize so we can move on to Question 2.

DR. ANDREWS: I think all of these points are excellent about the importance of frequently reminding and having redundancies in the message. But I'm having a hard time figuring out how to address No. 3 without jumping to No. 5 which is the monitoring of outcomes because I think that I guess what I would suggest is there could be graduated approach to the information dissemination that could be coupled with monitoring the actual impact and looking at utilization patterns and seeing if it appears that the message is getting across.

If so, then perhaps those mechanisms and messages have been effective. If not, then perhaps

different methods, perhaps jumping to a black box or something might be warranted. But I think I would approach it in a more gradual way monitoring to see what is working and what isn't.

CHAIRPERSON CHESNEY: Thank you. So let me try to summarize.

DR. WILKIN: Dr. Chesney.

CHAIRPERSON CHESNEY: Dr. Wilkin.

DR. WILKIN: Yes. I just wanted to "- The gentleman from Novartis gave the assertion that patients would reliably and predictably get the box with the patient package insert in that and it occurs to me that I see a lot of patients coming and they have their tubes but they don't the box and they have the label actually stuck on to the tube. I think it's with the idea that that's how they want the directions. I guess I've never asked what happens to the box, but Dr. Pitts is our expert pharmacist, registered and licensed and all that. Do you want to "-

DR. PITTS: Thank you. There's no requirement to dispense the tube with the box and

frequently and it depends really on your training and I think what area of the country you're in. Because I remember when I was in Michigan, I had a great old time pharmacist who insisted that you put the label on the tube because that's where the information needs to be for the patient. The patient is going to use the tube or product. So you place the label on the tube.

Now some people will place the label on the box but if the box is discolored or if there is some integrity, something is wrong with the box, we'll throw away the box and the label and place the label on the tube. Or if you're in a hospital setting, you don't send the tube product up to the patient's floor in the box. In fact, you don't have enough space on your shelves to stock all those boxes. So you'll take the tubes out and you'll label the tube. It's not a certainty that always the box and the label will go with the product to the patient.

CHAIRPERSON CHESNEY: Thank you for that reassurance. Let me try to summarize Question 3 because we do want to move along and I think that we heard the repetitive messages coming from different

areas is good. Dr. Andrews suggested that maybe they should be graduated repetitive messages with some interim evaluations to see that the message is getting across.

I didn't hear anybody speak against a Dear Healthcare Provider letter. And I didn't hear anybody speak against professional organization letters which I think all of us do respond to information from our professional organizations. I think CME is like mother and apple pie. Although Dr. Fost feels that these are not always ethical.

The patient package insert is discouraging to hear and I think we would all totally agree with that. I don't know if there's any way to assure that the patients do get these package inserts. I haven't heard anybody speak for a med guide at this point or for a public health advisory.

So I think if we could move on to Question "-

DR. MURPHY: Joan.

CHAIRPERSON CHESNEY: Yes.

DR. MURPHY: There is just one piece of

information, just to have it out on the table because I think someone did bring up a good point. We do have a medication guide with a product that has a black box based on animals. So that has animal data. Usually it is known human risk. You're correct.

DR. DAY: Which drug is that with only animal?

DR. MURPHY: Forteo.

DR. TRONTELL: The drug product, I know that there's a medication guide. I don't know the label to know if there's a black box. Forteo teraparatide. This is a product that has a box. It has dose related risk of osteosarcoma. It's also selectively detailed and so there's another mechanism. I just want to make one comment. If people feel that it's critically important the patient get the information, the only way we can guarantee that happens is to make a medication guide. Patient package inserts, as Dr. Pitts has told, don't necessarily get to the patient.

CHAIRPERSON CHESNEY: And I think you made that point very well that that's the only one that is

mandated. Dr. Newman and then we'll go to Question 2 and we can come back to these if we have any further thoughts.

DR. NEWMAN: I guess I would speak in favor of the med guide for that reason. I think what we were concerned about is widespread prescription by physician and use by patients because of the perception that because these drugs are steroid-free they're safer than steroids. I don't think that we would reliably be able to affect that perception unless we get something into the hand of the patient who was getting the medicine that addresses that question directly. Although we finished, I guess my impression was that we do have human data of cancer from the transplant patients that the transplant patients get the lymphoproliferative disorders and cancers and the longer they're on it the more they get.

CHAIRPERSON CHESNEY: I think we had suggested that the FDA consider including that in the message based on the oral dosing and human information. I think this issue of the med guide is

a very important one and I'd actually like to get a show of hands. But is there anybody that wants to make comments about why they do or don't feel that the med guide "- Ms. Dokken.

MS. DOKKEN: I just want someone to refresh my memory. How is the med guide distributed? How does it counteract the problems of the patient insert?

CHAIRPERSON CHESNEY: Dr. Trontell.

DR. TRONTELL: The Medication Guide Regulations require the manufacturer to make the medication guide available or a means available for the pharmacist to distribute it with each product. Again, that might make again and Dr. Pitts can speak to her experience if that says this product should be dispensed with a medication. Give it to them with the box.

MS. DOKKEN: I have a follow-up question. So it comes directly at the time you pick up the prescription. If you're going to one of those huge factory pharmacies where nobody knows you, it doesn't have any personal discussion that goes with it.

Correct?

DR. TRONTELL: That's a separate aspect of pharmacy practice that the medication guide doesn't cover. What you're doing with the medication guide is that you're giving a person a piece of information you hope they will take away and read. You don't necessarily have the guarantee that it will be read and not discarded.

CHAIRPERSON CHESNEY: Dr. Day.

DR. DAY: Isn't it also true that a medication guide must be given with every dispensing? It's not just with every prescribing because if you get a prescription and you can have multiple refills, without a medication guide you might get some piece of information once. But with a medication guide, it has to be given every time it is dispensed to a given patient no matter how many times he or she gets the medication.

DR. TRONTELL: That's correct and I can only speak to what we've heard from pharmacy groups who I think are increasingly interested in moving to unit of use so they do less pill counting and may have

more opportunity to do more counseling as you've just described. I think when they are co-packaged, again many busy pharmacies might be just as happy to hand the box as opposed to take the time to take it out of the box and hand out the tube. So it's our impression from feedback from pharmacy organizations that if it's co-packaged that that's probably the best way rather than have an array of stacks in their pharmacy they have to search and give the appropriate one.

CHAIRPERSON CHESNEY: Dr. Guinan, if you could make it just one or two minutes.

DR. GUINAN: I would just like to clarify something and Dr. Santana has tried several times to say this. But if you are making the argument that these drugs are of concern because they're topical immunosuppressants, then obviously you're concerned about something which is a fact. They are topical immunosuppressants. So are topical steroids.

Now when you talk about topical immunosuppressants, then presumably you are concerned about immunosuppressant-related lymphoproliferative disease and you do not have any evidence that what you

have seen is immunosuppressed-related lymphoproliferative disease. You don't have the right latency. You don't have the right presentation. You don't have the right phenotype. You don't have the right pathology. You don't have right response to therapy and you don't have the right outcome in those patients to defend a diagnosis in anything that has been presented today of immunosuppressant-related lymphoproliferative disease.

Now I wouldn't argue that you might not have some other mechanism or some other issue. But this is not IRLD by any token. Now you can talk about other issues, but you can't keep on saying that what you're seeing is IRLD because you're not seeing IRLD by any of these criteria.

Now if you want to make a statement that topical immunosuppressants are dangerous to patients, then you have the right to do that and that's a valuable conversation that's going around here. I think Dr. Glode said exactly the right thing which is then the onus on the Committee, I would think, is to actually establish for those of us who are using those

drugs whether steroids are safe.

If the question arises whether using topical immunosuppressants is appropriate, then how appropriate are steroids and should they be part of this warning? But you don't have data that you have specific agents causing a specific known syndrome because there is no mesh here.

DR. NEWMAN: Excuse me. But you're talking about the adverse event reports. Right? And I'm talking about the one child out of 14 who had an area under the curve that was the same as the adult transplant patients. So that's my concern.

DR. GUINAN: He didn't get a lymphoma as do most transplant patients not get lymphoma.

DR. NEWMAN: Right. But are we saying that adult transplant patients are at no higher risk of malignancy or lymphoproliferative disease because if they are at higher risk then we would assume that babies who have these same blood levels might also be at higher risk and the effects have been demonstrated in human beings.

DR. GUINAN: "- five years at continuous

levels.

DR. GEHA: May I have your permission to address.

CHAIRPERSON CHESNEY: One minute please. We really, really need to move ahead.

DR. GEHA: Yes, because this question has been raised by Dr. Fant and I think by Dr. Santana. I want to make two points very quickly. One is that we saw a study in which these individuals were on the cream were subjected to what I consider as a pediatric immunology and somebody who sees also patients with atopic dermatitis as a litmus test for in vivo immune function which is delayed hypersensitivity test while they were on the cream. And because that requires antigen uptake, antigen presentation, co-stimulatory molecule, T cell activation, secretion of cytokine, recruitment of bystander cells and they showed the same results.

The second thing is just we should not forget that steroids have even a broader immunosuppressive function than cyclosporin and calcineurin inhibitor. First they work on the same

pathway downstream because you have a complex of a transcription factor one component of which is blocked by calcineurin inhibitor and that's the NFkB. The other one is blocked by the steroids and that the AP1 and the two factors work together.

In addition as was pointed out in the morning, they do inhibit NFkB. They inhibit Langerhans cell function. They do inhibit other things. So I think we need to be concerned also about the potential immunosuppressive effect of steroids at least to the same extent as we would with the calcineurin inhibitors. Thank you.

CHAIRPERSON CHESNEY: Thank you. I don't think we would disagree with that but I think the whole issue is that we're seeing signals of malignancy. But I will let Dr. Stern address that.

DR. STERN: I'll say nothing about lymphoma since I know virtually nothing about it. But when it comes to skin cancer if you look at the data supplied by Novartis, there are two case control studies by the same author looking at systemic steroids and the risk of non-melanoma skin cancer.

Barely significant. Low level. Lots of confounders and in fact, in the more robust of the two, no dose risk relationship. No good temporal relationship. Therefore we don't think they probably do much to skin cancer risk in the skin.

If you look at immunosuppressives if you take a well characterized cohort in Sweden, low initial risk and you go out two years relative risk with immunosuppression primarily cyclosporin at that time, fifty-fold increase in risk. You go out fives years, 100-fold increase in risk. To tell me that skin cancer is mainly a central immunologic event and not a skin immunological event defies logic.

To tell me that when you apply it topically and get very high levels in the epidermis and dermis and influence the trafficking of T cells and other immunological events topically at least as much as you do with 3 milligrams per kilogram of cyclosporin when given orally for atopic dermatitis just defies logic. If long-term sufficient application of this doesn't cause skin cancer, I would be shocked and amazed and it just is contrary to

everything we know and every analogy you can make.

PARTICIPANT: (Off microphone) "- for skin cancer, is it?

DR. STERN: No. That's right, but I wanted to be sure that people understand that skin cancer is an issue. That's why I said I'm not saying anything about lymphoma.

CHAIRPERSON CHESNEY: Thank you, Dr. Stern. We've almost gotten through Question 3, but I think we are at the level of the med guide. I think that from what I've heard or at least what I interpret as what I've heard is that the only way to guarantee that this gets into the hands of patients and providers is to require a med guide. I think we probably need to go around the room and take a vote on how many people would support a med guide with the messages that we've already recommended to the FDA. Let us start with those who are voting. Dr. Day, can you vote? Dr. Day, yes or no?

DR. DAY: I can be pushed either way on this and I've spent a lot of time and hours on medication guides and so on. I'd like to hear from

everybody else.

CHAIRPERSON CHESNEY: Can we make you an abstain?

DR. DAY: I'd like to pass at this point.

CHAIRPERSON CHESNEY: Okay. Jan, are you keeping track? Dr. Andrews.

DR. ANDREWS: I don't think there's any harm in providing the med guide but I wouldn't necessarily advocate for it. I think the strongest messages need to be given to the provider. I think by the time the patient gets the med guide it's a little late. I think they should have already had the discussion with the physician. So I sort of pass.

CHAIRPERSON CHESNEY: No. All right. Pass to Dr. Epps.

DR. EPPS: I would tend to favor to say no. I guess I would prefer that there were more. The data were stronger or was stronger. I guess it depends if the Agency feels that they can be very specific that it would be confusing to the patient. I had a cohesive message to give to a patient each and every time they get a box of the medication.

Maybe it should say physician medication guide rather than patient medication guide. I think that would be the place to start because they are the ones who are prescribing it. If a patient went back with a question, I don't know whether some physicians would be able to answer them.

CHAIRPERSON CHESNEY: I think that was no. Dr. Mattison.

DR. MATTISON: I'd say yes and I'd say yes for the reasons that I've described earlier. There's substantial uncertainty about a very serious health event.

CHAIRPERSON CHESNEY: Thank you. Dr. Fost.

DR. FOST: I abstain.

CHAIRPERSON CHESNEY: Dr. Stern.

DR. STERN: Abstain.

CHAIRPERSON CHESNEY: Dr. Garofalo. Don't vote. Dr. Gorman. Don't vote. Ms. Knudson.

MS. KNUDSON: I'm looking for any way to get the information out and if it is the medication guide, by all means let's do it.

CHAIRPERSON CHESNEY: Dr. Fant.

DR. FANT: I vote yes for the reasons that Dr. Mattison articulated and I think there's absolutely no harm in providing complete information to the families and the physicians and to the extent that we effectively communicate information, you're far less effective in communicating information that we think is important than they say on TV and in *USA Today*. I think we need to be just effective in communicating information we think is important that they should consider in making healthcare decisions.

CHAIRPERSON CHESNEY: Thank you. Dr. Bier.

DR. BIER: From my earlier comments, I guess you can decide I would say no. I'm having trouble. Maybe I'm a poor communicator, but I'm having trouble understanding how we're going to tell the people who don't know how to apply a thin film how to deal with this potential risk that they can understand less.

DR. DIAZ: I will say no concentrating on the physicians.

CHAIRPERSON CHESNEY: Thank you. Dr. Moore.

DR. MOORE: I agree. I would say no and concentrate on the package insert.

DR. GLODE: I would absolutely yes. Knowledge is power and parents should be empowered.

CHAIRPERSON CHESNEY: I say yes also. I think that it can be written in a way that patients can understand and if they have questions, that's even to the better to ask physicians and pharmacists "What does this mean." So I vote wholeheartedly yes. Dr. Santana.

DR. SANTANA: I would vote yes with a caveat that this has to be linked to making sure we do surveillance so that we get adequate reporting and we know five years from now what's actually happening. My comments earlier were how does the Agency know whether these tools work and I don't want to recommend another thing without the link that we at the end of this discussion five, ten years from now have data to support that this intervention did help.

CHAIRPERSON CHESNEY: Thank you. Dr.

O'Fallon.

DR. O'FALLON: I definitely vote yes as a non-doctor.. I think that it is very important for the public, for the consumer to know what's going on. But of course I assume that the labels in these things will be updated as more data becomes available and both drug companies have very good studies in the works according to the packages that we got beforehand. I am assuming that we will have better data and these will be made better as time goes on. But I think the public needs, the people who are using the stuff need to know that there are some issues.

CHAIRPERSON CHESNEY: Thank you. Dr. Newman.

DR. NEWMAN: I'll vote yes for reasons as I said before, the implied extra safety of the steroid-free attachment to it. When they say that all the time, I think it needs to be counteracted.

CHAIRPERSON CHESNEY: Thank you. Ms. Dokken.

MS. DOKKEN: Yes.

DR. DAY: May I now make my vote? I

passed before. I wanted to hear from everyone. The reason I originally said no is that the nature of the evidence has not risen to the level of the other medication guides that I knew of and I did not know there was one out that was based only on animal studies. So that can push a little more towards the yes.

I think the most important information to get into the hands of the patients is something that will affect their behavior, not to decide not to take it, but to decide to be cautious in the application. And it's not just knowing or not knowing what's a thin layer, but not to keep using it continuously. I think there needs to be wherever it's going to happen in the package insert or in the medication guide something that says "Do not use continuously."

I don't even think intermittent is a good term in patient material. "Use during a flare up" and duh-di-duh-di-duh and just spell that out and use appropriate language. So if it's going to guide the behavior of the application of the product in a safe way so that they get the benefit but they minimize the

risk, that would be great.

CHAIRPERSON CHESNEY: Thank you. I think you summarized what we all felt which was the precise wording has to be looked at very, very clearly. What was the final vote, Dr. Johannessen?

DR. JOHANNESSEN: Nine yeses, four nos and several abstentions.

CHAIRPERSON CHESNEY: Thank you. The abstainers will be counted. So I think we will move on to Question 2. The following questions address ways to manage potential risks of topical calcineurin inhibitors, and presume that you have indicated that at least some communication of information is appropriate. Under 21 CFR 201.57(e) special problems, particularly those that may lead to death or serious injury may be required by the FDA to be placed in a prominently displayed box. The boxed warning is usually based on clinical data but serious animal toxicity may also be the basis for boxed warning.

Does the Committee believe that a boxed warning is appropriate for the topical immunosuppressant calcineurin inhibitors? Please

explain your answer, whether the decision is yes or no. Comments before we take a vote. Dr. Fost.

DR. FOST: Well, I'm in favor of the boxed warning and it's for reasons similar to what Tom Newman said. To me, the central problem here is the marketing.

CHAIRPERSON CHESNEY: (Cell phone ringing.) I think it's yours, Dr. Fost.

DR. FOST: That it's the widespread use of this in a way that is not approved. It's not consistent with the FDA label and I'm assuming that that's heavily due to industry advertising marketing through the various means that they do that which is just one example of it. So I wish that there were more finely-tuned ways for the Agency to control the marketing, but I'm gathering that there aren't. Therefore this somewhat blunt instrument of the box it seems to me as Tom says is one of the ways of getting the doctor's attention to counteract the ads. If the ads and the other marketing techniques were more responsible, it wouldn't be necessary.

So I'm in favor of the box, but what the

box should say in my view is not that these things cause cancer, but to me the main thing on the box is in the opinion of the FDA that this should be a second-line drug. That's the main thing that the doctor needs to know is that the FDA thinks this should be a second-line drug.

CHAIRPERSON CHESNEY: I think when we did Question 1 and abbreviated our message, that would be the message we would ask them to put in the boxed warning. I think what I would like to do is to go around and get everybody's vote about this and this gives everybody an opportunity to make an particular comments. Dr. Day.

DR. DAY: There's an inherent circularity in taking an action and trying to get an outcome measure later because if we institute a boxed warning, medication guide, whatever it is, and it does then reduce the exposure, then we're going to be reducing the exposure that could then pop up the cases later of the various cancers.

DR. FOST: I think that's the point.

DR. DAY: So the measures, therefore we're

going to have to look at other kinds of measures as to whether it's working in No. 5 which might be fewer prescriptions for kids under age two, a decline in sales per person and appropriate measure and so on and so forth. So sure. Yes.

CHAIRPERSON CHESNEY: The correction was that it was ten to four for the med guide with Dr. Day's vote. Dr. Andrews, yes or no?

DR. ANDREWS: I really don't want to give up on the other methods for affecting behavior by other kind of communication strategies and I think a leap to a black box may be an admission of defeat. So I would recommend a more graduated approach within intensive efforts to communicate the messages that we think are important and to measure the effectiveness of those and move to more extreme measures if those don't work.

CHAIRPERSON CHESNEY: Is that a no? Dr. Epps, yes or no?

DR. EPPS: Well, initially I was leaning more towards a no, but I think a black box certainly draws your attention. It grabs you particularly

physicians whom I'm trying to focus on. Perhaps it could be in bold writing, in PDR and bold writing. I don't know if that's an option as well. But it would make the physician think before they write a prescription. I assume that if more data became available, the black box would go away if it was proved that it did not cause cancer. I have no idea.

DR. MURPHY: We always would prefer to have accurate outcome "

DR. EPPS: More information.

DR. MURPHY: Yes. And if we did get information that contradicted that, yes, it would come out.

DR. EPPS: Has any black box ever been eliminated?

DR. MURPHY: I think yes. In the HIV arena, there have been products under Subpart D that have come in some other additional "- yes.

CHAIRPERSON CHESNEY: Yes? We can stay until 8:00 p.m. or 9:00 p.m. if you want.

DR. EPPS: I guess I would say yes.

CHAIRPERSON CHESNEY: Dr. Mattison.

DR. MATTISON: Yes and again I'd like it to focus on the uncertainty for this severe outcome. It would be helpful, I know it's difficult, but it would be helpful if the Agency could think a little bit about how to help practitioners communicate and discuss with patients that uncertainty. Clearly, the Academy can do that as well. And presumably because the post-marketing agreements of both manufacturers have included I believe some detailed follow-up studies. There will be information available to help address that uncertainty in time.

CHAIRPERSON CHESNEY: I think both this discussion and the anti-depressant discussion point out so clearly how important communication is and how difficult it is to do it. Dr. Fost, yes or no.

DR. FOST: Yes and the main content of it in my view should be that the FDA has approved these drugs in children over two as a second-line therapy.

CHAIRPERSON CHESNEY: Dr. Stern.

DR. STERN: Yes and although I almost always agree with Dr. Andrews, I think the data we've seen here today that in historic context is most

compelling is that when our Advisory Committee met in 2000, we said these are a useful addition to our therapies but should be used judicially. When we met 16 months ago, we emphasized the need for judition and in fact for at least one of these two agents roughly the sales since our last meeting are 90 percent higher than they were on an annualized basis in the first two years. You take that trend forward and a large proportion of our GDP will be going to this product.

CHAIRPERSON CHESNEY: Thank you. Dr. Gorman, you can't vote, can you?

DR. GORMAN: I can't vote but I'd like to make a comment.

CHAIRPERSON CHESNEY: Let me think about that a minute. Okay.

DR. GORMAN: Several black boxes have been notoriously in ineffective in changing prescribing patterns and my favorite example of that is a medicine widely used as a cough suppressant which has a black box for apnea in children less than two which is still used in children less than two as a cough suppressant. So I would not want to vote on whether or not to put

a black box on it, but the message I think needs to one that's actable on by physicians. While I think that Dr. Fost starts to get to that point, if there is any extra communication, I think the other thing that will be in the practice parameter that will be an easy sell to both parents and physicians is that these drugs should be used intermittently.

CHAIRPERSON CHESNEY: One of the messages, I don't know if you had that when we answered one but we want to be sure that it's not continuous. Please add that to the message. Ms. Knudson.

MS. KNUDSON: Yes, to the black box.

CHAIRPERSON CHESNEY: Dr. Fant.

DR. FANT: Yes.

CHAIRPERSON CHESNEY: Thank you. Dr. Bier.

DR. BIER: I'm going to abstain from this not because I don't think some of the messages are important but I'm not sure of all of the ramifications of the black box. So I'll abstain.

DR. DIAZ: Yes.

CHAIRPERSON CHESNEY: Dr. Moore.

DR. MOORE: Yes, but I disagree with some of the other comments about what should be in it. I think we should just put in the black box what we know about these agents and that is that seems to be data that is carcinogenic in animals and there's a plausible mechanism that it may increase risk in humans. I think as far as all the other comments go, the altering behavior comments on the part of physicians, that should be just in the content of an edited PI.

In other words, that it should be used intermittently. That it's a second-line drug. All of this stuff is really just speculative on our part. We don't know that any of these things really matter in terms of whether or not there's a cancer risk here. So I think these are just our recommendations about it and they're based on a lot of speculations. They do not raise to the level of being coated with a black box.

CHAIRPERSON CHESNEY: Thank you. Dr. Glode.

DR. GLODE: I would vote yes. It looks to

me from the information like as was mentioned it's over one million prescribers a year in young children less than age 16 down to zero. And I agree completely with Dr. Moore that I think the black box should emphasize the topical applications in animals resulting in lymphomas and the biologic plausible risk to humans.

CHAIRPERSON CHESNEY: We had, I think, in the message initially indicated that we wanted to include Bullet 3 which was increased potential risk of cancer with increase in the dose or duration of exposure as based on the animal studies. Is there a change in that now? Okay. Thank you.

DR. FOST: Just from my own view, I think a doctor reading about animal studies, the eyes glaze over. They don't know what it means. To me the more potent thing is "The FDA has approved this drug only for children over the age of two as a second-line drug." That is something every doctor will understand and it will cause him or her to think carefully. It should refer to information elsewhere that potential risk of malignancy, but that message will if for

reasons only of liability cause them to think carefully about prescribing it. That's the intent.

CHAIRPERSON CHESNEY: Thank you. And that was part of the original message we suggested. I vote yes. Dr. Santana.

DR. SANTANA;: I vote yes. No further discussion.

CHAIRPERSON CHESNEY: Dr. O'Fallon.

DR. O'FALLON: I vote yes. I have a reason. I think that first we know that the public are being influenced by the ads. There's a lot of evidence to that effect. I think that's an important thing to get a handle on. The second thing is what Dr. Gorman said about the physicians are being influenced by the drug reps number one. So I think this is a way of reigning in some of the free spirit stuff here. That's why I'm voting yes.

But I'd like to say that one other piece of information that might be of value is the fact that there really isn't any long term data that help us to assess something that has a long-term effect like cancer, latency period like cancer. That might be

something that would be considered for the box.

CHAIRPERSON CHESNEY: I think we mentioned the latency issue as something to include in the message.

DR. O'FALLON: But no long-term data. I don't think anybody said that yet.

CHAIRPERSON CHESNEY: Thank you. Dr. Newman and then Ms. Dokken.

DR. NEWMAN: I vote yes and including the things that we talked about for Question 1.

CHAIRPERSON CHESNEY: Thank you.

MS. DOKKEN: Yes.

CHAIRPERSON CHESNEY: Thank you. Dr. Day, we need clarification of your vote.

DR. DAY: I did end by saying sure. I should have said, "And I vote yes." Now I've been persuaded.

CHAIRPERSON CHESNEY: Thank you. We'll move on to Question 4, Risk Minimization. In addition to communicating information about risk, there are a number of ways to help ensure that products are used appropriately. A. Does the Committee recommend that

in addition to communicating risk information, additional mechanisms be employed to minimize risk to individual patients or to the population at large? If yes, what should the goal of such mechanisms, for example additional education, restrictive distribution, increased frequency of patient assessment)?

What should be the goal of such mechanisms? Let's start with Part A first. So do we recommend additional modes of communication in addition to the med guide and the black boxed warning and I think we also agree in Question 3 with a professional organization letter and patient package insert and continuing medical education courses although there wasn't much discussed about that. Are there other ways that people feel this risk could be communicated?

DR. FOST: This is wishful thinking but I just have to report that a cat cloning company has just opened up in Madison. It's called Genetic Savings & Clone. It's true. Their website, which is a model website for your information, includes all

published articles against cat cloning. That is very cogent articles by very thoughtful ethicists and others.

It's a model of responsible public information. It would admirable if a pharmaceutical company did that also. That is included in the information available to doctors articles like the steroid phobia article and whatever literature out there exists about what reasonable people say who have concerns about the use of the calcineurin inhibitors. Needless to say, the FDA can't make them do that.

CHAIRPERSON CHESNEY: Thank you. Other suggestions for additional ways to communicate this information to patients, healthcare providers?

DR. EPPS: Can I just comment that I think you've already done it by calling the meeting? I've already had several patients that said, "Oh, I saw the article in the paper last weekend." We're having our dermatology meeting later this week. I'm sure there will be discussion. So needless to say, we'll wait for the Agency to make their final determination, but I think simply by convening the meeting, I think that

has been very helpful.

Also as I stated earlier, articles on some of our unsubscribed journals and papers and Academy materials or even the *AMA News*, I don't know what else you want to put it in, that does reach a lot of people particularly if you don't subscribe and it shows up. If it's on the front, you tend to look at it.

CHAIRPERSON CHESNEY: Thank you. Let's go on to B and then Dr. Glode has a comment. Examples of approaches that have been used for other products are listed below. Does the Committee recommend any of these approaches, or other approaches, for these products at this time? If so, state how the intervention would address the goal cited previously, specialized training for prescribers, limiting use to prescribers with specific expertise or training, limiting the amount that can be dispensed to a patient in a given period of time or other? Dr. Glode, you had a comment.

DR. GLODE: Well, it was just back to the issue if there is a significant change in the label which I would have thought a black box warning would

constitute a significant change to the label. Is it common when that happens that the sponsor elects to send a "Dear Doctor" letter there's been a change in the label or anything like that? I would have thought that would follow rather naturally but it doesn't.

DR. TRONTELL: In general, that level of change in labeling in my experience has almost always been accompanied by a Dear Healthcare Practitioner letter. It would be the exception that that hasn't occurred.

CHAIRPERSON CHESNEY: Dr. Gorman and then Dr. Fant.

DR. GORMAN: A question for the FDA. When black boxes are added to the labels, are the labels then opened for the manufacturers to update the label in other areas as well?

DR. WILKIN: Yes.

CHAIRPERSON CHESNEY: Dr. Fant.

DR. FANT: Yes. I really can't see any other ways in addition to the ones we've already talked about that would have an impact on this. I'm not sure there's any need to. I think all of these

things the outcomes that we're concerned about as well as the prescribing practices, all of those sorts of things, are going to be monitored over the next few years.

If need be, things like limiting the amount that can be dispensed can be addressed and limiting use to prescribers with specific training or areas of expertise can be entertained, but I really don't see based on what we've spoken about today where anything else would be more effective in doing the things that we've talked about today.

CHAIRPERSON CHESNEY: I think that the FDA would like a vote on this as well. Is that correct?

DR. MURPHY: I think if you would like to vote that you don't need anything else, that would be helpful at this point. I do want to clarify one thing though, the healthcare provider letter. Is the Committee assuming that that's going to go in because there's a black box? Is that what we're hearing? Is that going to happen? That's what I'm trying to ascertain. We're saying it usually does, but we're asking you back in a way. Is that what you're

thinking should happen is what we're asking.

CHAIRPERSON CHESNEY: My understanding was that we were making the recommendation for a healthcare provider letter.

DR. MURPHY: I always want to clarify.

CHAIRPERSON CHESNEY: Yes.

DR. MURPHY: Okay. So you are making a recommendation for a healthcare provider letter and then as I said, you don't need to vote on every one of these because I'm getting the feedback that you think we ought to do things in stages and that this ought to be the first stage. But yes, it would be helpful to have a vote that you didn't think we needed to do any of the rest.

CHAIRPERSON CHESNEY: So I think if we could go around the room and vote on Question 4 and the question being "Do you think we need any additional mechanisms to communicate this information?" The answer would be "Yes, we do need to review additional mechanisms" or "No, we've already recommended strongly enough for this stage."

DR. DAY: No.

CHAIRPERSON CHESNEY: No, we do not need additional mechanisms. Dr. Andrews.

DR. ANDREWS: No, we don't need them now but we should look at the data on utilization patterns and see if we might change our views a year from now.

CHAIRPERSON CHESNEY: Thank you. Dr. Epps.

DR. EPPS: No, I agree with Dr. Andrews.

CHAIRPERSON CHESNEY: Dr. Mattison.

DR. MATTISON: No.

CHAIRPERSON CHESNEY: Dr. Fost.

DR. FOST: No.

CHAIRPERSON CHESNEY: Dr. Stern.

DR. STERN: No.

CHAIRPERSON CHESNEY: Ms. Knudson.

MS. KNUDSON: No.

CHAIRPERSON CHESNEY: Dr. Fant.

DR. FANT: No.

CHAIRPERSON CHESNEY: Dr. Bier.

DR. BIER: This is the only opportunity for my no vote to count. No.

DR. DIAZ: No.

CHAIRPERSON CHESNEY: Dr. Moore.

DR. MOORE: No.

CHAIRPERSON CHESNEY: Dr. Glode.

DR. GLODE: No.

CHAIRPERSON CHESNEY: Dr. Chesney. No. Dr. Santana.

DR. SANTANA: No.

CHAIRPERSON CHESNEY: Dr. O'Fallon.

DR. O'FALLON: No.

CHAIRPERSON CHESNEY: Dr. Newman.

DR. NEWMAN: I would say no to the first two issues, specialized training for prescribers and limiting use to prescribers with specific expertise of training because I don't think what to tell them. It seems like it might be reasonable to limit the amount that could be dispensed to a patient in a given time period. I guess that doesn't seem like that would be particularly burdensome. So I would vote to keep that open as a possibility. Although I'm not sure from what Dr. Stern said it couldn't still go a bunch of different pharmacies and doctors. But I would keep an open mind on that one.

CHAIRPERSON CHESNEY: Thank you. Ms. Dokken.

MS. DOKKEN: No.

CHAIRPERSON CHESNEY: Thank you. Dr. Johannesen, do we have votes for the black box warning and for Question 4 and then we'll move on to Question 5?

DR. JOHANNESSEN: Yes. For Question 4, it was one possible yes and the rest no. So we had 16 no. For the black box, it was 15 yes, 1 no, 1 abstention.

CHAIRPERSON CHESNEY: Thank you. Moving on to Question 5. Based on the goals for any of the recommended approaches in your answers to questions one through four, consider how the FDA should or could measure the success or failure of these approaches. (A) What would be reasonable performance measures and sources of data? Examples might include reports to MedWatch, active surveillance, additional clinical trials, drug utilization data, managed care databases, physician or consumer surveys, etc. and (B) how long or over what period of time should the FDA assess the

interventions? I think Dr. Day's reflection that best of all possible worlds would be that everything turned out to be negative. Dr. Santana.

DR. SANTANA: Before we take a vote on that, I heard various discussions today particularly from the sponsors that there were a number of trials that were either planned, ongoing or something that I think would be important for me in the bigger picture of where we're going to be five years from now and how I potentially could interpret how this particular intervention that we agreed upon today would impact that or would impact the modification of those studies.

So can somebody give a sense of the scope of those studies? What questions are going to be answered with those studies and where are we going to be because I think it relates to how we decide what further information we may want or how those studies need to be modified to be able to gather that information? It works both ways I think.

CHAIRPERSON CHESNEY: I think Novartis had in our background materials a fairly extensive

description of the registries that they have established. A brief comment.

DR. PAUL: Yes. A brief comment. We have a pharmacoepidemiologic study ten years of children for which there would be yearly evaluation of the data. There are two large clinical studies in infants evaluating the long-term safety for which an independent review by data safety monitoring board will be submitted on the quarterly basis. We have a series of case control studies to evaluate the risk of skin cancer. The first study will provide results two years from now and the second one in three years from now. That's for Elidel.

CHAIRPERSON CHESNEY: Thank you. Dr. Rico.

DR. RICO: For Protopic, there have been two recent studies initiated X-US that are long-term pharmcovigilant studies. There's an ongoing long-term safety study which has been ongoing for a number of years in Europe and will continue and in `05, a ten year registry study, multinational, will initiate which will focus on children and will evaluate the

risk for both systemic and cutaneous malignancies.

DR. SANTANA: So both of those studies, it's going to take us ten years to get data. Is that correct?

DR. RICO: However, the assessments will be ongoing in those studies. Patients who are eligible to enroll in those studies will particularly include subjects who participated in clinical trials for the product. Since those studies initiated in 1996 depending on how you begin to count, there are a number of children who have already accrued significant exposure over time. Thank you.

DR. MURPHY: Joan, we have two people from FDA who might wish to comment on this. Unfortunately, the primary reviewer on this just left. But Dr. Anne Trontell and Dr. Nikhar.

DR. TRONTELL: I can try and speak for Dr. Lagranade who had to leave that there have been some discussion back and forth between the Agency and the sponsors about the details particularly of the protocols and some important aspects of follow-up for patients in the registry sense. Ascertainment and

longer duration are obviously going to increase the power of such registries to inform this Committee and the Agency about safety.

I believe there are still some differences to be ironed out that we'll probably pursue. I think it's great that accrual has started but the protocols have not yet met the Agency's bar to my understanding.

CHAIRPERSON CHESNEY: Dr. Nikhar.

DR. NIKHAR: That's right. I think the main issues have been about the number of patients to be involved and the length of follow-up and also about how these patients will be followed over the years. One issue that's come up is that patients should have annual physical exams. That's an issue that's being negotiated with one of the companies. One of the companies has submitted a protocol that's more so in keeping with what we wanted as the other company hasn't. So that's being worked on right now.

CHAIRPERSON CHESNEY: Dr. Andrews.

DR. ANDREWS: Yes, I think there are several levels of possible outcomes. One is to look at the actual safety data and I haven't seen enough

information about the studies to be able to judge whether I would feel that they adequately address the issues of skin cancer and lymphoma.

But the other question that I interpreted No. 5 is was whether the interventions proposed today were deemed adequate and I think there are two types of assessments that could be done. One would be surveys of physicians, probably pediatricians and dermatologists, to assess their knowledge and awareness of the issues that are intended to be communicated and that could be done at different points in time depending on when the interventions took place.

Then an assessment of actually whether that knowledge translated into behavior and I would suggest that that's fairly easy to study in longitudinal databases where you could look at utilization by age and by prior use of corticosteroids and if you were clever, you could probably look at risk factors for cancer if we were suggesting that people who were immunocompromised should not be taking drugs. You could look at some prior exposures and

diagnoses.

CHAIRPERSON CHESNEY: Thank you. Dr. Day and then Dr. Epps.

DR. DAY: If you're going to survey physicians, you could also survey patients depending upon what communications you want to get out. If we are concerned about continuous use of these products, it would be very interesting to catch patients who are currently taking the products and all they have seen or not seen is a patient package insert and have either a laboratory study or a survey asking, "Is it all right to take this continuously," etc. and then catch them now versus when the medication guide has been out at certain points over time and compare their knowledge of whether that's okay to do. Now it's not exactly a surrogate endpoint, and it's not saying how much they're using it, but taken together with the drug utilization, that might be an interesting comparison.

CHAIRPERSON CHESNEY: Thank you. Dr. Santana.

DR. SANTANA: I wonder and this is

probably something that we need to explore more with the Children's Oncologist Group (COG) and the pediatric NCI branch is since most children with cancer will get registered on the SEER database whether it's lymphoma or unusual skin cancers. We're going to know about those kids. What we're not going to know is what the risk factors were or their exposure to these medications.

So I wonder if we should have a conversation with the COG and other institutions that treat children with lymphomas and skin cancer whether there is a way that through cancer and prevention control protocols or cancer and prevention control surveys we could get a mechanism to capture more data specifically on those patients that are being diagnosed in the U.S. I can't tell you right now how to do it but I know that there may be through the cancer and prevention control program at COG there may be a way to ascertain this with more information prospectively. That may be something we could do.

DR. MURPHY: So you're suggesting that we try to hook the trial, the registry, that we're

developing and in addition there would be linkage. In other words, the company needs to have somehow have contact with people at COG so that they can communicate how this information would relate back to COG.

DR. SANTANA: Right.

DR. MURPHY: When someone shows up because you guys do. You pick up most of the kids in this country. So what you need is to make those links back with the company is all I'm trying to say so that then you can make some sort of ascertainment, confounded through it will be by a number of things over time.

DR. SANTANA: Right. I mean if the company has a registry of all the kids, for example, in the U.S. that are receiving these products and they ascertain a number of lymphoma cases, we should be able to pick those up at the other end. Right? We should be asking our patients who develop lymphomas "Have you been exposed to these drugs?" So there should be some cross communication between those two sets of data.

CHAIRPERSON CHESNEY: I like that idea.

Dr. Epps and then Dr. Glode.

DR. EPPS: I agree whether it's the children's cancer study group or perhaps even through some NHANES surveys, perhaps incorporate a question there. Maybe that's a possibility, but I would definitely plug in with the children oncologists perhaps whether they incorporate that into routine exposures or perhaps promoters or other factors. That may be a helpful way to pick them up on the other end.

A lot of children don't remember having atopic dermatitis or eczema. It's gone by they're one. Or my mother told me I had it but I don't remember. It is a childhood disease and we've been talking about the more severe ones, but there are a lot of ones who are very mild who are getting these medications and are being exposed and it resolves and it's gone. As recently as a couple of weeks ago, I had an eight week old who had been treated with one of these. So whether that was indicated or not, it's happening.

CHAIRPERSON CHESNEY: Dr. Glode and then Dr. Mattison.

DR. GLODE: I would absolutely defer to the epidemiologists around the table here, but on page 56 of the Novartis briefing materials are a series of their proposed studies, long-term safety studies, and while I certainly agree with the long-term registries, I was surprised that I didn't see some sort of case control study looking at an outcome of interest of lymphomas since there are according to some of these materials 1700 children less than 16 years old who develop lymphoma every year in the U.S., most of whom I believe are probably previously healthy children if you will if the prevalence of atopic dermatitis is 20 percent in the population. It seems to me that even though it's not a perfect study it would give you quicker information about risk factors of lymphoma in previously healthy children if you had controls.

CHAIRPERSON CHESNEY: Thank you. Dr. Mattison and then Dr. Andrews.

DR. MATTISON: Yes. I'd like to ask that the monitoring of outcomes discussion focus a little bit more on how the FDA and the sponsors assess the

beneficial impact of the black box and of the patient information. I guess what I would propose is that some attention be given to a periodic reporting on prescriptions in under two year old kids, perhaps a modification of prescription patterns and then characterization of practitioner and parent understanding of the information about the uncertainty that's prompted these warnings to be evaluated.

CHAIRPERSON CHESNEY: Thank you. Dr. Andrews.

DR. ANDREWS: In response to the question about a case control study for lymphoma, I think because of the long latency case control studies typically rely on patient recall or position recall and I think it's hopeless with something that's a topical product. I think a more effective way trying to be efficient in the design is to enroll a large cohort as is proposed and then not looking at SEER because that only covers a fairly small portion of the U.S. population, but all states have cancer registries.

You could actually if you conduct the

study in the states where you have good quality reporting, then you can do full follow-up on virtually everybody that's enrolled through linkage with these cancer registries for long latency. Then you need to be concerned about what are the intervening exposures and changes of exposure. That's certainly doable.

CHAIRPERSON CHESNEY: Could I just ask you to expand on that? So you would identify the patient based on the fact that they had come to the attention of the registry and then you would have to go back and look at recall.

DR. ANDREWS: Then you could if you have good prospective data on the patients who are receiving treatment and consent. Then perhaps on an annual basis you can link the information on the patients enrolled in your registry with the cancer registry and then you'll get the actual date of cancer diagnosis and pathologic confirmation and virtually complete ascertainment assuming the patient is still in that state.

CHAIRPERSON CHESNEY: So it's almost active surveillance in the sense that you have a

registry. It's just that you're not contacting them in an ongoing fashion.

DR. ANDREWS: You could contact them on an ongoing fashion. It's a prospective cohort study with ascertainment verified by cancer registries of the outcome and you could also supplement for people, for us, to follow up a search in the National Death Index for patients who might have died and get cause of death.

CHAIRPERSON CHESNEY: It's a prospective cohort study with active surveillance and checking through the cancer registry. Thank you. Other comments or suggestions for Question 5? Let me ask Dr. Murphy and Dr. Cummins if you need a vote on this or have we provided enough?

DR. MURPHY: Just a summary. It's a clear that everybody agrees we need ongoing surveillance and we're going to try to do that through a registry. We're going to try to link it up with the cancer registries and some other aspects of that type of trial. I guess the other thing that we just need to know because a number of things have been mentioned

here is the periodic reporting in child under two who are using the product under two was mentioned as something. What are we going to measure? Everybody's been saying we have to stage this effect.

We know we're not going to get these reports. So what are our outcome measures? Is it going to be a decrease in the use in children under two? Is that going to be the main outcome goal that we want to look at? I'm asking because that's what I sort of heard thus far. If others have heard something else, please let me know. Did you hear anything else, Anne?

DR. TRONTELL: You know as Dr. Andrews said drug utilization data will tell us, but can we say at this point is there some level of use in the under two population that we would want to target as appropriate? If it goes down from one million to 900,000, is that enough? Is that what you're asking?

DR. MURPHY: Yes. Are we saying we want to see "- Because we've also heard that we know again that there are going to be some kids that are going to fail other therapies and they need to be able to have

access to this and we're not trying to deny that access. But is there a reasonable boundary on this we're asking you because if we're saying, let's just pick the million because that's a nice round number. Let's say we have one million right now who are using this product who are under two, and I have to do the math, 20 percent of the population have and how many in the population of under two and do that. Is that the kind of number you want us to come up with?

DR. FOST: Well, first of all, if it goes down rather than up, that would be given Dr. Stern's comment about the rate of rise. If that even plateaued or went down, obviously that would suggest that the prescribing is more in keeping with the FDA approval. But I don't know how we can answer your question precisely without knowing what the incidence of failed steroid therapy is or contraindications that need the dermatologists for a ballpark figure of that.

CHAIRPERSON CHESNEY: Dr. Gorman and then Dr. Stern and Dr. Newman.

DR. GORMAN: One of the wonderful things about not being an epidemiologist is I can give

epidemiology outcomes which is that I would like to see the proportion of Elidel prescriptions in children less than two fall. So if the use goes up, the percentage of use goes down. That would tell us that the message that we're trying to drive home has gotten out there and that is independent of future Elidel sales.

CHAIRPERSON CHESNEY: Dr. Stern.

DR. STERN: I guess I'm even more ambitious. I would consider it a great stride for public health if prescriptions leveled off and the proportion under two went down.

CHAIRPERSON CHESNEY: Thank you. Dr. Newman.

DR. NEWMAN: Actually, I agree with Dr. Andrews and Dr. Mattison both said. I think Dr. Andrews' first comment was about using managed care databases to look at things like whether these were being used first-line or whether there was a previous prescription for steroids and to see what the trends are and usage at different age groups.

I think Dr. Mattison suggested if we're

going to do this black box warning and Dr. Trontell had previously said we don't really have data on how they work. Some sort of patient surveys are about whether they understand it. Whether people who are using these medications are aware that there's this uncertainty about cancer risk and have decided to use it or whether they just never got that message at all.

CHAIRPERSON CHESNEY: Thank you.

DR. MURPHY: I think you have it. Thank you.

CHAIRPERSON CHESNEY: Thank you very much. Dr. Murphy or Dr. Wilkin or Dr. Cummins, do you want to make any closing remarks?

DR. MURPHY: I just wanted to say what somebody echoed. We wouldn't have brought it to you if it were easy. We know it's not easy and we know there are people who need the product. Yet we know there's uncertainty and we appreciate your help in trying to manage this while we find more certainty.

CHAIRPERSON CHESNEY: And I want as always to thank you all really and the companies for the excellence of the background materials we received and

again for the excellence of the presentations. They really are very helpful. So thank you. Dr. Wilkin, the final word.

DR. MURPHY: And Jan, we want to thank you.

DR. WILKIN: I'd also like to thank Ms. LaDonna Williams and Mr. James Hendricks. They did come and talk to us about their children and how atopic dermatitis impacted on their families. I think that's a story the dermatologists, pediatricians and others hear all the time and there is a need for safe and effective products and there's especially a need for when there is a product getting the labeling as correct as we possibly can given the limited information we have. I deeply thank the Committee for wrestling with the uncertain database that we have and giving us suggestions on how we might improve labeling. Thanks.

CHAIRPERSON CHESNEY: Thank you and, yes, thank you to Dr. Johannessen because none of this would have happened without all of his efforts. Thank you.

(Whereupon, at 5:24 p.m., the above-entitled matter concluded.)