FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

Friday, April 15, 2016

8:00 a.m. to 2:35 p.m.

Hilton Washington D.C./Gaithersburg

620 Perry Parkway

Gaithersburg, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. ROUMIE: Good morning. I would like to remind everyone to please silence their cell phones, smartphones, and any other devices if you have not already done so. I'd also like to identify the FDA press contact, Andrea Fischer.

My name is Christianne Roumie. I'm the chairperson of the Nonprescription Drugs Advisory Committee, and I'll be chairing this meeting. I will now call the Nonprescription Drugs Advisory Committee meeting to order.

We'll start by going around the table and introducing ourselves, and we'll start with the FDA to my left and go around the table.

DR. GANLEY: I'm Charlie Ganley. I'm the director of the Office of Drug Evaluation IV.

DR. MICHELE: Terri Michele, division director, Nonprescription Drug Products.

DR. OUSSOVA: Tatiana Oussova, deputy

director for safety, Division of Dermatology and Dental Products.

DR. FILIE: Jane Filie, lead medical officer, Division of Nonprescription Drug Products.

DR. BROWN: Paul Brown. I'm an associate director for pharmacology and toxicology in the Office of New Drugs.

DR. ENGLE: Good morning. I'm Jane Engle. I'm a pharmacist, and I'm professor and head of pharmacy practice at the University of Illinois at Chicago.

DR. GUDAS: Good morning. I'm Lorraine Gudas. I'm the chairman of the pharmacology department at Weill Cornell Medical College of Cornell University in New York City.

DR. KATZ: Good morning. I'm Ken Katz, dermatologist at Kaiser Permanente in Pleasanton, California.

DR. BIGBY: Hi. Michael Bigby, dermatologist, Beth Israel Deaconess Medical Center, Boston.

DR. PISARIK: Paul Pisarik, family

physician, St. John Health System in Tulsa, Oklahoma.

DR. CHOI: Moon Hee Choi, designated federal officer.

DR. ROUMIE: Christianne Roumie. I'm an associate professor of internal medicine and pediatrics and also a staff physician at the VA Medical Center in Nashville.

DR. SCIALLI: I'm Tony Scialli. I do OB/GYN at George Washington University, and I'm a consultant in reproductive and developmental toxicology.

DR. HARRIS: Good morning. My name is Steve Harris. I'm from San Diego, California. I'm a consultant. I practice in the world of developmental and reproductive toxicology in the preclinical sector.

DR. WU: Good morning. I'm Victor Wu. I'm a managing director for population health at Evolent Health here in Washington, D.C. and a staff physician at the Washington, D.C. VA Hospital.

DR. JONIAK-GRANT: Good morning. I'm

Elizabeth Joniak-Grant. I am here as the patient representative.

MS. BERNSTEIN: Hi. I'm Cheryl Bernstein. I'm a registered nurse. I'm the director of Bernstein Clinical Research Center, and I represent -- I'm a consumer representative for the panel.

DR. D'AGOSTINO: Ralph D'Agostino from Boston University, statistician and also with the Framingham study.

DR. PRUCHNICKI: Maria Pruchnicki. I'm a pharmacist and associate professor at the Ohio State University College of Pharmacy.

DR. MICHAEL COHEN: I'm Mike Cohen. I'm a pharmacist with the Institute for Safe Medication Practices, and our focus is on drug safety, specifically medication error prevention.

DR. OBICAN: Good morning. Sarah Obican. I'm a maternal fetal medicine specialist at the University of South Florida and assistant professor and teratologist.

DR. RASMUSSEN: Sonja Rasmussen. I'm a

pediatrician and a clinical geneticist at the CDC.

DR. SULTAN: I'm Marla Sultan, clinical development at Pfizer. I'm the acting industry representative.

DR. ROUMIE: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

Now, I'll pass it to Moon Hee Choi, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's meeting of the Nonprescription Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of

this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of the regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services, which the government may expect from the employee.

Related to discussions of today's meeting, members and temporary voting members of this

committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves a discussion of data submitted by Galderma Laboratories to support a supplemental new drug application 20-380 for over-the-counter marketing of adapalene gel 0.1 percent. The proposed OTC use is for the treatment of acne and to clear up acne pimples and acne blemishes.

The applicant proposes to label the product for 12 years and older. The committee will be asked to consider whether data support an acceptable risk-benefit profile for the nonprescription use of adapalene gel 0.1 percent by OTC consumers. This is a particular matters

meeting during which specific matters related to Galderma's sNDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee member and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Marla Sultan is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Sultan's role at this meeting is to represent industry in general and not any particular company. Dr. Sultan is employed by Pfizer.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on

the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. ROUMIE: We will now proceed with Dr. Michele's introductory remarks.

FDA Introductory Remarks

DR. MICHELE: Good morning, Dr. Roumie, members of the committee, as well as our guests from Galderma, and members of the public. My name is Terri Michele. I'm the division director of Nonprescription Drug Products, and on behalf of the division and all of us here at FDA, it's really my pleasure to welcome you here to the Washington area.

So today we're here to discuss, as you heard, the new drug application for over-the-counter marketing for adapalene 0.1 percent gel

for the treatment of adults and children ages 12 and older with acne.

Before we get started, I just wanted to take a moment to thank the members of the committee for taking time out of their very busy schedules to thoughtfully review the briefing package and to be here today. Please know that your input today is extremely valuable to the FDA, and we take your comments very seriously.

So adapalene, known under the prescription trade name of Differin, is a topical retinoid. While we do have other acne medications available over the counter under the OTC drug monograph, if approved, adapalene would be a first-in-class switch. It would also be the first NDA product that's available for the treatment of acne for OTC use.

Adapalene 0.1 percent gel was approved in 1996 for the topical treatment of acne vulgaris in adults and children 12 years of age and older. As you see on this slide, it's available in a variety of different formulations, but today we're talking

about only the 0.1 percent gel.

I just wanted to note a couple of things about the other formulations that may be pertinent. First off, know that dermal absorption varies with formulation, and that's why we require testing for each formulation individually. For products with a potential toxicology signal such as this one, that's extremely critical in order to calculate the exposure margin.

I also want to point out that while most of these products are labeled down to age 12, the combination with benzoyl peroxide of 0.1 percent adapalene is approved down to age 9, and of course, as you all know, benzoyl peroxide is available over the counter.

The adapalene OTC development program relies on the safety and efficacy that was established for prescription use since an indication for acne is considered to be very similar between the OTC and the prescription settings. As such, it's not necessary to reestablish efficacy for OTC use.

The safety is also supported by a very long

history of marketing both in the United States as well as a worldwide safety database in 83 different countries.

As a topical retinoid, adapalene has been shown to be teratogenic when given orally in animals at doses above those that can be achieved with dermal distribution in humans. Although we don't typically discuss toxicology at advisory committees specifically, we do have specific presentations on this today since this is really a key factor in the decision-making of the benefit-risk for adapalene.

I'll note that the prescription labeling for adapalene does not specifically list a contraindication for use during pregnancy or require a pregnancy prevention program as we have in place for the oral retinoids.

So in order to better evaluate the benefit-risk profile for adapalene, Galderma conducted a pharmacokinetic study under maximal-use conditions to determine exactly what blood levels could be achieved in humans. This trial was used

to establish the exposure margin that you'll hear about in the presentations today and was compared to the no-effect level seen in the animal studies.

Now, in order to determine whether consumers could appropriately use the product in the OTC setting without the intervention of a healthcare professional, Galderma conducted three consumer studies.

The first was a label comprehension study in adults and adolescents testing the endpoints of use once daily and do not use on damaged skin. This was an all-comers population, and of note, this study did not test comprehension of the pregnancy warning.

The second study was a self-selection study in pregnant and lactating women, specifically evaluating whether pregnant and lactating women would consult a physician before use.

Finally, the third study was an actual-use study in adults and adolescents with acne, testing the two primary endpoints of use once daily and use for acne only.

As you hear the presentations this morning, we ask you to keep the topics for discussion in mind. These will focus on the benefit-risk profile of adapalene for over-the-counter treatment for acne in adults and adolescents 12 years of age and older.

We anticipate that the discussion today will revolve primarily around safety, and we intend to focus these safety discussions on pregnancy outcomes as well as the potential for use during pregnancy, although we will touch on a number of general safety issues as well.

In your discussion, please include areas of potential concern; namely, use by females of reproductive potential, the potential for teratogenic risk. We also ask you to consider pediatric use and the potential for misuse, which includes excessive use or use for non-acne conditions.

There's a separate discussion question to talk about the Drug Facts label and the consumer information leaflet. Finally, we ask you to

discuss the benefit-risk profile of adapalene.

So this is the tough part, and as a general philosophy, products for over-the-counter use are expected to have a very high bar for safety. Given that these products are sold widely on the U.S. market, they're available to any consumer without the intervention of a healthcare professional.

This advisory committee is somewhat precedent setting since this would be the first time we've considered placing over the counter a product that does have a significant toxicology signal for teratogenicity. And as such, what we're asking you to weigh is where do you set that bar? What's an appropriate level of risk in the over-the-counter setting given the absorption profile that we see for adapalene?

Before I close, I just wanted to mention the legal framework that gives FDA the ability to hold advisory committees to ask for scientific advice and recommendation from experts such as yourself in the field.

As I noted previously, FDA takes very

seriously the advice of the committee. However, the commissioner does have sole discretion on actions taken with regard to drug approval, especially since there may be other issues such as chemistry that impact approval decisions that are not discussed at these meetings.

So with that, I'll stop and turn the podium back to Dr. Roumie. Thank you.

DR. ROUMIE: Thank you.

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 advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interest in the sponsor,

including equity interest and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation 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 presentation, it will not preclude you from speaking.

We will now proceed with the sponsor's presentations.

Applicant Presentation - Howard Marsh

DR. MARSH: Members of the FDA advisory committee, good morning. My name is Dr. Howard Marsh. I'm the vice president for medical affairs of Galderma U.S. Galderma is a global pharmaceutical company that focuses wholly on dermatology. We have a wealth of experience in both the prescription and the OTC areas.

My colleagues and I are grateful for the opportunity to discuss the suitability of the switch of adapalene 0.1 percent gel from

prescription status to OTC use. I will refer to the product as Differin gel.

Acne is a highly prevalent disease with a wide range of sufferers across different age groups. Acne is extremely common, affecting over 50 million Americans. It is both a chronic and inflammatory condition. It is the most common condition seen by dermatologists affecting over 85 percent of teenagers, but also can persist into adulthood. Indeed, the prevalence in adult women is about 12 percent. However, most acne sufferers do not see their doctor.

Acne is an inflammatory condition, and the visible impact of acne is profound. Acne is prevalent across all skin types and ethnicities. But the impact of acne is not confined to the skin. Numerous studies have documented the high emotional, psychological, and social impact.

Patients regularly report feeling self-conscious and depressed. They can lack confidence and self-esteem, and they speak about their feelings of embarrassment and shame. The

condition can frequently lead to social withdrawal, and sufferers can be subject to bullying and teasing.

Acne is already a well-established OTC condition. Topical medications have been available for the treatment of acne for decades. Five active ingredients are currently allowed in monograph. However, more than 99 percent of the currently available drugs include benzoyl peroxide or salicylic acid. Notably, there have been no new OTC acne active ingredients since the 1980s.

The chemical entity of adapalene was developed in 1984. The structure was designed to be more rigid and thus more stable in the presence of sunlight, and less susceptible to oxidation than retinoic acid while retaining its biological activity. This structure also led to adapalene being stable in the presence of powerful oxidizing agents such as benzoyl peroxide.

Differin's modes of action are different to current OTC acne preparations in that it has a direct anti-inflammatory action and inhibits comedo

formation.

The first adapalene product, the 0.1 percent gel, was approved by FDA in 1996. Since then, FDA has approved six other formulations, including a 0.3 percent gel and two combination products with benzoyl peroxide. Only the 0.1 percent gel has been submitted for OTC use, and this is the topic of discussion today.

As you will see, Differin gel meets the criteria for OTC drugs. Consumers must be able to recognize the condition and understand and follow the label, and the product must be effective and safe when used as recommended. We have considered these matters carefully, and our presentations this morning will focus on demonstrating that Differin gel meets these criteria.

Being able to recognize a condition is a key criteria for an OTC medication. The characteristic appearance and wide prevalence assures sufferers or their parents can readily diagnose the condition. Indeed, as I have said, topical medications have been available for the treatment of acne for

decades, so acne is already a well-established OTC condition.

The label is similar to current OTC acne medications, but it will be the only product that is labeled only for once-daily use. In order to assess consumer behavior, we conducted label comprehension, actual-use, and self-selection studies. My colleague Julie Aker will present data from these studies and show that consumers are able to adequately comprehend the label and appropriately use the product in accordance with the directions.

The efficacy of Differin gel is well established. The NDA included five clinical studies. In addition, efficacy up to 12 months has been demonstrated in postmarketing studies.

The safety profile of Differin gel is well established. Galderma has considered the safety concerns associated with an established medicine when moving to OTC. Each has been carefully assessed and will be addressed in our presentations.

Differin gel was first marketed in Europe in 1995, and since that time, 40 million people have used adapalene-containing drugs. The product has been widely studied in more than 140 clinical trials involving more than 6,000 subjects. Further, the postmarketing surveillance program has been comprehensive.

The most common adverse events are limited to the skin and include dry skin, erythema, itching, and burning. The safety profile is well established and has not changed in the 21 years since first marketed.

We have carefully evaluated the risk of teratogenicity, and Professor DeSesso will provide a detailed assessment. This is an important consideration. The critical point to make here is that while teratogenicity has been demonstrated in animal models after high oral doses, this was not seen after dermal application.

Pharmacokinetic studies conducted under conditions of maximal use have consistently shown that systemic exposure following topical use is

very low in humans, providing a wide and reassuring margin of safety.

This is supported by our review of the exposures during pregnancy reported in both clinical studies and other data sources such as the published literature, the FDA Adverse Event Reporting System, and the WHO databases.

Data collected in the original clinical development program, our postmarketing experience, and consumer studies all support OTC use. Nonprescription Differin gel would provide broad access to a once-daily safe and effective treatment.

It would provide an additional OTC treatment option for a condition that impacts the lives of millions of acne sufferers. In summary, as you will hear today, we believe that Differin gel is appropriate for nonprescription use.

I would like to introduce my colleagues who will make further presentations this morning. All external experts have been compensated for their time and their travel.

Dr. Guy Webster will discuss the impact of acne and the need for additional OTC acne medications. Matthew Meckfessel will present data covering the efficacy and safety of Differin gel. Professor John DeSesso will address the concern of teratogenicity and present data and rationale as to why topical Differin gel has a wide margin of safety and is appropriate for OTC use.

Julie Aker will present data from consumer studies demonstrating that consumers understand the label and can safely use the product in accordance with the proposed label. Dr. Jonathan Wilkin will present a benefit-risk assessment of Differin gel in an OTC setting, and finally, I will make some concluding remarks. In addition, three of my colleagues from Galderma are available to answer specific questions.

Dr. Webster will now continue with the dermatologist's perspective.

Applicant Presentation - Guy Webster

DR. WEBSTER: Good morning. I'm Guy Webster, clinical professor of dermatology at

Jefferson Medical College in Philadelphia, and I've been treating acne or researching the disease for 40 years or so. I was happy when Galderma asked me to come here because I think this is a really important step for treating the acne patients. We need something like this over the counter.

Acne is almost a universal disease predominantly affecting teens and young adults. The variation in severity is great from a few pimples and blackheads to widespread lesions and nodules that can be disfiguring. Poorly managed acne can result in permanent scars on both the skin and the emotions.

In a questionnaire-based study of thousands of adolescents with acne, there was a pronounced effect on mental health. They reported reduced well-being, not thriving in school or in interpersonal relationships. There was a higher incidence of self-consciousness and depression. Among those with the worst acne, suicidal ideation was twice as high in girls at 25 percent and three times as high in boys, 22 percent.

There's good data showing that treatment of acne improves the patient's mental status. Patient reported higher self-perception, less embarrassment, decreased depression. The data is both in controlled studies and in the experience of physicians who treat the disease.

We've seen their frustration and the sense of futility with what they've used in the past, and we've seen the improvement in their interactions, a grin when they come back for a second visit as their acne improves.

Acne is a disease that isn't trivial if you have it, and it isn't merely a cosmetic issue. It isn't a rite of passage. The scars of acne are lifelong whether they're on the skin or on the psyche.

As you heard from Dr. Marsh, adapalene's mechanism of action is unique. However, to appreciate how it works, I'd like to walk you through the progression of an acne lesion.

To start, this figure shows the pilosebaceous unit on the skin. The darker color

represents the epidermis or outermost layers of the skin, and the lighter pink color is the dermis. Also shown is the hair follicle in the sebaceous gland, which produce and excrete an oily substance known as sebum, which is the location of the acne lesion.

Acne begins well before any lesions are visible. Research in the past decade has evolved our understanding of acne, and it's now widely accepted to be an inflammatory disease regardless of lesion type. Acne lesions are preceded by subclinical inflammation with mediators, shown here as colored dots within the dermis.

Additionally, sebum production is increased, which creates an environment conducive to proliferation of P. acnes, a common skin bacteria, which is shown by orange dots on the surface of the skin and within the follicle.

Generation of the microcomedo, the little blackhead, initiates with hyperproliferation and abnormal shedding of keratinocytes, which results in blockage of the follicle, illustrated by the

darker yellow shape in the middle of the figure.

Inflammatory mediators increase, and P. acnes proliferates, further activating inflammatory cascades. As the lesion progresses, inflammatory infiltrates accumulate, and the lesion enlarges and becomes visible.

Two main OTC acne active ingredients are benzoyl peroxide and salicylic acid. Benzoyl peroxide is a strong antimicrobial and acts to kill P. acnes, thereby indirectly impacting one aspect of inflammation.

Salicylic acid is thought to unblock the follicle. It's in a majority of OTC acne products, but this mechanism of action is not well understood or documented.

Adapalene has well-characterized differentiating effects from current OTC options. Adapalene inhibits the formation of the microcomedo and exerts anti-inflammatory effects, directly attacking acne on two fronts that are not targeted by existing OTC medications. And it has a long record of safety and tolerability and is in a drug

class that's widely considered to be foundational in acne therapy.

Just this year, an American Academy of Dermatology independent panel of expert clinicians published treatment guidelines for acne. Their conclusions were based on mechanism of action and addressing causative factors, evidence and clinical experience.

There was a clear consensus that topic retinoids, including adapalene, are the core of topical therapy for acne because they're comedolytic, resolve the precursor microcomedo, and are anti-inflammatory.

Benzoyl peroxide was also recommended in this guidelines, but salicylic acid and other OTC acne medications were not. Indeed, in my clinical practice, I frequently observe a good clinical response to Differin in those patients who have not responded well to current OTC acne drugs, including benzoyl peroxide.

Of the 50 million acne sufferers, 64 percent of adults and 78 percent of teens do not seek

professional advice on treatment for their disease, so this is definitely a largely self-managed OTC condition.

It's been found that teens and young adults try many acne treatments, and this mirrors what I see in my practice as patients are telling me they're looking for additional options.

Furthermore, there have been no OTC acne medications with new active ingredients for 30 years, and based on the latest AAD guidelines, consumers only have direct access to a single recommended acne therapy. Because of this, new options that provide an additional way of treating the disease are needed.

So in summary, the choices for OTC acne therapy are limited. There have been no new nonprescription active ingredients for acne since the 1980s, which I think is unthinkable for such a common disease. Differin gel would be a valuable and effective medicine to add to the OTC market in that it addresses factors in acne that are not targeted by what's currently available.

Additionally, Differin gel is once-daily dosing versus up to three times a day for other OTC acne treatments. This convenience may help with compliance, which cannot help but to affect outcomes.

Based on the available data and my professional opinion, Differin gel is safe, has proven efficacy, and I truly believe it's appropriate for the nonprescription setting.

Matthew Meckfessel will now review the efficacy and safety data for Differin gel.

Applicant Presentation - Matthew Meckfessel

DR. MECKFESSEL: Thank you, Dr. Webster.

Over the next several minutes, I will walk you through the efficacy, tolerability, and safety of Differin gel with a specific focus on safety in key aspects that were evaluated to support its switch from prescription to OTC.

The clinical development program for the initial NDA for Differin gel consisted of 16 clinical studies, 11 of which evaluated the effects of Differin gel in healthy subjects and 5 pivotal

studies that established the safety and efficacy in acne subjects.

The overall clinical data for Differin gel is robust and extensive with over 140 clinical studies involving over 6,000 subjects treated with Differin gel. The efficacy of Differin gel was established in five pivotal trials which included two vehicle-controlled trials and three active-controlled trials.

Significant improvement in inflammatory, non-inflammatory, and total lesion counts were observed at the end of these studies after 12 weeks of treatment with mean improvement in total lesion counts in the pivotal studies between 30 to 50 percent.

Additionally, Differin gel has an onset of action with a total reduction in lesion count seen within 2 weeks. Differin gel also has long-term efficacy with continued improvement demonstrated in a postmarketing study lasting up to 12 months.

Safety was also a key aspect evaluated in this five pivotal studies. Local tolerability

assessments included erythema, dryness, scaling, pruritus, and burning, which are typical side effects of topical acne medications. These tolerability assessments were made on a 4-point scale ranging from zero or none through 3 or severe. Adverse events were also recorded.

In these five studies, these effects were all observed with Differin gel, but the majority were mild and peaked within the first 2 weeks of treatment and declined in frequency and intensity thereafter.

Dryness and erythema were the most common followed by scaling, pruritus, and burning. However, it should be noted that mean tolerability scores for all five assessments were less than 1 or mild for the entire study duration.

The table shown on this slide gives an overview of the adverse events from the five pivotal studies. Data shown here is pooled only from the Differin gel and vehicle gel groups. The overall incidence of adverse events was similar between the two groups with 8.7 percent of subjects

in the Differin gel group experiencing a dermatologic adverse event compared to 2.5 percent in the vehicle group. The majority of these adverse events were mild and transient.

Dermatologic adverse events in the pivotal studies were mostly observed with the Differin gel group and were consistent with the safety profile of topical acne medications. This includes dry skin, erythema, and skin discomfort.

Ten subjects in the Differin pooled group discontinued due to adverse events. Eight of these were dermatologic in nature and are shown on this slide.

Over 40 million people have been treated globally with adapalene, including all formulations. Safety data is available from Galderma's global pharmacovigilance database as well as the FDA AERS and WHO databases and from published literature.

The observed safety data is consistent with the phase 2 and phase 3 studies from the development program with the most common adverse

events being dermatologic in nature. In over 20 years of Differin gel use, no new safety signals have been noted.

Additionally, potential off-label use was considered for Differin gel. Differin gel was indicated in label for the treatment of acne only and will only be marketed for the treatment of acne. However, retinoids, including adapalene, have been studied for other indications.

The actual use of the product off label is similar to how it is used to treat acne, and as expected, observed adverse events are similar. Therefore, even if Differin gel were to be used off label, there is not an incremental safety risk.

We also carefully considered use by those younger than 18 years of age. Most trials included adolescents-aged subjects between the ages of 12 to 17 years. These subjects had a similar safety profile to adults with adverse events being primarily dermatologic in nature. Maximal-use PK studies also included adolescent subjects, and no differences in systemic exposure were observed.

The proposed Drug Facts label for Differin gel states that it is for use for those 12 years and older. However, children younger than 12 do have acne, and there is potential use by these subjects.

Although no studies have investigated the safety of Differin gel in subjects younger than 12 years, Epiduo Gel is indicated for children as young as 9 years old. A study specifically in children age 9 to 11 years was conducted to support this indication, and safety for this population was similar to subjects ages 12 and up.

This table summarize dermatologic adverse events that occurred during the 12-week Epiduo study in 9 to 11 year olds. These adverse events were similar to those originally reported in the Epiduo pivotal studies of subjects aged 12 and older. These adverse events are also very comparable to what has been consistently observed with Differin gel.

Although this formulation contains the addition of benzoyl peroxide, the data certainly

support that Differin gel would pose no incremental safety risk in children younger than 12. Furthermore, no safety signals have been noted in children younger than 12 exposed to all dosage forms of adapalene.

Seventy-eight cases have been identified, and the most common adverse events were dermatologic in nature. Although Differin gel will be indicated for and marketed for those 12 years and older, based on the totality of the data, even if Differin gel were to be used by those younger than 12, this will not pose a safety risk.

Other aspects of Differin gel have also been carefully evaluated. Studies have demonstrated that adapalene is not a carcinogen. Differin gel has been shown to be neither phototoxic nor photoallergenic, and no drug-drug interactions have been identified.

In addition to these key aspects, a thorough review of data was conducted to look for signs of teratogenicity associated with the use of Differin gel during pregnancy. Dr. John DeSesso will now

present a detailed assessment of why topical Differin gel does not pose a teratogenic risk.

Applicant Presentation - John DeSesso

DR. DeSESSO: Thank you. Thank you, Matt.

It's really a pleasure to be here and talk to you this morning. My name is Dr. John DeSesso, and I'm the director for the Center of Toxicology and Mechanistic Biology at Exponent, which is a scientific and engineering firm. And I'm also a professor of biochemistry, cellular and molecular biology at Georgetown University School of Medicine.

I've got 40 years of postdoctoral experience specializing in developmental and reproductive toxicology, as well as other areas of toxicology and risk assessment, and I've published over 100 papers and chapters in these areas.

I've carefully reviewed the safety data for adapalene, and I've concluded that the topical application of adapalene poses no risk for teratogenicity in humans. And I'm here this morning to discuss with you the evidence that

supports my conclusion.

Now, let me begin by saying that retinoids are molecules that are related to vitamin A. Now, currently, retinoids are available without a prescription in topical creams such as Retinol, and of course in vitamin A-containing supplements that you can get at the nutrition stores.

Retinoids are essential for adult health and for normal embryonic development. Typical retinoid plasma concentrations in normal adults are 1 to 7 nanograms per milliliter of plasma, and retinoids must be maintained within a physiological range. Both excess vitamin A and deficiency of vitamin A have adverse health consequences, including formation of malformations.

Retinoids cannot be synthesized by embryos, and this means that the source for all embryonic retinoids is the maternal organism. Retinoids act within the cell nucleus where they bind to specific nuclear receptors called retinoic acid receptors, or RARs, and this allows them to interact with the cell's DNA and lead to biological effects.

Now, as you-all know, the cell's nuclear material is contained within the nuclear envelope, and that nuclear envelope restricts the access of most molecules in the cytoplasm from reaching the DNA. However, there's a certain cellular retinoic acid binding protein, CRABP-II, which is present in the cells of the skin and which facilitates the transfer of retinoids into the nucleus.

Now, once within the nucleus, the retinoids bind to one of the retinoic acid receptors of which there are three types. There's RAR alpha, beta, and gamma, and each of these RARs interacts with a different part of the set of genes.

So various synthetic and natural retinoids preferentially bind to one of these RARs and because they have different activation of nuclear material, these are what produce different biological effects for the different retinoids.

The structural relationship for vitamin A and retinol are shown on this slide. Vitamin A is an alcohol, and inside the body, vitamin A is converted to its active form, which is a carboxylic

acid, retinoic acid. Retinoic acid is also sold and is known as the compound tretinoin.

Now, the structures of adapalene on the left and retinoic acid are compared on this slide, and you see that the chain of double bonds in retinoic acids has been replaced with a more stable aromatic backbone of naphthoic acid in the adapalene molecule. And these aromatic rings provide a number of benefits, including increased stability in the presence of light.

In the chemical structure of adapalene also differs from that of retinoic acid in that an adamantyl constituent group has been placed on the nonpolar end of the molecule, where it interferes with adapalene's ability to bind to the CRABP-II molecule.

Now, this greatly diminishes the access of adapalene to the cell nucleus. However, if some of the adapalene molecules do get into the nucleus once adapalene gets there, adapalene has a very low affinity for the RAR alpha. And these differences in affinity translate to a different profile for

adapalene compared to that retinoic acid.

Now, a large amount of research is showing that in cases where the fetus is exposed to high levels of retinoic acid, there's a constellation of malformations that may occur, which is known retinoid embryopathy, and this slide shows the constellation of what those malformations are. And interestingly, all of those malformations, with the possible exception of hydrocephalus, involve cranial neural crest cells.

Cranial neural crest cells are specialized cells that move out of the anterior part of the embryo, and they require to be exposed to specific concentrations of retinoic acid at specific times during gestation for proper development to occur. So retinoic acid is important. Timing is also important.

Now, the point I want to emphasize about retinoid embryopathy is that we're talking about a characteristic set of malformations. These malformations appear as a group, not as isolated individual malformations, and they're different

from the more commons spontaneous malformations that occur in people. So consequently, if malformations were seen in safety studies of adapalene and if they included some of the malformations we see in that set, then that would help us to attribute the possibility of cause to the malformations.

I want to provide you with a brief introduction to teratology because I realize not all of you are teratologists, and the point is to let you know that the endpoints of concern in the tests called embryo fetal development studies are three: death of the offspring, malformation of the offspring, which is teratogenesis, or growth retardation of the offspring.

These endpoints are assessed by examining litters of mothers that have been exposed to the test agent during development and then taking the embryos just before term at the end of the study.

Now, unfortunately, even in the absence of a recognized toxic or teratogenic exposure, malformations occur spontaneously, and they do at a

background rate. And embryonic development is a very complicated process, so it's not surprising that sometimes things go wrong.

Now, as shown on this slide, each species has a background rate of spontaneous malformations. In humans, it's considered to be approximately 3 percent of babies that have malformations. In most strains of rats, it's probably between 1 and 2 percent, and in rabbits, it's somewhere between 2 and 5 percent.

Now, in order for an exogenous agent to cause a malformation, there's a couple of conditions that have to exist. First, the exposure to the agent has to occur when the organs are actually forming. This is a period called the period of organogenesis. Organogenesis is approximately from day 6 to day 17 in a rat. In rabbits, it's from approximately day 7 to 19, and in humans, it's in gestational weeks 3 to 6.

Now, the mother must not only be exposed to the agent during this period of time, but the agent also has to cross the placenta and get to the

embryo. And once it reaches the embryo where the target tissue is, its concentration must exceed a threshold. Now, this means that exposures which result in target tissue concentrations that are below the threshold will not cause malformations even if they occur during a period of organogenesis.

Now, because there's a background rate of spontaneous malformations, there's some observations that you look for in these studies to conclude that malformations were due to a test agent. And these include the following:

You would expect to see that multiple fetuses would have the problem. You would also expect that these would be shown in not just one litter but in several litters. You would expect there would be the same malformation or at least in the same organ system that the malformations occurred, and you would certainly expect to see a dose response relationships. If you have all of these things present, you can feel pretty confident that your agent is a teratogen.

Now, what I'd like to do next is to discuss the non-clinical safety data for adapalene, and I want to concentrate on the placental transfer of adapalene in rats, which is where we measured it, to see that it gets to the fetus, and then discuss the embryo-fetal development studies, including both the oral and the topical studies.

Now, because an agent that causes teratogenicity must cross the placenta, Galderma conducted an experiment to look at placental transfer of adapalene. The study involved 24 pregnant animals per group. They were treated orally with adapalene at 2 doses, either 0.1 milligrams per kilogram daily or 1.0 milligrams per kilogram daily, from gestation day 6 to gestational day 13. And after the last treatment, the blood levels were measured at various times.

In this slide, the purplish lines represent the blood levels seen in the mothers, and the green lines represent the fetal concentrations that were measured. And the important thing is to notice that regardless of the dose, you can see that the

Cmax is approximately five to six times higher in the mother than it is in the fetus. And this is a case where there's pretty poor transfer of adapalene across the placenta.

Thus, so far, we've seen that adapalene's pharmacology minimizes its binding to RAR alpha and to CRABP, and we've also seen that the pharmacokinetics minimize placental transfer.

Now, these findings support the concept that it would take extremely high maternal systemic exposures for a sufficient amount of adapalene to gain access to the embryo and induce teratogenicity. So with that in mind, let's take a look at the animal data.

First, we'll discuss the findings of the oral embryo-fetal and development studies that were performed both in rats and rabbits.

In summary of that data, Galderma found that oral doses of 25 milligrams per kilogram per day and higher, there was a low incidence of malformation seen, which includes some neural tube defects and cleft palates in rats. In rabbits, the

findings were post-implantation loss as well as tail defects, and birth defects of the abdominal wall near the umbilicus.

These malformations are not like the ones you would typically see for the retinoid embryopathy, which we mentioned on a previous slide, and it suggests that retinoid embryopathy malformations of that type are not an issue after maternal exposure to adapalene during pregnancy.

While the weak teratogenic potential of adapalene was established through these high-dose oral experiments, the relevance of the findings through our discussion today is the time to find out what happens when topical application occurs. Because teratogenic potential is linked to maternal systemic exposure and because systemic exposures are likely to be very low after topical administration, we need to do these topical studies in the animals of interest.

So with regard to the dermal embryo-fetal development studies, I'll first discuss a study in rats, which included 25 mated females per group,

and the doses were 0, 0.6, 2, and 6 milligrams per kilogram per day, and the dosing covered the period of organogenesis.

The results of this study were there were no malformations reported in any of the treated dose groups. The highest topical dose that was tested can be concluded to be safe for rats. The systemic exposure was determined to be 204 nanogram hours per milliliter, and we call this the no observed adverse effect level or the NOAEL. Note that the higher doses of adapalene may also be safe, but we conservatively use the measured dose that we have as a NOAEL.

Now, a similarly designed study was conducted in rabbits, same doses, same number of mated females, and once again, no malformations were observed. In terms of systemic exposures in rabbits, the NOAEL was 1,036 nanogram hours per milliliter based on the AUC. Remember, it was 204 in the rat. This suggests that the higher systemic exposure in the rabbit is also safe, but to be fully conservative, we'll use the lower systemic

exposure in the rat as a NOAEL.

We can thus conclude so far that adapalene applied dermally to both rats and rabbits does not result in birth defects and is not teratogenic. More importantly, these doses can now be used to define a conservative NOAEL for systemic exposure to be used in further analyses.

In order to compare the systemic doses of acne patients who use topical adapalene with the NOAEL in the systemic exposure we saw in the rat, Galderma conducted a dermal maximal-use study.

A maximal-use study involves a highly artificial exposure to a much larger area of the body than would typically be expected under normal use conditions. The mean amount of drug applied in this study was 2 grams per exposure. Normal usage would be much less than half of that.

This dose was applied in a clinic once daily for 4 weeks, every day for 4 weeks, and it included application to the face, shoulders, upper chest, and back. The subjects included both adults and adolescents, and they were essentially distributed

equally between males and females. The pharmacokinetic profiles were developed on day 1 of treatment as well as on day 15 and day 30.

The pharmacokinetic profiles for adapalene over the 30 days of the study are shown on this slide, and what you are seeing are clusters of data at days 1, 15, and 30. These represent the individual plasma concentrations for all subjects who had measurable concentrations of adapalene on these days, and the standard deviations are the bars that you see on the graph.

You'll note that the plasma concentrations did not increase between day 15 and day 30, and what this tells us is that steady state was attained at least by day 15. And it also tells us that there was no systemic accumulation over the 30-day period that we studied.

What we can conclude from this dermal maximal-use study is that the systemic adapalene exposure after topical application of Differin gel is low, very low. In fact, the measurement of adapalene, which at the highest level, the highest

measurement made in this study, was 0.17 nanograms per milliliter was only approximately 1 percent of the Cmax seen in the rat, which was the more sensitive of the two test species.

It should also be noted that the maximal-use study found no difference in the plasma concentrations of adapalene by sex or any differences between adolescents and adults.

Now, because oral adapalene is weakly teratogenic in both the rat and the rabbit, this becomes the endpoint of concern for doing our safety margins. And from the dermal embryo-fetal development studies, we have the systemic exposure values for the dermal NOAEL and the toxicity for rats, and we can use this to establish our safety margin.

The rat was conservatively chosen, as we mentioned before, because it had the lower of the two systemic NOAELs. The safety margin would then be defined by the margin of the difference in multiples between the no effect level in the most sensitive species divided by the highest

concentration we've seen in humans.

So if you take this equation using the smallest amount of the most sensitive animal, which is 204 nanogram hours per mL in the rat, and you divide it by the 0.17 nanogram per mL in the human, which is the highest measurement we saw, you'll get a safety margin. You want to see a large safety margin. The larger the number, the more confident you can be that the exposure is safe.

So when you do that equation, you find that the safety margin is approximately 70. This is very reassuring for a topical product. Instead of using the highest dose, if you say, well, let's look at the mean dose for all measurements we had, that safety margin actually expands to 234.

So the notion is this is really a very safe drug, and remember, that the safety margin is consistent with other maximal-use studies that Galderma conducted over previous two decades, so they all came out at approximately the same range, somewhere right around 70.

Now, it's difficult to imagine a situation

where a topical application with a product like this, which has a safety margin of 70, could be used in such a way that it would even remotely the safety threshold. You'd have to use 70 times that amount, and when you get to that safety threshold, remember, that safety threshold was based on a no-effect level, not an effect level.

Now, over the past 20 years, Galderma has performed numerous clinical studies, and they've evaluated inadvertent exposures to pregnant women to adapalene reported in other sources such as published literature. And in total, they found 47 retrospective cases in studies and 123 prospective cases in studies that were identified both in the clinical studies and in the postmarketing surveillance.

With regard to the retrospective cases of exposure during pregnancy, as I told you, there were 47 cases identified at the time of submission of this document, and these cases were picked up due to adverse event reports from clinical studies, postmarketing surveillance, and sometimes they were

even in the open literature.

That said, it's important to recognize that these reports can be somewhat biased because they're positive, but they're important to look at anyway. Of the 47 events, 15 of these resulted in elective abortions, 16 miscarriages took place. Hence, there were 16 reports of abnormal outcomes or malformations.

Upon reviewing the malformations, I can tell you that I found only one case of anophthalmia, which is potentially related to retinoid embryopathy because it's that list that we saw, but there were significant other cerebral malformations in that child, which make it unlikely that retinoids had anything to do with it. These were massive changes in the brain other than just the eyes.

So as I discussed previously, there are certain patterns of malformations that might suggest an association with an exogenous agent. However, in this evaluation, there were various malformations found in multiple infants, but they

weren't consistent. They weren't in the same organ system, and so the signals for concern really are not present.

Now, turning to 123 prospective cases, which is a more informative way to evaluate pregnancy outcomes, and focusing on the last column, you can see that the miscarriage rate was approximately 5.7 percent. The malformation rate was about 1.8 percent, meaning that about 98 percent of the babies born were healthy. And those rates are actually quite in line with the background population rates for miscarriage and for malformations in humans.

So in summary, no teratogenicity was observed in animals after topical application, and teratogenicity was only seen after high, very high, oral doses in animals. The systemic exposure after topical application has been shown to be very low, as you would expect, and consequently, there are wide safety margins.

So in conclusion, it's very clear to me, and I hope to you as well, that topical application of

Differin gel poses no risk for teratogenicity in humans. And I'll now turn the podium over to Julie Aker, who will present the results of the consumer studies.

Applicant Presentation - Julie Aker

MS. AKER: Thank you, Dr. DeSesso.

Good morning. I'm Julie Aker, and I'm president and CEO of Concentrics Research. Concentrics has been conducting Rx to OTC switch programs and consumer research for over 30 years. I'm going to highlight the consumer studies that were conducted for this Rx to OTC switch program.

There is an established and final monograph for OTC topical acne products, and as such, it is established that consumers know how to self-diagnose and self-treat acne. The Differin gel label is largely comprised of information from the established monograph. We focused our consumer behavior studies primarily on the new information on the Differin gel label.

The OTC development program is based on a foundation comprised of clinical studies that

provided evidence that Differin is safe and effective and minimally absorbed; a pivotal label comprehension study, which demonstrated that consumers understand the new information on the Drug Facts label; an actual-use study, which demonstrated that consumers comply with the indication, warnings, and directions on the Drug Facts label; and a targeted self-selection study evaluated the effectiveness of the existing OTC pregnancy and breastfeeding warning found on the labeling for all OTC products intended for systemic use.

The central focus of most consumer studies is the Drug Facts label. This has been included in your handouts this morning. This label has a specific format outlined in the regulations. It's found on OTC products, and it's familiar to consumers.

The Differin gel label is comprised of information found on the current OTC acne monograph, a copy of which is included in the sponsor briefing document. There are several new

messages. There is one contraindication, "Do not use on damaged skin," which is defined as cuts, abrasions, eczema, or sunburn.

There are four messages that are informational or educational: number one, irritation is more likely in the first few weeks of use; number two, moisturizers may be used to relieve dry skin; number three, during the early weeks of use, your acne may appear to worsen before it improves, and this is not a reason to stop using the product; and number four, do not use wax to remove hair in the areas where the product has been applied.

There are three new directions: number one, for ages 12 and older; two, use once daily; and three, if under 12 years of age, consult a doctor.

The consumer studies evaluated various study populations. The qualitative and pivotal label comprehension studies were conducted with general populations. This means we recruited individuals that did not necessarily have acne and included both those of normal and lower literacy.

The actual-use study was recruited in an all-comers population. This means the consumers responded to ads similar to those that would be used in a real-life setting referencing the condition or the symptoms found on the Drug Facts label. This is done for all actual-use studies.

The targeted self-selection study recruited a specific population of pregnant or breastfeeding women. All studies included subjects who were at least 12 to 13 years of age or older and subjects of lower literacy.

I'm now going to highlight our label comprehension study. The study design was based on principles found in the FDA guidance for label comprehension studies. 586 people were recruited across the United States and were given the Drug Facts label to review at their own pace.

Emphasis was placed on recruitment of adolescents, ages 12 to 17 and young adults ages 18 to 34, which together make up 62 percent of the study population. One-on-one interviews were conducted, and questions were posed in hypothetical

scenarios that might occur in real life. These scenarios were posed in the third party, so they were not directly applicable to the participant.

Iterative testing was conducted to optimize the Drug Facts label and the questionnaire prior to the pivotal study. Success thresholds are defined in advance for the primary objectives. These thresholds are not the same as those in a clinical trial. Thresholds for consumer studies are estimates of comprehension or behavior response.

In the end, we must look at the totality of the data. All responses must be considered in determining if the scores were correct, incorrect, or could be mitigated in a reasonable way.

The primary endpoints for the study reflect new information. One was a warning, "Do not use on damaged skin." And one was in the directions, "Use once daily." These were set as primary endpoints due to the fact that they are new instructions and they give important information about proper use.

These endpoints do not represent serious safety concerns. However, increased irritation

could occur if the product is used on damaged skin or more than once daily. Based on these factors, the threshold was set at a lower bound of 85 percent with an observed rate of approximately 90 percent.

The pregnancy warning was not tested in the label comprehension study since it is an approved warning and it has been for decades and is presumed to be understood. However, this warning was the focus of a separate targeted self-selection study, which focused exclusively on this warning in a population of women who were currently pregnant or breastfeeding versus testing this in a general population in the label comprehension study.

A two-sided 95 percent confidence interval is calculated for objectives in consumer studies. The lower bound and the upper bound are determined for the confidence interval. A success threshold is defined for the primary endpoints.

For this study, a lower bound of 85 percent was defined as the success threshold for the primary endpoints. The success threshold was set

for the general population.

The 85 percent lower bound threshold was exceeded in the general population. Do not use on damaged skin had a lower bound of 96 percent, and the direction to use once daily had a lower bound of 94 percent. Based on our experience of conducting over 300 label comprehension studies, these are excellent results for primary endpoints. As expected, scores were slightly lower for the low literacy cohort.

As you can see, the threshold was still met when considering the total population, which had 22 percent low literacy versus the general population with 11 percent low literacy.

There were 10 secondary endpoints. Success thresholds are not required for secondary endpoints per the FDA guidance, however, point estimates and confidence intervals were calculated.

Comprehension scores were 98 percent or higher for these four objectives: number one, product purpose; number two, use in ages 12 and older; number three, do not wax to remove hair in

areas where the product is applied; and number four, avoid unnecessary sun exposure, including tanning beds. The new information in the sun exposure warning was tested related to tanning beds. As you've already heard, this product is not photoallergenic or phototoxic.

The total population had scores similar to the general population. Comprehension scores were 88 percent or higher for these objectives: number one, moisturizers may be used; two, use in ages 12 and under, consult a physician; three, irritation may occur in the first few weeks of use; and number four, acne may appear to worsen before it improves. Again, the total population had scores similar to the general population.

Comprehension scores for two objectives were initially lower. Both of these elements are required in the final acne monograph. The warning to stop use and ask a doctor if irritation becomes severe initially scored a 78 percent correct, and the warning irritation is more likely to occur if using more than one topical acne product initially

scored a 63 percent correct. However, when the verbatim responses were considered, it was clear that consumers understood the need for caution.

When these responses were considered, the acceptable and the cautious responses elevated the scores to 87 percent for the stop-use warning and to 85 percent for the use of more than one topical medication at the same time. These scores were considered acceptable, and they were similar for the total study population.

So in summary, consumers comprehend the Drug Facts label. The primary endpoint exceeded the 85 percent threshold. All secondary endpoints scored 85 percent or higher, and scores were acceptable for adolescents and consumers of lower literacy.

Next, I'd like to review the results of our actual-use study. An actual-use study is conducted to understand how the drug will be used in an unsupervised OTC environment. The goal is to emulate to the extent possible a real-life experience from the time the consumer sees an ad or

sees the product on the shelf through their purchase decision and their use of the product at home.

For this study, we evaluated three new label warnings and one established label warning. The new messages included use once daily, use for acne only -- that means do not use off label -- and use on correct body areas, which was defined as not using on damaged skin, or on eyes, lips, or mouth.

The established warning was the codified, required OTC pregnancy and breastfeeding warning: to ask a healthcare provider before using if pregnant or breastfeeding.

There were other areas of interest that were also evaluated. These included who used the product, where they used the product, the quantity that was used, concomitant medication use, adverse events, and use in subjects with eczema.

The actual-use study was an open-label, 6-week study in an all-comers population of any age, race or gender. Thirty-one pharmacy sites in 24 markets were used as study sites. The study was

not designed as a self-selection study since acne is already well-established as an OTC condition.

To encourage the broadest population possible, the screening criteria were minimal. The recruitment was consistent with methods used in a real-life approach. So advertising is typically used.

The study flow was comprised of four main parts. Recruitment included an all-comers population with minimal screening criteria. Those interested in the study were referred to a central call center.

Visit one was the enrollment visit. The subject reviewed the package labeling and then made a personal purchase decision. Women of childbearing potential were given a home pregnancy test to take. The product and the diary were dispensed for home use, and the subjects were told they could return for repurchase if they wished to do so.

It's important to note there was no coaching of any type on how to use the product, when to use

the product, how much to use, for what indication to use it, or on what body parts to use. The use period was 6 weeks. An adverse event line was available 24/7, and subjects documented their use in a diary.

Subjects returned for visit 2, which was the end-of-study visit. The diary, unused product, and packaging were collected. A repeat pregnancy test was conducted for women of childbearing potential. The diary was reviewed for any adverse events, and an end-of-study questionnaire was administered; 3,234 consumers were screened. Of these, 947 were included in the actual-use population, and 938 subjects completed the study.

Of the 1,197 consumers who were not scheduled to the pharmacy by the call center, these were mostly for administrative reasons. For example, they did not schedule due to convenience or screen failures; 760 consumers were no-shows to visit 1; 330 subjects were not included in the actual-use population primarily due to not wanting to purchase the product or because they were a

screen failure. There were 9 subjects who discontinued during the study period.

The demographics of those included in the actual-use population included 21 percent of the population being 12 to 17 years of age with a gender split of approximately one-third male and two-thirds female. The racial mix was primarily comprised of Caucasians and African Americans as well as those of Hispanic origin.

There were two primary endpoints. These related to the possibility of increased irritation with more frequent use and the potential for off-label use. Primary endpoint 1 was the proportion of subjects who used the product only once per day. The success threshold was defined as a lower bound of 85 percent. These data were obtained from the diary.

As is typical for actual-use studies, the total correct results include both the initial correct response plus mitigated responses. Responses or behaviors that represent a reasonable response or a safe course of action are mitigated.

For primary endpoint 1, 89 percent of the consumers correctly used the product only once per day. Eighty-one percent of these behaviors were initially correct. When adding the mitigating responses, the final score was 89 percent. The lower bound was 87 percent. So the primary endpoint for once daily use was met.

The primary endpoint 2 was the proportion of subjects who used the product only for acne; that is, they did not use it off label. The success threshold was defined at a lower bound of 85 percent. These data were obtained from the end-of-study questionnaire.

For primary endpoint 2, 99 percent of the consumers correctly used the product only for acne; that is, no off-label use. Ninety-eight percent of these behaviors were initially correct, and when adding the mitigating responses, the final score was 99.9 percent correct. The lower bound was 98.5 percent, and the primary endpoint for use only for acne was met.

I also want to point out there were

9 subjects excluded at screening because they did not self-report acne. We did an analysis, and if those 9 subjects were added to the analysis, this primary endpoint was still met.

There were two secondary endpoints. Secondary endpoint 1 was comprised of two criteria: do not use on damaged skin, which included cuts, abrasions, eczema, or sunburn; and avoid contact with eyes, lips, and mouth.

Scores were summarized, and confidence intervals were calculated. However, there were no thresholds set for the secondary endpoints. These data were obtained from the diary and the end-of-study questionnaire.

For secondary endpoint 1, 97 percent of the consumers used the product on the correct body area. Ninety-six percent of the behaviors were initially correct, and when adding the mitigating responses, the final score was 97 percent.

The secondary endpoint 2 was comprised of the codified and required pregnancy and breastfeeding warning that is found on many OTC

product labels. It states that a health professional should be asked before using the product if pregnant or breastfeeding.

There were 1,277 people in the all-comers population who came to the pharmacy site for visit 1, and of these, 44 percent were women of childbearing potential; 16 women were pregnant or breastfeeding at visit 1, 6 were pregnant, and 10 were breastfeeding. Of the 16, 8 were scored as correct due to their initial response or a mitigation; for example, if they did not know they were pregnant or if they had been previously prescribed adapalene while breastfeeding.

These women had to state that they would ask the doctor before use unprompted at the purchase decision. That means they had to offer this response on their own without being asked or prompted, and they had to state they would consult a healthcare professional before using the product. These women were not permitted to enter the actual-use phase of the study, so it's unknown if they would have asked a doctor before they actually

used the product.

A separate powered self-selection study was conducted specifically in a group of women who were pregnant and breastfeeding, and I will present those results next.

Additional patterns for use were gathered in the actual-use study. We evaluated the number of tubes that subjects purchased. As you can see, 94 percent of the subjects purchased only one tube. Only 5 percent of the subjects purchased more than one tube at visit 1, and very few subjects, 1.5 percent, returned for a repurchase. For those who did repurchase, the median number of days between purchases was 27 days with a range of 13 to 42 days.

There were only two subjects who purchased additional tubes in the last week of the study. Of the 4 subjects who reported using the most product, there were no reported adverse events. This suggests they may have kept the product for future use as is common in these studies. Dermatologic adverse events included related and unrelated

events, and they were evaluated. Twenty-two percent of the study population reported a dermatologic adverse event.

When reviewing adverse events occurring in at least 1 percent of subjects, there were no new adverse events, and there were no serious adverse events. The most common AEs were dry skin reported by 11 percent of subjects, and erythema reported by 5 percent of subjects.

So in summary, consumers complied with the new information on the Drug Facts label. Approximately 90 percent used the product once daily. Ninety-nine percent of subjects used the product for the labeled indication of acne, and 97 percent used the product on the correct body location.

The study results were similar for adolescents and those of lower literacy. The drug was used as instructed on the DFL, and there were no potential safety concerns that would alter the known safety profile for the study product.

Finally, I would like to review the results

of the targeted self-selection study that was conducted in a population of women who were currently pregnant and/or breastfeeding.

Despite the minimal systemic availability of Differin gel, which means exposure by pregnant women to adapalene is not a safety concern, a targeted self-selection study was conducted based on principles outlined in the FDA guidance for self-selection studies.

The objective was to provide self-selection data on the effectiveness of the codified and required warning statement, which is currently used, and to do so in a special population of women who were currently pregnant or breastfeeding. The targeted nature of the study means that only the special population was recruited, and they were the focus of the study.

The study population was comprised of pregnant or breastfeeding women ages 13 and older who self-reported acne. The recruitment was masked, which means that the women did not know the reason they were being recruited.

Women were intercepted in malls if they met one of four criteria: number one, if they appeared to be between the ages of 18 and 50; two, if they had visible acne; three, if they were visibly pregnant; or four, if they had children who appeared to be 18 months of age or younger.

Three of these four criteria were not based on being visibly pregnant. This was done to recruit women at all stages of pregnancy, and pregnancy tests were conducted to confirm the pregnancy. Recruitment was conducted at 25 mall sites and one specialty clinic for pregnant teens. Over 19,000 women were intercepted in order to find the required study population.

The codified OTC warning is required on OTC products intended for systemic absorption. That is not the case for this topical product, but Galderma decided to put it on the Differin gel label. It states, "If pregnant or breastfeeding, ask a health professional before use." So it is not a do-not-use contraindication. The warning simply states a woman should ask a health professional

before she uses the product.

The study population was comprised of younger women, primarily between the ages of 18 and 34. Races were primarily comprised of Caucasian and African American women as well as those of Hispanic origin. Thirty-three percent of the women were pregnant, and 63 percent of the women were breastfeeding; 4 percent of the women reported being both pregnant and breastfeeding, And 38 percent of the study population was of lower literacy.

A success threshold was set at a lower bound of the two-sided 95 percent confidence interval. This threshold was set at 90 percent because the warning is established and approved. Seventy-four percent of the general population correctly answered the self-selection question in this cohort. Approximately 25 percent were of lower literacy. The results were similar for the total study population with approximately 38 percent being of lower literacy.

So for the targeted self-selection study,

about three-quarters of pregnant or breastfeeding women who self-reported acne stated that they would ask a health professional prior to using Differin gel. The endpoint was not met, and not all women may comply with the warning. But as previously presented, large margins of safety exist to ensure that Differin gel does not pose a risk of teratogenicity in a nonprescription environment.

So in summary, for the consumer studies, consumers understand the Drug Facts label. Consumers can use Differin gel according to the DFL in an unsupervised OTC environment. Consumers will use the product once daily on the correct body areas and for the indication of acne. None of the incorrect responses or behaviors posed any clinically relevant safety concerns.

Dr. Wilkin will now provide the benefit-risk assessment of Differin gel in the OTC setting.

Applicant Presentation - Jonathan Wilkin

DR. WILKIN: Thank you, Ms. Aker.

So the descriptor under my name lists my last two positions, but really doesn't say anything

about the 18 years I spent in academic dermatology where I had a very active clinical practice. There's a lot of enjoyment in the practice of dermatology in the clinic. There's short-term positive feedback that's very objective when you see patients. And one of the real joys is seeing the acne patient when they come back on their very first visit after you've started therapy.

When they come in the clinic, it's like seeing a totally different individual. When they walk in, they give you eye contact for the first time. There's a bounce in their step. They're smiling, and a totally different person.

I was glad when about three months Galderma asked if I would give my assessment of adapalene, Differin gel, going over the counter. And to do that, I looked at the benefit-risk assessment tool that FDA has published for use and chose to use the decision factors in that.

The benefit-risk assessment approach indicates that we should consider five decision factors. The first two are not specific to the

drug. They're called therapeutic area considerations. The first is analysis of the condition, in this case, acne in the OTC setting. Current treatment options is second. So that would be current treatment options again in the over-the-counter setting.

Then there are the three drug specific decision factors, specifically about Differin gel and what we know about its benefits, its risks and how to manage those risks. We will go in order through these five decision factors.

The first decision factor is the analysis of the condition. Dr. Webster has reviewed the clinical picture of this well-recognized condition and the mechanisms of acting pathogenesis. Both Dr. Webster and the FDA in their briefing document point out the potential for scarring and emotional impact, and there is also agreement that in the OTC setting, acne is a well-established indication.

Next, I will discuss the acne treatment options that are currently available over the counter. The current OTC treatment options are

allowed to be marketed under the OTC monograph, and on this slide, the percent behind the active ingredients is the 2015 market share.

Of these currently available OTC products, only benzoyl peroxide is recommended in the recent American Academy of Dermatology guideline for acne care, and the market share for benzoyl peroxide is a little less than one-third. The antimicrobial role for benzoyl peroxide is well-established, and some of these can be quite effective products over the counter.

Salicylic acid products make up almost 70 percent of the market share. The 2016 AAD guidelines stated that the clinical trials demonstrating the efficacy of salicylic acid in acne are limited.

Then there are the smaller market share products that are combinations of resorcinol with sulfur, resorcinol monoacetate with sulfur, which do not get reviewed at all in the AAD guidelines.

Lastly, because of their multiple mechanisms of action against acne, topical retinoids are the

first-line therapy recommended in the AAD guidelines as pointed out by FDA also in their briefing document, and these are not available currently without a prescription.

Next, we will move from therapeutic area considerations to drug specific consideration and first examine the benefits Differin gel will bring to acne sufferers. First, the properties of Differin gel provide a different mode of action relative to the current OTC products in that it is comedolytic, resolving the precursor microcomedo lesion, and it's also anti-inflammatory.

Once again, topical retinoids are the first-line therapy in modern dermatology, and there's several and different modes of action have the potential to help consumers who are not adequately treated with the current OTC monograph products.

Next, Differin gel is a once-daily product offering a potential advantage over current OTC acne treatments labeled for use up to three times a day. It is interesting to note that the OTC

monograph requires labeling that implicitly charges the OTC consumer with this self-titration according to toleration and benefit from the product. So in my view, once-daily product without requiring this consumer self-titration could actually help with adherence.

If approved for nonprescription use, Differin gel would be the very first OTC acne drug product actually approved and regulated by FDA under a new drug application and will provide an additional valuable medication option for consumers.

Next, I will review the potential risks of nonprescription Differin gel that are well characterized. In consideration of these risks, a large number of clinical studies and extensive postmarketing history confirm that the product's well-established safety profile, confirmed and consistent with over 20 years of marketing experience.

Phototoxicity and photoallergenicity are not concerns because neither phototoxic potential nor

photoallergenic potential has been shown in the animal or human studies. Moreover, phototoxicity and photoallergy have not emerged as issued in postmarketing safety reports.

Acne is a well-understood over-the-counter indication, and thus off-label use is unlikely. Data from the actual-use study support this conclusion. However, if Differin gel is used off label for other skin conditions, its excellent safety profile should mean that any adverse outcomes would be minimal.

With regard to the final risk issue and the most important one to consider, teratogenicity, this too is not a concern for topical Differin gel. Vitamin A dietary supplements and retinoid creams marketed as cosmetics are available without a prescription today.

Although Differin gel would not be the first retinoid available without a prescription, it would be the first thoroughly studied retinoid or vitamin A approved under an NDA by FDA with a proven margin of safety to confirm that it is safe

for nonprescription use.

While high oral doses of retinoids and vitamin A can be teratogenic, there is no signal of any teratogenicity for topical adapalene in any of the many and different sources of information available. Teratogenicity is ultimately in the dose, and Differin gel has a substantial safety margin.

Finally, the last decision factor, risk management. First, the local side effects of Differin gel are largely and successfully self-managed. I think that's also implicit in the OTC monograph. The skin has a limited repertoire. It gets scaly and red and may burn a little bit every time it doesn't like something, and these local side effects are well-known, generally mild dermatologic in nature, localized, and they resolve on discontinuation of the product.

The risk management is also embedded in the nonprescription labeling proposed by the sponsor, which includes elements from the prescription labeling, the OTC monograph labeling, and the

codified OTC pregnancy and breastfeeding warning. Then finally, the consumer development program has evaluated consumer behavior and has confirmed appropriate use for this over-the-counter condition.

As we come to my last slide, one of the most compelling aspects for me is that retinoids with their dual mechanism of action can work for patients that currently are not finding success with the limited mechanisms of action of benzoyl peroxide and salicylic acid.

So in sum, looking at all the decision factors for the benefit-risk calculus, there is robust support for Differin gel going over the counter where it will be a safe and very valuable medication for acne sufferers. Thank you.

Dr. Marsh will give concluding comments.

Applicant Presentation - Howard Marsh

DR. MARSH: Thank you, Dr. Wilkin.

In conclusion, I would like to review criteria for an OTC medicine and how Differin gel meets those criteria.

Consumers can recognize acne. They've been doing so and have been self-treating for decades. We have heard that the proposed Differin label is similar to current acne labeling for OTC drugs and introduces no new instructions that would pose any new safety concerns.

Consumers are able to understand the label and generally use the product appropriately. Even if pregnant women did not always follow the advice that's currently seen in many OTC labels to see their doctor prior to use, there would be no consequences because systemic exposure is very low, and there is a very wide and reassuring margin of safety for teratogenicity.

Data presented by Dr. Meckfessel demonstrates the efficacy of the product. In all, there have been 140 clinical studies involving over 6,000 subjects. This product has been thoroughly studied. Data from an extensive clinical program and 20 years of postmarketing experience in over 40 million users has provided a well-established safety profile with adverse events being

dermatologic in nature, localized, generally mild and transient. Since first marketed over 21 years ago, no new safety concerns have been identified.

The potential for misuse is low. Consumers are unlikely to use the product in areas beyond that tested in the maximal-use PK studies. Even if consumers were to use the product more than once per day, the potential impact would be an increase in the incidence of localized dermatologic effects, which tend to be transient and improve on stopping the treatment.

Whilst the product is indicated for 12 years and over, use by children under 12 years does not pose any safety concern. As we have heard, a study using the combination of adapalene of benzoyl peroxide in the 9 to 11 age group demonstrated a similar safety profile to older subjects.

We have carefully evaluated the issue of teratogenicity. The risk of teratogenicity is low with a very wide margin of safety. To put this margin of safety into context, it is important to

remember that the margin of safety is based on an exposure level at which no adverse teratogenic effects were observed in the most sensitive animal species using the highest blood levels seen from one subject under the maximal-use PK study.

Put in another way, if the exposure level was 70 times higher, we would still expect to see no adverse teratogenic effects even in the most sensitive species.

For an intravenous drug or even an oral drug, it is possible that massive inadvertent or deliberate overdose might occur. However, in the context of a pre-formulated topically applied product, it is virtually impossible to foresee any realistic scenario of abuse or misuse where the level of exposure could approach the level that might be teratogenic.

It would require the application and absorption of four of the largest tubes each day just to reach the level for which the no adverse effect was calculated. This would be equivalent to a whole year's supply of the largest tubes in one

day. And further, overly excessive exposure would almost certainly be limited by skin irritation.

So our assessment of the decision factors that define the benefit-risk framework is that all are positive. Differin gel is safe and effective, and consumers will be able to appropriately use the product in an OTC setting. The two modes of action are different from the current OTC acne drugs and will provide an additional OTC option for a condition that impacts the lives of millions of acne sufferers in the U.S.

I would like to thank my presenters and the advisory committee and the FDA for their attention. The presenters and the other Galderma colleagues and I are ready to answer your questions. Thank you.

Clarifying Questions

DR. ROUMIE: Okay. Are there any clarifying questions for the sponsor? Please remember to state your name for the record before you speak, and if you can, direct your questions to a specific presenter.

I guess I'll use chair's prerogative first. My question is for Dr. Meckfessel. Most of his efficacy studies that were presented were 12 weeks in duration, and the actual-use study appeared to be 6 weeks in duration. I did not see any type of upper limit on the use on the Drug Facts Label.

Have any chronicity studies been done in any of the kind of long-term use studies been conducted by the sponsor?

DR. MECKFESSEL: Matthew Meckfessel, medical lead, Galderma. With regards to duration, most of the studies have been 12 weeks. We have conducted a single study that lasted up to 12 months. Use beyond that has not been investigated.

DR. ROUMIE: Dr. D'Agostino?

DR. D'AGOSTINO: Ralph D'Agostino. In terms of some of these actual-use studies and comprehension studies, I tend to think of them oftentimes more we have a very safe drug, and so we're trying to see how people will use it.

In the studies, did you have any selection criteria on your side, some people who came forth

were not selected in the study, any sort of eligibility criteria that might impact on safety? Was there such a list of eligibility criteria?

DR. MARSH: I can understand the question. Ms. Aker?

MS. AKER: Julie Aker, Concentrics Research. I believe you asked about both the comprehension and the actual-use study; is that correct?

DR. D'AGOSTINO: Right, even the targeted study, too.

MS. AKER: And the targeted study. Okay. So what we can do is we can look at the inclusion/exclusion criteria for each study. Would that address your question?

DR. D'AGOSTINO: Yes, yes.

MS. AKER: Okay. So for the label comprehension study, these are general population studies. These studies are intended to bring in people, either a random sampling in a mall intercept or in large databases in a random sampling. These individuals don't have to have the condition. These studies are done to prove that

anyone walking up to the shelf, whether it's a brother, a sister or a family member, anyone can actually purchase this.

So inclusion/exclusion criteria for the label comprehension study are very, very minimal. So it usually is -- let's do slide 1 up -- inclusion were broad. Anyone who could potentially use the drug, so there was no -- any kind of screening against that. It was a general population. They had to agree to participate. They had to be 12 years of age or older.

The exclusions were also minimal, and so participants were not required to have an interest in the drug product as you can see. But we did exclude people if they had participated in a study in the last 12 months. They were not permitted if they had participated in another study in the last 12 months or what we call employment security, which means if they work for a drug company, if they work for a market research company and so forth.

Very similar inclusions were used for the

other two studies. Let's go to the targeted self-selection study inclusion and exclusion criteria. This was an all-comers recruit. Excuse me. The targeted self-selection study was a special population, and so these were intercepted. And as we spoke earlier, these people were intercepted in malls. We went through 19,000 subjects to actually find these individuals.

For those individuals, we approached them in the four criteria that I mentioned in my presentation. Then once they came in, we did a confirmatory pregnancy test. We self-report -- it was a self-report for the breastfeeding individuals.

So that was the only inclusion criteria. Same exclusion criteria, if they had participated in a study in 12 months or worked for a drug company or market research company or so forth.

Now, in the actual-use study -- slide 1 -- they needed to be male or female of any race, self-report experiencing acne, able to read, speak, or understand English. These are very

common inclusion/exclusion criteria. They had to sign a CDA and a HIPAA agreement. They had to be willing to read and sign an informed consent, and for the children, for the adolescents 12 to 17, they signed an assent.

The individuals not self-reporting acne, there were only 9 that were excluded, and those are the ones I wanted to point out that we still met the endpoint. The exclusions I won't read, but we'll pull those up.

Slide 2 up. These are very, very common for consumer and behavior studies, and so these again are those employment, security types of questions I mentioned earlier about working for any type of a competing company, a market research company, an advertising company, a drug company, and if they had been trained as a healthcare provider.

DR. D'AGOSTINO: Just one more. Is it all right to ask another question?

DR. ROUMIE: Is it a follow-up?

DR. D'AGOSTINO: It's a follow-up, yes.

DR. ROUMIE: Yes.

DR. D'AGOSTINO: In the targeted self-selection where you failed the endpoint, I always thought 85 percent was kind of generous. Getting lower is sort of realistic. But anyway, in terms of they failed your prespecified endpoint, so the fallback is that even though that happened, the safety is in general so good that --

MS. AKER: Correct, correct. And keeping in mind that three-fourths of the population out there did get this right. So you're correct, we did not hit the endpoint, but three-quarters of the population did. And even those with -- we had a 38 percent low literacy in this rate in this study, which is high. And even when that was the case, it was 74, 75 percent correct.

DR. D'AGOSTINO: Thank you.

DR. ROUMIE: Dr. Katz?

DR. KATZ: Ken Katz. The concern I think is mostly here with pregnant women rather than breastfeeding, but some of the outcomes that Ms. Aker presented for the self-selection and the actual-use study gave us the results in a group

combined of both pregnant and lactating women. I'm wondering why that was done.

Are we to be concerned about those women to the same extent that we're concerned about pregnant women? And if not, do you just simply have the data for pregnant women only rather than in the combined group of pregnant and breastfeeding women?

DR. MARSH: Ms. Aker?

MS. AKER: We do have those data, and I'll show them to you. The reason that -- I'm sorry. Julie Aker, Concentrics Research -- we did combine them because if you read the warning, it says "pregnant or breastfeeding." So that's why we combined them. But to your point, we did actually assess them for pregnant only.

Slide 1 up. So for the pregnant population only, you can see that their self-selection for pregnant only was 73 percent correct overall. And about 73 percent of them were -- well, they were all correct initially, and then you can see the scores in the next column for breastfeeding only, which was slightly higher at 77 percent. And then

for those who mentioned that they were pregnant and breastfeeding, 76.9 percent correct.

DR. ROUMIE: Dr. Cohen?

(No response.)

DR. ROUMIE: Dr. Cohen?

DR. MICHAEL COHEN: Yes, I'm sorry. I wasn't sleeping either, honest.

(Laughter.)

DR. MICHAEL COHEN: I just had a quick question about availability of patient information, and mainly the question is, is there additional information available for consumers? Is that planned or does that exist right now? And perhaps that has also been tested, and we just aren't being told about that. I don't know, but I'd be curious to know that.

DR. MARSH: Sean Griffin?

MR. GRIFFIN: Good morning, everyone. My name is Sean Griffin. I'm director of regulatory affairs at Galderma, and I'm happy to answer that question for you.

So there is a proposed patient leaflet that

will be included with the package. And if I can see slide 1 up, please. So essentially, what we've done is we've taken the Drug Facts label and put it kind of in a consumer-friendly question-and-answer format. So the information is very similar. It actually contains everything from the Drug Facts label, again, in a goal to be a bit more consumer friendly.

So as you'll see here, you've got examples like what is different and what is it used for. We start off with the fact that it's a once-daily topical medication and so on. We mention that it's for patients 12 years and older.

If I could see slide 2 up, please. It goes on. This is the second page of the consumer leaflet, and it goes into more additional information such as when is my skin most likely to become irritated, what should I do if it becomes severely irritated, and so on.

DR. MICHAEL COHEN: Does it expand at all on the pregnancy information?

MR. GRIFFIN: It does not.

DR. MICHAEL COHEN: Right now, it says "consult a health professional." And there are all kinds of health professionals. It's not very specific, and we know that that might even be a turn-off to some people. It means extra steps have to be taken, and I'm just wondering if you've considered or FDA has considered even more focused language there.

MR. GRIFFIN: Yes, sure. So actually, we proposed to use the current codified pregnancy and breastfeeding warning, as Ms. Aker alluded to earlier this morning. We thought that was labeling or information that's well understood by consumers and used for a long period of time. We have not proposed to change that warning at all.

So if I could get slide 1 up, please. So essentially, this is from 21 CFR 201.63. As you see here, pregnant or breastfeeding, as you mentioned, ask a health professional before use. It's pretty broad and non-specific, but again, we elected to remain consistent with the current OTC medications.

DR. MICHAEL COHEN: We also know from experience that that isn't done often, or even if it is done, the health professionals just aren't aware of the medication, or what to say, or they just don't have knowledge of it when you just say health profession. So I think that's important to keep in mind.

DR. ROUMIE: Dr. Scialli -- help me with your last name.

DR. SCIALLI: Tony Scialli.

DR. ROUMIE: Scialli.

DR. SCIALLI: Dr. Katz asked my question so I'll stand down.

DR. ROUMIE: Dr. Bigby?

DR. BIGBY: I don't actually know who to address this to. Michael Bigby.

Of the current use for adapalene, what percentage of it is for acne and what percentage for photoaging?

DR. MARSH: I don't have those data to hand, but it's indicated for acne. And in the OTC proposed label, it will only be indicated for acne

from 12 years and up.

DR. BIGBY: But you don't have it at hand, but can you get it?

DR. MARSH: We'll look into that.

DR. ROUMIE: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Hi, Elizabeth Joniak-Grant. It says in the brief several times that most adverse events did not require medical intervention, but some did. What were those medical interventions that were required?

DR. MARSH: I don't have those data to hand. I can show you the -- no, I don't have those data to hand.

DR. ROUMIE: Dr. Bernstein?

MS. BERNSTEIN: Cheryl Bernstein. I'm not a doctor yet.

I was going to also ask the question about the pregnancy that was down there. I was wondering why it does not say do not use if pregnant or breastfeeding just really plain so that people get a quick view of what that means.

My main question is on the study, it said

that no instructions were given to the patients. Of course, they read the informed consent. So what was the indication of reading the package insert? My experience is people don't automatically look at the package insert. They just start taking the drug. That's just based on years working in clinical research where they don't always follow the directions.

So I was just wondering how did they know to read it or what was the instructions in the study.

DR. MARSH: Let me answer the first part of the question. The difference between do not use and ask a doctor is quite specific. In this particular instance, the label only says ask a doctor for use. We believe that there is no risk of teratogenicity based on the evaluation that we've done, and so that's why the label says ask a doctor for use rather than simply do not use. Even the ask a doctor for use is a cautious approach given that we do not consider there's any risk of teratogenicity.

Ms. Aker, would you like to answer the

second part of the question?

MS. AKER: Julie Aker, Concentrics Research. When the patients or the subjects came in for the actual-use trial, they were given -- I'll start with what were they given to see. They were given the Drug Facts label. So they were given a commercially available box, so what we anticipated would be commercially available and it had the Drug Facts label on the back.

So that's what they were given. They were able to just -- they were able to look at it at their own pace just as they would if they were going into a store and taking it off a shelf. They were able to do that. They weren't told anything, and so those were the comments I was making about not being coached. They were left alone, and they were not given any information.

To your point about the consumer leaflet, that was actually inside the box, and so everyone had that -- as they took it home, but they were not pointed to it or told to read it or anything like that. It was there for the reference just like it

would be in a real-life situation.

DR. ROUMIE: I believe Dr. Harris is next.

DR. HARRIS: I have a couple of questions for Dr. DeSesso. Do I turn to Dr. DeSesso, or does Dr. DeSesso want to get up?

DR. DeSESSO: John DeSesso from Exponent and Georgetown University.

DR. HARRIS: This is for personal information, Dr. DeSesso. When were all the developmental reproductive toxicology studies done?

DR. DeSESSO: They were done about 12 years ago.

DR. HARRIS: About 12 years ago? Were they done at one particular contract research organization, or were they split?

DR. DeSESSO: They were -- I don't recall. I will look that up.

DR. HARRIS: Do you know what lab they were?

DR. DeSESSO: I'll look it up.

DR. HARRIS: Look that up? Okay. That's all the information I need. I like that. If I can get that information, I'd appreciate it.

DR. MARSH: We'll do our best to get that information during the break.

DR. HARRIS: Thank you.

DR. ROUMIE: Dr. Obican?

DR. OBICAN: Yes, thank you, Sarah Obican. I have a question regarding some of the information in the packet, what should I know before using the product. The first thing that's listed is if pregnant or breastfeeding, ask a health professional. We kind of spoke about that.

I was actually more interested in the second one, considering the safety profile of the first. Keep out of the reach of children. What would be the expected results if a child got this and orally taken the medication? And I'm kind of wondering whether or not that should be more highlighted and placed first. Thank you.

DR. MARSH: So if I understand the question correctly, you're wondering what would happen if children got hold of it and accidentally ingested it?

DR. OBICAN: Yes, correct. Thank you.

DR. MARSH: There have been very few reports of that, but I have six reports of oral exposure from children ranging from 9 months to 3 years. The amounts ingested were up to 2 grams of the product. There were no adverse events reported in five of those cases, and in one case, it was associated with abdominal pain and nasopharyngitis in the child that already had nasopharyngitis. So we didn't see any really bad untoward effects.

DR. OBICAN: Thank you.

DR. ROUMIE: Dr. Joniak-Grant.

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. I just wanted to follow up with, I believe, Julie Aker about how the DFL was given to them. What were study personnel doing at this time? I'm thinking to hand somebody a paper and then wander off is going to kind of give someone more impetus to actually read it or standing there looking over them might give them more impetus to read it. So my question is, what were the study personnel doing at that point?

MS. AKER: Julie Aker, Concentrics Research.

Thanks for the question. The consistent approach that we use in these studies is to bring someone in. They usually do a confidentiality agreement, and then we explain that we're here today to do a consumer study. Then we hand them the product label, and that is not on a piece of paper; it's on the box.

So it's exactly the way it would be if someone walked into a pharmacy this afternoon, you walked up to the shelf, you said you were curious about something, you took it down and took a look at it. It's the very same process is being emulated.

So during that time, no one is standing over them, and no one's pressuring them. We give them as much time as they want on their own to read it just like they would in a store situation where they would take as much time as they want to look at it.

DR. ROUMIE: Dr. Katz?

DR. KATZ: Thanks. Ken Katz. My question is for Dr. DeSesso about the PK study. It seems

like it was a relatively small study with 24 subjects. So my question is about the confidence of that highest concentration seen, which was 0.17. Was this person an outlier? Do you have a sense of the distribution of the concentrations, and what was the condition of his or her skin, and how much was that person applying?

DR. DeSESSO: The person was a 16-year-old male of Hispanic origin. The one study or the one measurement that was 0.17 was very high for him. He was not -- from the terms of the amount applied to his body, the total dose, it was not the highest of the doses. So it was just he had that one very high measurement.

DR. KATZ: So given that he didn't apply that much but absorbed a lot, is it possible that this Cmax is underestimated?

DR. DeSESSO: Well, he didn't apply it. It was applied by the technician. Is it an underestimate? I sort of doubt it in the way these things are applied, and given that his other measurements were not that high, I would think that

that would -- it was one of those things where it was the highest, but I don't know that the others were all artificially low, the other two measurements for him.

DR. MARSH: One of my colleagues has a little more detail about the study, Natalie Wagner.

MS. WAGNER: Natalie Wagner, clinical PK manager from Galderma. Indeed to answer to your question, we have conducted several PK studies with Differin gel, 0.1 percent -- slide PK-1, please -- and among -- indeed we have conducted three different studies. Slide 2 up, please.

Yes, and among these studies, two different studies were conducted with adapalene 0.1 percent gel, one study conducted with 25 adolescents and one study conducted with 24 subjects, including 18 adolescents and 6 adults. And among these two studies, we have shown consistency across systemic exposure.

Slide PK 17 up, please. This slide summarizes the results of these three studies, so the first study was conducted with a gel containing

adapalene and 2.5 percent benzoyl peroxide. In this study, subjects applied 2 grams of drug product on a fixed area of 1,000 square centimeters. And in these studies, the most exposed subject had an area under the curve of 2.65 nanogram hour per mL.

The two other studies were conducted specifically with adapalene 0.1 percent gel, the gel proposed for the OTC switch. And in these two studies, the first one was conducted using a fixed dose of 2 grams applied every day for 4 weeks on a fixed surface area of 1,000 square centimeters. And the most exposed subject in this study had an area under curve of 3.47 nanogram hour per mL.

Lastly, the more recent study was conducted in the so-called maximal-use condition based on FDA advice, and in this study, subjects, the product has to be applied to all the area potentially affected by acne, including the face, shoulder, upper chest, and upper back with no limitation of 1,000 square centimeters as compared to previous studies.

So in this study, you can see the subject, the product was applied to an area ranging from 1,000 to 3,000 square centimeters, and the applied dose varied from 1 gram to 3 grams. And in this study, again, the most exposed subject had an area under the curve of 2.9. And this subject is not the one who applied the highest quantity of drug product.

So we do have data to compare the area under the curve. This is the applied dose. So I would be happy to share this data with you if I do not answer completely to your question.

DR. KATZ: I guess the question was more for the Cmax for the calculation for the NOAEL.

MS. WAGNER: Yes, the NOAEL was calculated based on the area under the curve. This is a ratio of the two areas under the curve. So the 70 is a ratio between the area under the curve obtained from the most exposed subject divided by the area under the curve obtained in the rat species at the NOAEL dose.

DR. ROUMIE: Dr. Oussova?

DR. OUSSOVA: Tatiana Oussova, Division of Dermatology and Dental Products, and I have a clarifying question for Dr. DeSesso. On your slide 65, you mentioned that there were 91 cases of prospectively identified cases of pregnancy exposure during postmarketing surveillance.

I'm just wondering what were the settings in which those cases were identified. Was it an epi study or what? Thank you.

DR. MARSH: The question was for you, but I think Dr. DeSesso has the answer. Could you answer the question, Dr. DeSesso, please?

DR. DeSESSO: So your question was you wanted to know where --

DR. OUSSOVA: How they were identified and in what kind of settings, because you are saying they were identified prospectively. I just wanted to clarify.

DR. MARSH: I understand the question better. So in terms of postmarketing surveillance, the report was given to us knowing that there was an exposure before we knew the outcome of the

study. So we were able to follow that exposure through the study. The retrospective ones were ones that were reported to us where the outcome was already noted.

DR. OUSSOVA: Okay. Thank you.

DR. MARSH: Thank you. Sorry I misunderstood the question.

DR. ROUMIE: Dr. Engle.

DR. ENGLE: Jan Engle. My question relates to the label comprehension study. On the label, it says to cover the entire affected area with a thin layer under the directions. But when you look at the patient information leaflet that's inside the package, it states that Differin is not a spot treatment and should not be used to treat a single pimple or blemish and that it should be applied to the entire face, et cetera, et cetera.

So my question is, was that tested at all in label comprehension? Because those directions are somewhat different. Where it says on the label to cover the entire affected area, I could see a teen or somebody thinking that's just a pimple. So I

just wondered, was there any -- did you look at that at all in terms of comprehension, and if that's important, why is it not on the label?

MS. AKER: Julie Aker, Concentrics Research. So we did not test that particular element. That element is on many other labels, and it's also in the monograph. And so that's one reason why. It's a well-understood to apply a thin layer.

DR. ENGLE: But across the entire face?

MS. AKER: Yes, that -- we did not test that particular element.

DR. ROUMIE: Two questions, Ms. Bernstein, Dr. Pisarik, and then we're going to have to pause.

MS. BERNSTEIN: My question has to do with perception. In the patient studies, they read the information, and then I'm kind of back to the statement ask a professional before use if you're pregnant. In terms of understanding the difference between applying like a gel or a cream in terms of whether it gets into your body as the skin being a barrier or taking an oral medication, in terms of perception of whether that was part of the study,

to see if people had different -- if that was tested, if they understood that applying something to the skin can also be absorbed into the body or not as a potential problem if you're pregnant or if you have another medical condition.

DR. MARSH: So if I understand the question correctly, you're asking us whether we specifically tested whether there could be absorption through the skin versus taking the product orally?

MS. BERNSTEIN: The patients' perception, if taking something on the skin has the same implication as taking it orally or even an injection from a physician like because --

DR. MARSH: Okay. I understand the question. The answer is we didn't test that specifically.

DR. ROUMIE: Dr. Pisarik.

DR. PISARIK: Paul Pisarik. I just have a question about the "if pregnant or breastfeeding" label there. In all the stuff that I read that you supplied us, you were very adamant that there was no teratogenicity due to the medication, but why

put that label on there? Is there any residual concern? Is it medical legal? Why do we need to have that if pregnant or breastfeeding on there at all?

DR. MARSH: The instructions to see a doctor before use is very common in OTC medications. We do not think there is a risk. Personally as a clinician and with many years of clinical practice, I think it's good practice for ladies who become pregnant to see their doctors, and as a practicing physician, I would always ask ladies in early pregnancy not just about their prescription drugs but all the OTC medications they were using as well.

So I think it's a cautious approach, but I would say that it's sound clinical practice.

DR. PISARIK: Thank you.

DR. ROUMIE: We'll now take a 15-minute break. Panel members, please remember there should be no discussion of the meeting topic during the break amongst yourself or with any member of the audience. We will resume at 10:25.

(Whereupon, at 10:11 a.m., a recess was taken.)

DR. ROUMIE: We will now proceed with the FDA presentation.

FDA Presentation - Chinmay Shukla

DR. SHUKLA: Good morning. I'm Chinmay Shukla, and I'm a clinical pharmacologist with the U.S. Food and Drug Administration. The topic of my presentation today is maximal usage trial data.

Now, before we delve into the design of the maximal-use trial for Differin gel, I will give you a brief background on the concept of maximal usage; following which, we will look at the pharmacokinetic results from the new maximal usage trial with Differin gel. This presentation will also include cross-trial comparison of PK data for all adapalene [indiscernible] of 0.1 percent strength for qualitative purposes only.

Now let's begin with looking at the factors that influence topical drug absorption. Dermatological diseases are unique as topically applied drugs are delivered directly to the target

tissue. Topical bioavailability is determined by a complex interaction of drug substance, the formulation, and the effect of disease itself on the barrier functions of the skin. These factors ultimately determine systemic drug exposure.

Now, before we look at the general design of maximal usage trial, let's answer some basic questions and understand the reasons why a maximal usage trial is conducted. The first question that we would like to answer is why assess systemic exposure for topical products, and the answer is for the assessment of systemic safety.

The second question that we would like to answer is why assess systemic exposure of adapalene following topical application of Differin gel. The answer is adapalene is a retinoid-like drug, and there is a concern for teratogenicity based on animal toxicity data. Hence, assessment of systemic exposure in humans will help us calculate the relative exposure margin based on animal toxicity data.

Now, the third question is how to evaluate

the systemic exposure of Differin gel. The answer is maximal usage trial, which is currently recommended by the agency. In fact, this trial has been recommended by the agency since the mid-1990s.

So with this background, let's look at what is a maximal usage trial. A maximal usage trial is a pharmacokinetic trial designed to maximize the potential for drug absorption to occur by incorporating the following design elements: frequency and duration of dosing, amount applied per square centimeter, use of highest proposed strength, dermatological disease of interest at the upper range of severity, total involved surface area to be treated at one time, method of application, and site preparation.

I hope with this background, you will appreciate that a maximal usage trial is not an impractical trial. Rather, it is designed to capture the worst case scenario under the label conditions of use.

With this general background, let's delve into the specific design of the maximal usage trial

for Differin gel 0.1 percent. This was a multicenter open-label PK trial in 24 subjects aged 12 years and older with moderate to severe acne vulgaris. Drug was applied once daily for 29 days on the face, shoulders, upper chest, and upper back.

Now, this is the region where acne vulgaris usually occurs. The mean amount of medication applied was 1.95 grams per day with a range of 1.2 to 2.9 grams per day. And the mean body surface area treated was 1865 centimeters square with a range of 1387 to 2894 centimeters square. All 24 subjects completed the trial, and this included 18 adolescent subjects aged 12 to 17 years and six adults.

Pharmacokinetic assessment was done via serial plasma sampling on days 1, 15, and 29, and additional trough concentrations were assessed on days 2, 10, 16 and 22 in adults and days 2 and 16 in adolescent subjects.

Now, this slide basically shows the pharmacokinetic profile of adapalene. The profile

in the blue on the screen is on day 1. The profile in the green is on day 15, and in the red is on day 29. By day 29, all or 24 subjects had quantifiable adapalene concentrations, and steady state was reached by day 15.

This slide summarizes the PK parameters on day 1, day 15, and day 29. The mean Cmax on day 29 was 0.49 nanograms per mL, and the mean AUC on day 29 was 0.83 nanograms x hour per mL. The highest area under the concentration time curve was 2.9 nanograms x hour per mL. And this highest value of AUC is used by the pharmacology/toxicology reviewer in order to calculate the relative exposure margin based on animal toxicity data.

Now, this slide shows cross-trial comparison of PK data for all adapalene products of 0.1 percent strength. Please bear in mind this cross-trial comparison is made for qualitative purposes only. The reason is the study designs were different, and the bioanalytical method validations were different.

With the progression of time, as you can see

in the last column, the lower limit of quantification was improved. Differin cream was approved in 2010, where the lower limit of quantification at that time was 0.3 nanograms per mL. Sorry. Differin cream was approved in 2000. Lotion was approved in 2010 where the lower limit of quantification is 0.1, and the later study, the new maximal usage trial, the new lower limit of quantification is 0.02 nanograms per mL.

Now, this is busy slide, but I plan to go through it in a stepwise fashion in order to get my message across.

The data for the new maxima usage trial is in the first row, and that is highlighted on your screen. In the case of Differin cream, which was approved back in 2000, there were no quantifiable concentrations observed in adult subjects with acne vulgaris in the maximal usage trial.

The lower limit of quantification, which is shown in the last column, was 0.35 nanograms per mL. But when you look at the range of the Cmax observed in the new maximal usage trial, the

highest concentration or the highest Cmax was 0.17 nanograms per mL. And this highest concentration is below the lower limit of quantification for Differin cream.

With Differin lotion, there were two maximal usage trials conducted at the time of approval. There was a trial in adults. In that case, quantifiable concentrations are observed only in 2 out of 14 adult subjects. Post-approval, another trial was conducted in adolescent subjects, and in that case, five out of 14 subjects had quantifiable concentrations.

Now, when you look at the Cmax and AUC across all different trials and different products of adapalene with 0.1 strength, we can say that the systemic concentrations of adapalene produced in the new maximal usage trial well within range of those produced with other adapalene products of 0.1 percent strength.

So in summary, a maximal usage trial was conducted in subjects 12 years of age and older with acne vulgaris. Adapalene concentrations were

quantifiable in all 24 subjects, and the systemic concentrations were at steady state by day 15. The mean area under the curve and Cmax on day 29 were 0.83 nanograms x hour per mL and 0.049 nanograms per mL respectively. And the highest value of area under the curve observed on day 29 was 2.9 nanograms x hour per mL.

As I mentioned in my presentation, this highest value was used by the pharmacology/toxicology reviewer in order to estimate the relative exposure margin based on animal toxicity data.

That's all from my side this morning, and it's my pleasure to welcome the pharmacology/toxicology reviewer, Dr. Cindy Li, who will present the nonclinical summary. Thank you.

FDA Presentation - Cindy Li

DR. LI: Thank you, Dr. Shukla.

Good morning. My name is Cindy Li. I'm a pharmacology and toxicology reviewer at FDA. Next, I'm going to present the nonclinical summary on adapalene. Dr. Michele just mentioned that you

don't see nonclinical reviewer very often in the AC meetings. So why nonclinical? Well, if the toxic effect of a compound cannot be well-characterized in humans, nonclinical studies inform the risks and provide an estimate of margin as is the case with adapalene.

Here is the outline of my presentation. As you all know, adapalene is an approved prescription product. The nonclinical studies supporting previous approval have already been reviewed by the agency under relevant application. Therefore, the nonclinical information I'm going to present today will be at high levels, and I will focus on the specific concerns related to the nonprescription switch.

I will start with an overview of the nonclinical studies that have been conducted with adapalene. Out of all these studies, I will briefly review the major toxicology studies. Among the findings of the toxicology studies, teratogenicity associated with adapalene will be my focus.

I will start with a summarization of the animal studies. To relate the findings in animal studies, a margin of exposure calculation will be provided. And several points of consideration will be discussed regarding the margin from a nonclinical perspective. The last part of my presentation will be the conclusion.

Overall, no new nonclinical studies have been submitted to support the current nonprescription switch. The nonclinical studies supporting the previous approval include the data on pharmacology, pharmacokinetics, and the toxicology. The toxicology studies include assessment of carcinogenicity, reproductive and developmental toxicity, and other toxicities such as genetic toxicity, general toxicity, local tolerance, and more.

Due to the time limits and the purpose of today's meeting, I will only be discussing the studies of carcinogenicity and the reproductive and the developmental toxicity.

First, let's review the findings of

carcinogenicity studies. Two-year carcinogenicity studies have been conducted through two routes of administration, dermal and oral. The dermal study was conducted in mice. The dermal route is the clinical route. No drug-related neoplastic lesions were observed at all doses tested. The high dose 4 mg per kg body weight is 9.8 times of the maximum recommended human dose based on a body surface area comparison.

The second study was conducted in rats through oral route. The oral route is intended to have a higher systemic exposure. Increased incidence of pheochromocytoma was observed in the adrenal medullas in the male rats at 1.5 mg per kg. This 1.5 mg per kg is 7.4-fold higher than the human dose.

High incidence of pheochromocytoma has been observed with other retinoids. However, there are many differences between the adrenal glands of the rats and the humans. In addition, pheochromocytoma are more specific to the rats. Therefore, this finding is not considered to represent a risk in

humans.

In total, the carcinogenicity studies showed no significant or relevant concerns associated with adapalene treatment.

Before I go over the results of the reproductive and the developmental toxicity studies, I would like to give a brief review of these studies in order to help you better understand the findings of these studies.

The center of the slide shows a complete reproductive cycle covering different stages of the development. Toxicities during this cycle are typically assessed by three types of nonclinical studies shown in the orange boxes. The first type on your right side is the fertility and reproductive function studies. It informs the risk of fertility and reproductive performance covering from pre-mating stage, which is on the top of the circle, through implantation.

The second type down at the bottom is the embryo-fetal development studies. These types of study help characterize the risk of teratogenicity.

It covers implantation through the end of pregnancy.

The third type is the prenatal and postnatal development study shown on the left side. These studies help assess the prenatal and postnatal developmental toxicities through the sexual maturation. These three types of study could also be combined or overlapped.

The three types of study I just described on the previous slide have been conducted with adapalene treatment. In the oral fertility and reproductive function study, no drug-related adverse effects were observed at doses up to 20 mg per kg in rats. In the embryo-fetal development study, teratogenicity findings were observed. The details will be discussed on the next slide.

In the oral prenatal and the postnatal development study, no drug-related adverse effects were observed at 15 mg per kg in rats.

So let's look at the findings of the embryo-fetal development studies. Similar to the carcinogenicity study, these studies were also

conducted through two routes, dermal and oral. The dermal route is the clinical route where the drug exposure and the metabolism is most relevant to human use. The oral route is intended to provide a higher systemic exposure that the dermal route may not be able to provide due to the limitation of the formulation.

The dermal study was conducted in both rats and rabbits at three dose levels, 0.6, 2, and 6 mg per kg. Adapalene showed no evidence of teratogenicity. Findings of variation were observed in animal fetuses, but were considered to be minor and not result in permanent development effects. The no observed adverse effect level also known as NOAEL is identified as the highest dose tested in the study, 6 milligrams per kilogram.

When adapalene is given orally, teratogenic effects were observed at 25 mg per kg and above for both rats and rabbits. The teratogenicity findings include cleft palate have been observed with other retinoid. The NOAEL in the oral study was identified as 5 mg per kg for both species. In

total, these studies indicated that adapalene was capable of inducing teratogenicity at sufficiently high systemic doses in animals. The NOAEL was also identified in the studies.

So what does this mean to humans? Let's move to the next slide to find out if the findings in animals could be translated.

The bridge connecting the animal findings to the potential human effects could start from a dose comparison. Dose comparisons between animals and human can be determined on the basis of many different ways such as body weight, body surface area, or systemic exposure. In general, it is more relevant to compare the systemic exposure when data are available.

For the current nonprescription switch of adapalene, the anticipated level of teratogenicity in humans may be quantified by using a margin of exposure calculation based on animal data. Here, we defined the margin of exposure as the ratio of animal systemic exposure at NOAEL over the human systemic exposure under their maximum use.

The formula shown down here will be used on the next slide for calculation. Keep in mind that a smaller margin may suggest more concerns.

Just now, you heard Dr. DeSesso mentioned the calculation of the margin of safety. You hear it by ear. This may be more visual. So this table here describes the calculation of margin of exposure for teratogenicity associated with adapalene treatment. The third column is the systemic exposure corresponding to the species in the first column and the dermal NOAEL in the second column.

The systemic exposure will be expressed as AUC throughout my presentation. The dermal NOAEL is used here because dermal is the clinical route for adapalene.

Based on the pharmacokinetics animal data, at NOAEL of 6 mg per kg, the rat AUC value is 204 and the rabbit is 1036. For human data, Dr. Shukla just showed us that in the recently conducted maximum use trial with 0.1 percent adapalene gel, the highest individual AUC value was 2.9. Based on

the calculation formula, the rat AUC 204 divided by human AUC 2.9, the margin is determined to be 70. For rabbits, it is 357.

So the take home message is that the overall margin of exposure for adapalene associated teratogenicity potential in humans is estimated to be at least 70-fold. So now the question is, is the 70-fold adequate to address the current nonprescription switch associated with the adapalene-induced teratogenicity?

Here, we provide several points of consideration from nonclinical perspective. The considerations include the factors that could increase or decrease the level of concerns. Some may carry greater weight than others. On one hand, the level of concern could be decreased because the margin was calculated in the relatively conservative manner.

First, for the animal data, the actual dermal NOAEL may be higher than the highest dose tested in the study. The actual teratogenic effects were not observed in the dermal study.

Second, for the human data, the highest individual systemic exposure, rather than the average value, was used as the denominator of the calculation formula. In addition, the 70-fold margin is based on the rat data, not the rabbit data, which would give us 300-fold margin.

On the other hand, the level of concern could be increased by certain factors. First, adapalene as a retinoid-like compound can induce teratogenicity in animals, and adapalene as a retinoid-like, the whole retinoid class is human teratogens.

On the next slide, I will present a comparison between adapalene and other topical retinoid in terms of the lowest doses necessary to induce teratogenic effect. This may help learn the relative teratogenicity potency of adapalene within its class.

Another factor that could increase the level of concern is the unknown human sensitivity. I will discuss this factor after next slide.

This table here provides a side-by-side

comparison among three retinoid or retinoid-like prescription products, adapalene, tretinoin or known as Retin-A or Renova, and tazarotene. The first several rows of this table shows the background information. They indicated that the three products are similar in terms of the route, indication, and the formulation. However, adapalene and the tretinoin are not contraindicated in pregnancy whereas tazarotene is.

For the comparison of the lowest teratogenicity dose, higher value of the dose suggests the lower teratogenicity potency. Among all three products, adapalene requires the highest doses to induce the teratogenic effects. It appears reasonable to surmise that the teratogenic effects occurred at higher doses with adapalene when compared with other topical retinoids treating acne.

Another factor that could increase the level of concern is the unknown human sensitivity. While there does appear a significant margin between the animal NOAEL for teratogenicity and the highest

human exposure, there is still uncertainty about the human sensitivity to adapalene. The actual level of systemic exposure necessary to cause an effect in humans may be different compared to animals.

As we all know, animal studies do not always predict human effects. Furthermore, there are no well-controlled clinical studies in pregnant women with adapalene.

As I mentioned earlier, nonclinical studies inform the risks and provide a margin. In closing, the nonclinical information I just presented demonstrated that adapalene, a retinoid-like compound, can induce teratogenic effects in animals at sufficiently high systemic doses. And based on systemic exposure data, the margin is estimated to be at least a 70-fold through dermal application. However, the human sensitivity to adapalene is not known, and the animal studies do not always predict the human effects.

Later today, Dr. Lopa Thambi from FDA is going to present the findings in humans from over

20 years of postmarketing experiences. This may provide some insight on adapalene-associated teratogenicity in humans based upon clinical surveillance data.

With that, I thank you for your time and attention. Next, I would like to invite Dr. Barbara Cohen, our social scientist from FDA, to the podium.

FDA Presentation - Barbara Cohen

DR. BARBARA COHEN: Thank you, Dr. Li.

Good morning. I'm Barbara Cohen. I'm a social science reviewer for the division of nonprescription drug products. I'm here to present this morning on the label comprehension and self-selection studies conducted by the applicant in support of Differin.

Here's an outline of my presentation. I provided detail in the background as to an explanation of what these studies involve, so I'm just going to touch upon these concepts here and focus my talk on the actual studies that were conducted by the applicant, first, label

comprehension and then self-selection.

Label comprehension studies are conducted for virtually Rx to OTC switch products. They're foundational. If consumers can't understand or even aren't aware of what the label says relative to safe and effective use, chances are they won't be able to correctly use the product.

FDA wants to know, is the wording understandable to the average consumer, does it contain technical or medical jargon or terms that are unfamiliar to the average person, and does it convey the concepts that we feel needed to be conveyed?

One important point is that the phrasing used on the Drug Facts labels for currently marketed OTC products, for example, ask a doctor or pharmacist before use, can and should be retested for a new product in certain circumstances such as when it's critical to safe and effective use of the product. It can be particularly useful to test these phrases in label comprehension so as to optimize understanding before proceeding with other

consumer studies.

This slide describes the key element of a successful label comprehension study. First, the applicant needs to identify the most important communication objectives from the Drug Facts label that need to be assessed.

Second, target thresholds are established a priori based on the clinical implications if consumers fail to adequately understand the labeled items. Adequate comprehension is assessed by comparing the established threshold with the lower bound of the two-sided 95 percent confidence interval.

Finally, we need to try to ensure that consumers with low literacy can adequately comprehend the instructions. Therefore, we ask the applicants to have at least 22 to 28 percent low literacy representation in their studies.

Secondary communication objectives often assess areas most critical to safe and effective appropriate use such as general health information and are typically not assessed against thresholds.

Generally, label comprehension studies are conducted with all comers. They're usually intentionally not limited to sufferers of the condition because the idea is that anyone should be able to pick up a Drug Facts label and understand what it says.

Caregivers are involved in administering drugs to people who have the conditions that they the caregivers do not have, and also, anyone can newly develop a condition as two examples.

In a label comprehension study, consumers are given the Drug Facts label to read at their own pace. They're then asked questions about the label and can refer back to it as much as they want. It's not a test of memory. It's an open book test in which the idea is that FDA wants to know if consumers are aware of and can understand key elements when the Drug Facts label is right in front of them.

Label comprehension studies employ many scenario questions, describing a hypothetical medical situation that tests the ability of the

consumer to apply information from the label.

The primary objectives of this label comprehension study were comprehension of use once daily and do not use on damaged skin. The applicants set the target threshold for comprehension of both at 85 percent, stating that these objectives did not represent serious safety concerns but that increased irritation could occur if the product was used on damaged skin or if it was used more than once daily. Therefore, these statements provided important information about proper use.

FDA had strongly advised the applicant that awareness of the Drug Facts labeled statement on pregnancy needed to be assessed as the primary objective. However, the applicant did not include this for testing in the study, stating that the statement already appeared on other marketed products. There were also secondary objectives of the study, and I'll discuss those shortly.

The label comprehension study was conducted in the spring of 2014 in eight geographically

dispersed sites across the United States with 586 participants, males and females, ages 12 to 70. Notably, the general population cohort had only 11 percent low literacy, so for that reason, we focused on that cohort and the augmented low literacy cohort in our analyses.

As noted, there was a very good adolescent representation in this study with 282 participants. However, there were only 33 study participants ages 18 to 24. By contrast, there were 78 participants ages 45 to 54, an age group with perhaps less acne. This was disappointing because the agency would have liked to have seen a robust sample in the 18- to 24-year-old age group as well.

Here are the results. For the primary objective of use once daily, the general population cohort did very well. There were no significant differences between age groups or genders, and even just looking at low literacy participants in this study, the point estimate for comprehension of use once daily was 86.9 percent. That's versus 96.5 percent for normal literacy.

This 10-point difference in comprehension between literacy groups was significant statistically, but it is common. It's typical, and it is not uncommon for FDA to approve products with these kind of differences.

Looking further at literacy, here are data from adolescent females, a subgroup of particular concern due to the acne prevalence in this group. Here, we can see that normal literacy adolescent females had 96 percent comprehension of use once daily while low literacy females were at 83.9 percent.

Interestingly, the other primary objective, do not use on damaged skin, did very well among all literacy levels. It had virtually no comprehension differences between normal and low literacy participants. Therefore, it's unclear as to whether low literacy participants were not able to understand use once daily quite as well.

Overall, 10 secondary objectives were assessed including the avoidance of sun exposure due to tanning beds. The applicant did not conduct

testing on comprehension of the avoidance of overall sun exposure, which FDA had requested. Nonetheless, knowledge about tanning bed avoidance tested very well in the general population cohort with a total comprehension rate of 97.5 percent. Importantly, there were no significant differences between normal and low literacy or between adults and adolescents.

Another secondary objective of the study involved the age at which the drug can be used. For the statement "under 12 years of age, consult a physician," 93.8 percent of general population cohort participants ages 12 to 70 understood this.

Here, there were some comprehension differences between normal and low literacy participants, but again, these are generally typical. There were no significant comprehension differences between adults and adolescents for this statement.

Ultimately, label comprehension studies assess comprehension and not behavior. Therefore, although they're usually necessary, they're not

always sufficient. Self-selection studies assess whether consumers can apply their understanding not to a hypothetical person as in label comp, but to themselves and their own personal medical situation. Typically, examples of when they may be required might be when there is a new OTC indication or when there is a concern about a certain subpopulation using a product.

FDA may want to see consumer research demonstrating that these consumers would correctly not self-select or to restate, they would correctly de-select to use the product. Target thresholds or endpoints are established a priori based on strong clinical rationale, what the implications are if there was a failure to correctly self-select.

Consumers were recruited for a specific contraindicated condition or a medication or another specific do-not-use category such as minimum age or gender. The subjects themselves are usually blinded as to why they're being recruited.

A consumer development program can encompass one or more self-selection studies each focusing on

a different subpopulation of clinical concern. Typically, these involve in total from 250 to 800 subjects, and typically, FDA looks for a low literacy representation in these self-selection studies as well.

In a self-selection study, when subjects arrive at the testing site, they're given a product package, asked to look at it, and then say whether the drug would be appropriate for them or not for them personally to use. They're not given the opportunity to actually use the product. They're then probed to assess the reasons why they gave the answers that they did.

Typically, self-selection decisions are validated afterwards through self-reported information, but increasingly, physicians are involved in administering medical tests to subjects or obtaining detailed medical histories in order to assess the appropriateness of the self-selection decision.

The objective of the applicant's self-selection study was to assess whether pregnant or

breastfeeding women would state that they would ask a healthcare professional prior to use. During the product development process, FDA had advised the applicant to conduct self-selection research among pregnant women to assess whether they intended to follow the label precaution to ask a healthcare professional before use.

The applicant established a target threshold of 90 percent, which is typically the threshold where there are issues of significant clinical concern. In this case, the applicant did not provide a rationale for the 90 percent threshold, stating that it was derived from FDA's stated concern during development.

The self-selection study was conducted in late 2013 among 293 pregnant and breastfeeding women ages 13 to 54. The majority of the women in the study were breastfeeding and not pregnant, although it was pregnancy that had been the stated concern of FDA.

In the general population cohort of 242 women, 37 percent were pregnant with 11 of these

women also breastfeeding. The remaining 63 percent were breastfeeding only. The general population cohort did have a reasonable percentage of low literacy subjects at 25 percent, and additionally, the applicant fielded an augmented low literacy cohort with an additional 51 subjects.

It's important to note the asterisk on the bottom of this page. Only two of the 293 subjects were adolescents. The rest of the subjects were over age 18, and I'll discuss that more in a moment.

Adults were recruited at mall intercepts at 25 sites across the country. Women were recruited if they appeared to be in at least one of four buckets: between the ages of 18 and 50, with noticeable acne, visibly pregnant, or accompanied by a baby who appeared to be under 18 months of age.

They were asked if they had several types of medical conditions, including but not limited to pregnancy or breastfeeding and acne. They didn't know it, but they were only included in the study

if they had these conditions. Pregnant subjects were not asked about which trimester of pregnancy they were in.

Subjects who qualified for the study were directed to a research facility where the REALM illiteracy test was administered. They were then asked to review the principal display panel and Drug Facts label at their own pace, and then the interviewer asked them, "Is it okay for you to use this product today or not" followed by, "Why did you say that?"

If the subjects mentioned that they needed to ask a healthcare professional first or if they said that they did not feel comfortable using the product because they were pregnant or breastfeeding, they were considered to have selected correctly. If they said that it was fine for them to use the product without mentioning the need to consult a healthcare professional, they were considered to have selected incorrectly.

All those who selected incorrectly were then asked, "Earlier you said that this product was okay

for you personally to use. However, the warning on the package states that you should ask a health professional because you're pregnant or breastfeeding. Please tell me why you thought it would be okay to use the product even though you are pregnant and breastfeeding."

Recruiting for adolescents was different. According to the applicant's protocol, there was a target of nine adolescents in total. Adolescents were recruited from pregnancy centers and support groups, so unlike in the adult pregnancy subjects, pregnancy was not verified. They were administered an online questionnaire in a private room instead of a face-to-face interview in order to ensure maximal privacy and sensitivity.

The online questionnaire ended at the self-selection question. The clarification probe was not asked. At any rate, only two adolescents ended up being recruited for the study due to delayed IRB approval. Therefore, the end result does not give us a clear picture of how pregnant adolescents might view the label precaution to ask

a doctor.

This slide shows overall results. The applicant was not able to demonstrate that pregnant or breastfeeding women could adequately follow the directions to ask a healthcare professional before use. For cohort 1, the general population cohort against which the threshold was assessed, 74.4 percent self-selected correctly with a lower bound of a confidence interval of 68.4 percent.

As this was more than 20 percentage points below the target threshold of 90 percent, it didn't only not meet the target threshold, but was found to be statistically significantly lower than the target threshold.

Looking at the overall study population across the two cohorts, normal literacy women had a correct self-selection rate of 78.5 percent with a lower bound of 71.1 percent. And low literacy women had a correct self-selection rate of 70.5 percent with a lower bound of 61.2 percent. There was no statistically significant difference by literacy group.

Next, we look at pregnant women exclusively since FDA had been most interested in that cohort. The relatively small number of pregnant women in this study led to low statistical power to detect any differences in subgroups such as age or literacy. Nonetheless, as a whole, the applicant was not able to demonstrate that pregnant could adequately self-select to use the product.

Cohort 1, the general population against which the threshold was measured, had a correct self-selection rate of 70 percent with a lower bound of the confidence interval of 58.7 percent. This was more than 30 percentage points below the target threshold of 90 percent.

So as in the overall study population, which included breastfeeding women, looking only at pregnant women, we see another statistically significant difference below threshold.

While age was not associated with correct self-selection for the general population, it did impact correct self-selection for low literacy women under age 45. Looking at younger women of

childbearing age, the 18- to 24-year-old age group had a correct self-selection rate of 55 percent as contrasted with 87.5 percent for ages 25 to 34 and 100 percent with the three subjects for ages 35 to 44.

This next slide shows examples of reasons that subjects gave when they were asked why they had decided it was okay for them to use the product without asking a healthcare professional first. This is just a sampling:

Ingredients that don't seem harmful. I don't have sensitive skin. I don't see what it has to do with me being pregnant. Literally, everything has that warning on it, and after repeatedly asking a doctor, you learn that it's usually okay as long as it doesn't say do not take. This is over the counter. Because I put it on my face and not my baby and I put it on my skin and not in my blood so it wouldn't affect the baby. What does my face have to do with my pregnancy?

Additionally, 15 subjects explicitly stated that they hadn't seen the warning on the label.

In conclusion, regarding the potential for either over-use or younger pediatric use, the applicant did successfully demonstrate that use once daily and ask a doctor if under age 12 had solid comprehension among males and females between the ages of 12 and 70.

Regarding the potential for use in pregnant women, there is no evidence that pregnant adolescents would understand that they should ask a healthcare professional before use because there were only two adolescents in the self-selection study. Moreover, the applicants also did not successfully demonstrate that pregnant women of other ages would ask a healthcare professional before use.

Unfortunately, the pregnancy statement was not also assessed in the label comprehension study, which might have optimized its understanding by consumers before proceeding with the self-selection phase of the consumer development program.

Thank you for your time. I'll now turn the podium over to Dr. Ryan Raffaelli, who will discuss

the actual-use study and its clinical perspective.

FDA Presentation - Ryan Raffaelli

DR. RAFFAELLI: Thanks, Barbara.

Good morning. My name is Ryan Raffaelli, and I'm the medical reviewer in the Division of Nonprescription Drug Products. Today, I'm responsible for presenting findings from an actual-use trial and other clinical data included in Galderma's application to market adapalene gel, or Differin, for treatment of acne in the OTC setting.

So during my presentation, I'll describe the actual-use trial, which I'll refer to as the Juno trial. I'll briefly introduce actual-use trials to you and present the purchase decisions of subjects enrolled in the trial and the findings that inform the primary and main secondary endpoints.

Relevant to safety, I'll present data from the MUsT, or the maximal usage trial, that you've already heard about from Dr. Shukla and from the Juno trial. That data will include findings from pregnant subjects. I'll also provide an

introduction to safety data submitted by Galderma from the postmarketing experience for Differin in the prescription-only setting.

The information I present is intended to help you determine whether Differin gel is likely to be used safety and properly in the OTC setting.

So the Juno trial was an open-label, single-arm, multisite trial of 31 geographically dispersed pharmacy sites. The use phase was 6 weeks in duration. There's more information in the background material, but actual-use trials help to assess in a naturalistic OTC setting how consumers, typically all-comers, might determine a product is right for them and how they might use the drug that was previously available by prescription only.

The major endpoints were established in consultation with FDA to assess correct use, a typical goal of actual-use trials. Two primary endpoints were set to determine whether subjects correctly used the product once daily and if they used it for acne only.

The applicant set thresholds for success as the lower bounds of the two-sided 95 percent confidence intervals greater than 85 percent for both endpoints. The rationale for setting those thresholds was acceptable to FDA.

Secondary endpoints included evaluation of use on correct body areas while avoiding damaged skin areas or proximity to eyes, lips, and mouth and determining whether pregnant or breastfeeding women would ask a healthcare professional before use.

While the targeted self-selection study that Ms. Cohen previously discussed was intended to better address selection decisions by pregnant or breastfeeding women, the few pregnant or breastfeeding women who enrolled in this trial contributed to demonstrating how Differin might be used in the OTC setting.

So the Juno trial's advertising and recruitment plan intended to enroll subjects with acne who would review the product package and make a decision whether or not to purchase. Because the

product is approved for treatment of acne and the intent of the trial is to assess correct use, the applicant recruited for the trial by seeking out people who had acne. You might surmise then, and you'd be correct, that based on the endpoints listed in my previous slide, that subject behavior was quite good overall in the question of use for acne only.

On this slide is an example of the type of ad that's used to recruit interested subjects to study sites for actual-use trials. In these types of trials, potential subjects call the number on the ad to schedule an appointment at a pharmacy site. During the phone call for this particular trial, an early limited screening plan excluded interested person who had recently participated in studies who might work in certain specific fields or who met other administrative exclusion criteria.

Once subjects arrived for their appointment at the site and sought to participate; that is, to enroll, they were given the product package to review. Then they were asked if they'd like to

purchase the product. If they had any questions about the product before deciding, they could choose to speak to a pharmacist, call a healthcare professional participating in the trial, or contact their own healthcare provider and reschedule if necessary.

So after subjects selected to purchase, any unprompted questions were unanswered. To confirm eligibility to enter the use phase of the trial, additional interviewing, screening, and testing, including a urine pregnancy test for all women of childbearing potential, were undertaken before the product was purchased and taken home.

In the blue box on the right are those clinical criteria used to help to determine eligibility: so not self-reporting acne, if subjects were under the age of 12, if they were pregnant or breastfeeding, if they reported any allergy to any ingredients, or who in the investigator's opinion were likely to be harmed or unlikely to follow the trial procedures.

Next, a REALM test, a literacy test, was

conducted. At this point, subjects deemed eligible were allowed to purchase the product for home use. Following purchase, subjects or the users were provided instructions on how to complete their diaries.

At the end of the trial, the final evaluation of the endpoints utilized data combined from the diaries kept during the use phase, the return product tubes that were determined the quantity of product that was used over the duration of the trial. That was determined by a tube weight comparison, and findings from the subject interviews at the end of the trial.

So greater than 99 percent of the users completed the end-of-trial interview and returned their diaries and used product. And subjects were compensated for their time to participate in the trial, but they were not reimbursed for any of the product that they purchased over the duration of the trial.

This slide, I'll go through the trial subjects' disposition. So from 3200 callers

answering the recruitment ad and inquiring about the trial, 1277 kept their appointment, expressed interest in participating, and were enrolled in the trial. Eight hundred and thirty-four or 65 percent of those enrolled were female. Only 164 failed the early screening process described on the previous slide. The remainder of the initial callers, almost 1800, did not make or keep a trial site appointment.

Next, after viewing the product package and being asked to make a purchase decision, 1108 enrollees said yes, they'd like to purchase; 169 said no. Of the 1108 who said yes, 947 or 85 percent were eligible to continue into the use phase of the trial. They made correct decisions and were the, quote, "user population."

Among the users, 643 or 68 percent were female with 493 or 52 percent considered of childbearing potential; 161 who said, yes, they would like to purchase were excluded from entering the use phase, and these subjects will be presented shortly.

Finally, all 947 of the user population, or the verified users, used the product at least once and participated in at least some end-of-trial procedure, and 938 completed the trial with only 9 discontinuations. I'll present those subjects shortly as well.

So here I'll provide more detail on the subsets of the subjects in the Juno trial. Of the 1100 who said yes, they wanted to purchase, 161 were excluded from purchasing the drug and participating in the use phase.

The top reasons for these exclusions were screening failures as per the inclusion/exclusion criteria, which I'll discuss shortly; no shows are those subjects who left without purchasing the product; female subjects who were unable to provide adequate urine samples, and those who were excluded for various administrative reasons.

At the bottom of the slide, you can see that that of the 9 discontinuations, 8 were due to adverse events. The 9th subject was withdrawn by the investigators over questions about data

documentation, and three of those who discontinued due to adverse events were pediatric subjects.

So regarding pregnant subjects, 5 of 9 incorrectly said yes to purchase without first seeking medical advice. Investigators explored those decisions in light of the label precautions for this product. One subject who said no had asked the site pharmacist if it was okay to take the product and was told that pregnancy was an exclusion criterion of the trial. So we don't really know what she would have decided on her own.

Two of the five incorrect yeses stated that they were pregnant in spite of having negative pregnancy tests. The final three subjects each stated that they either did not see the warning to ask a healthcare provider before using the product, that their pregnancy did not change their decision, or that all medications say ask a doctor, and since it's a topical product, it shouldn't hurt my baby.

Two of the noes said they said so after first discovering that they were pregnant at visit 1. So they had the pregnancy test, they found out

they were pregnant at that interview visit, and then determined that the product wasn't right for them. The last no was mitigated because the subject stated that after purchasing the product, she would talk to her doctor who she said in the past had told her the use of the product was okay.

The actual-use population can be further described as follows: The mean age of subjects was 29.9 years with ages ranging from 12 to 73. Adolescent subjects age 12 to 17 accounted for 21 percent of the total user population. Females accounted for 68 percent of the population.

In order to capture use of adapalene for non-acne conditions, the applicant inquired of subjects about eczema during their interviews, and 1.4 percent of the user population reported having both eczema and acne.

Finally, the results from the REALM testing indicated that 13.8 percent of adults and 10.8 percent of adolescents were considered low literacy. FDA had previously recommended 20 to 25 percent of enrollees be of low literacy.

Here are those reasons why subjects who said yes to purchase failed the screening process, thus excluding them from entering the use phase of the Juno trial. At the bottom of this slide, note that the mitigation factors were applied to some of these yes decisions; that is, incorrect decisions or behaviors were considered correct in some specified circumstances.

As listed in the blue box, 9 subjects without acne sought to purchase the product. They reported concerns such as acne prevention. They wanted to unclog their pores. They wanted to remove blemishes or even out their skin tone. Six of 7 enrolled children that were younger than 12 expressed interest in using the product. All but one was at least 11. One was 10. The yes decisions by 11-year-olds were mitigated since the subjects were within 12 months of their 12th birthday and had acne.

Note here that 10 pregnant or breastfeeding subjects made an incorrect decision to want to purchase the product. No subjects were excluded

due to allergy.

Twenty-five subjects were excluded by judgments of the pharmacy staff investigators onsite in collaboration with the centralized telemedicine group of healthcare professionals if the subjects were likely to be harmed or unlikely to follow the trial procedures if they entered the use phase. None of the judgments raised any concerns about the screening process.

The majority of the judgments were due simply to concerns over adherence to trial procedures. For example, things like keeping the diary or attending the end-of-trial interview.

Administrative reasons to exclude such as incomplete documentation, concerns about subject's capacity to participate in the trial, or ineligible backgrounds accounted for the remainder. Note that subjects may have had more than one reason to warrant exclusion.

So regarding the endpoint assessments, correct usage exceeded the established a priori threshold of 85 percent set by the applicant for

both primary endpoints, the once daily use and the acne only use, which had point estimates of, as you can see, 89.1 percent and 99.3 percent, respectively. Note the footnotes that two subjects had missing diary data to assess the acne only primary endpoint, thus the 945 denominator.

The 97.5 percent point estimate for the main secondary endpoint was also quite high. Except for low literacy subjects in the assessment of the primary endpoint addressing once daily use of the product, a rate of 83 percent, all the other subgroup analyses by age, gender, and literacy resulted in usage rates above the threshold.

So back at the top left of the slide regarding the 103 incorrect users of the product by the first primary endpoint, categories of misuse that might raise some concern were those where subjects were seeking to achieve greater or faster benefit or treat more severe acne breakouts. Forty-three percent of the 103 incorrect users fell into one of these two categories.

For the second primary endpoint, the seven

incorrect users reported applying the product to a variety of skin issues, for example, psoriasis, puffiness under the eye or skin discoloration. They generally wanted to see if there would be any improvement. Finally, there was another small subset of incorrect users who reported applying the product, quote, "like a lotion all over the face."

As I stated previously, misuse by the major endpoints were mitigated in circumstances that did not impact the safe use of the product. And based on my review, the mitigation strategies were reasonably applied and not result in any significant adjustments to the point estimates.

So no subjects became pregnant during the MUsT PK trial, but in the Juno trial, subjects were to be withdrawn if they voluntarily reported pregnancy, but this did not occur for the 4 confirmed pregnancies during this trial.

Reporting was voluntary as there were no interval interviews in this naturalistic trial, nor were there any labeled warnings to stop use and ask a doctor if pregnancy occurred while using

adapalene. So the subjects would have not known to seek medical advice.

As I stated, 4 subjects all over 18 years of age became pregnant during the trial. One subject only discovered she was pregnant after her end-of-trial urine pregnancy test came back positive. Three subjects reported visiting a doctor during the trial to confirm their pregnancies. None of these three discussed their use of adapalene with their doctors.

One had applied her last dose, so she found that disclosure was irrelevant. Two continued using the product after confirming the pregnancy, and one of those subjects chose to terminate her pregnancy for personal reasons.

Although the applicant and investigators have attempted to contact these subjects on multiple occasions to ascertain the outcomes of the pregnancies, they've been unsuccessful for two out of three. One subject reported having a healthy newborn.

So here, I'll provide some comparison of the

extent of use in the clinical trials conducted to support the application. This is a measure of likely safe use in the OTC setting.

In the MUsT, as Dr. Shukla discussed, average application was a little under 2 grams per day over an application area of about 1865 centimeters squared. Over the entire 29-day duration of that trial, this would average approximately 56.5 grams applied over about 10 percent body surface area.

In the Juno trial, average total use was 24.3 grams with up to 94 percent of the subjects, 886 of them, using a maximum of only one tube of adapalene or about 45 grams total. Note that 17 percent of pediatric subjects 12 to 17 years of age used more than 40 grams compared to 12 percent of adult subjects.

There was a mean treatment duration of 41.4 days and over 93 percent of the subjects remained in the trial for at least 35 days or 5 weeks of the 6-week trial duration. Thus, you could estimate that an average subject applied a

little more than half a gram of product per day compared to the nearly 2 grams per day applied in the MUsT.

So maximum recorded use by the tube weight comparison was 129.5 grams, but only 4 subjects purchased the maximum 3 tubes or 135 grams of adapalene over the trial's duration. Thirteen subjects or 1.4 percent of users used greater than 80 grams, and 9 of these subjects were 12 to 17 years of age.

Regarding the subgroups, there were no major differences in the mean use of the product by age, gender or literacy.

So half of all the users reported at least one adverse event. None of them were serious. There were no deaths, and 88 percent of the adverse events reported were mild. There were no major differences in reporting by either age or gender. Topping the list of reported events were headache, dry skin, and erythema, and skin-related events accounted for four of the top seven, and findings from the MUsT study were very similar to this.

Relevant to the major endpoints and to precautions noted in labeling, 49 percent of subjects used adapalene more than once per day reported an adverse event. Of the seven highest quantity users; that is, subjects who used more than 91 grams of the product, none of them reported any skin-related adverse events.

Two percent of subjects or 20 of them used the product on damaged skin where their acne was located. They generally reported that the condition was mild and not worsened by continued application, and many recognized that adapalene may be irritating early in treatment.

Three percent of subjects reported mild sunburn, and as you may know, retinoids are known photosensitizers. All continued using the product with one-third taking a brief dosing holiday or reducing their applied dose.

Only 8 subjects discontinued participation in the trial due to adverse events. Three of them were less than 18 years of age. All of them reported skin-related events, and all the events

but one were reported to be resolved after discontinuing use. The reporting did not raise any safety issues.

So now I'll briefly introduce some postmarketing safety experience for adapalene in the prescription-only setting based on data submitted by the applicant. Dr. Thambi from FDA 's office of surveillance and epidemiology will provide some further insight into the safety experience of adapalene in the prescription setting.

Typically for circumstances such as an Rx to OTC switch, we will review data from the applicant's pharmacovigilance database, the FDA Adverse Event Reporting System or FAERS, and the World Health Organization's database.

Following discussions with FDA during product development, the applicant focused its search of those databases on teratogenicity, fetotoxocity, carcinogenicity, skin-related events, and topical drug interactions.

The applicant reports that over 40 million

patients have been prescribed adapalene at 0.1 percent or 0.3 percent since first approval; 4,176 events have been reported worldwide since 1998, only 70 were serious. Seventy percent of all reports are skin related, and 239 described an exposure in pregnancy with very few and quite large variety of malformations with new discernible pattern described.

The applicant states in its application that postmarketing safety findings mirror those from the Juno trial. Dry skin and erythema account for approximately 30 percent of all reported postmarketing events. As expected, skin-related events predominant reports of over-use and reports where adapalene is used with other topical acne products, including those containing sulfur, resorcinol, or salicylic acid.

The applicant addressed photosensitivity, identifying 48 reports of skin irritations after sun exposure, 9 skin-related reports of events where tetracycline derivatives were used concomitantly. And as you may know, those drugs

are also known photosensitizers.

In summary, the Juno trial demonstrated high rates of correct usage by dosing regimen once daily for acne only and on acceptable skin areas. The findings were consistent across age, gender, and literacy subgroups, and mitigation strategies were deemed acceptable. Recall that categories of misuse that raised some concern were those where subjects reapplied to achieve greater or faster benefit or to treat more severe acne breakouts.

There was some limitation to the design and population of the Juno trial that may impact interpretation of the findings. Note that with these type of trials since data must be collected, a true naturalistic environment cannot be perfectly achieved. We also sometimes have concern about the potential lack of generalizability to the true OTC consumer.

The short 6-week duration of the trial captured only 4 women who became pregnant while using adapalene, providing a limited assessment of decisions in that population. Although I'll note

that the selection and usage decisions by pregnant women or women who became pregnant during the trial demonstrate that pregnant women are likely to select to use the product and may continue to use it once pregnant unless possibly there are some additional label warnings.

The low literacy cohort was lower than recommended, and the recruited population of users were acne sufferers. Therefore, assessment of off-label usage was somewhat limited.

Five out of nine pregnant subjects incorrectly wished to purchase the product without the advice of a learned intermediary. In this short trial, 4 on-treatment pregnancies occurred with no poor outcomes reported, but there's no proposed label warning to stop use if subjects become pregnant while using the product.

Twenty-one percent of actual use trial users were pediatric subjects; 6 subjects were excluded due to the interest in purchasing, but their age was younger than 12.

There were no major differences in any of

the endpoint assessments or findings from safety reporting for pediatric subjects. While more pediatric subjects used greater than 40 grams of the product over the duration of the trial, recall the nearly 94 percent of all the subjects used one tube or less, so the absolute numbers were quite small.

Also, recall that in the MUsT, the highest systemic drug exposure, was seen in a 16-year-old male and he reported no adverse events.

Finally, the safety data from the trials in the postmarketing experience indicate that safety-related adverse events are common but mostly mild and non-serious, and there were no safety issues identified overall by age or gender.

Coming up, Dr. Jane Filie will summarize some additional clinical perspectives in her presentation.

Thank you. That concludes my presentation. I'd like to welcome Dr. Lopa Thambi to the podium, and I'll be happy to answer any questions during the designated time.

FDA Presentation – Lopa Thambi

DR. THAMBI: Thank you, Ryan.

Good morning. My name is Lopa Thambi. I'm a safety evaluator with the Division of Pharmacovigilance II in the Office of Surveillance and Epidemiology. I will provide an overview of the postmarketing data, including drug utilization, pharmacovigilance, and epidemiology data associated with single ingredient adapalene products.

First, I will discuss trends for adapalene products in recent years. This information can serve as context for a discussion regarding adapalene use. Then, I will discuss postmarketing cases of two events of interest. The first are congenital anomalies, and the second is adapalene used on large body surface areas from FAERS and the medical literature.

Lastly, I will discuss the literature search of epidemiologic studies pertinent to topical retinoids and adverse reproductive outcomes.

This graph displays the total number of patients who received a dispensed prescription for

single ingredient adapalene from U.S. outpatient retail pharmacies. Total patients decreased by 16 percent from 672,000 patients to 562,000 patients during the examined time. The majority of patients were age 12 to 45 years old. Pediatric patients under the age of 12 accounted for 3 percent of the total patients.

Although the reasons for the recent decline in patient utilization of single ingredient of adapalene are unknown at the time of this review, the results of this analysis support the fact that adapalene is still commonly used in the retail pharmacy setting.

This figure displays patient count stratified by age and gender from December 2014 through November 2015, cumulatively. Female patients accounted for the majority of use for adapalene products compared to male patients across all age groups.

Dermatology was the top prescribing specialty accounting for approximately 49 percent of prescriptions dispensed for adapalene, followed

by physician assistants at 15 percent and pediatrics at 10 percent. Acne not elsewhere classified was the top diagnosis reported by office-based physician surveys.

Now I would like to focus on the postmarketing cases. First, I will provide an overview of the FDA Adverse Event Reporting System, also known as FAERS, then an analysis of the postmarketing reports of congenital anomaly and use on large body surface areas in the FAERS database and the medical literature. Finally, I will conclude the presentation with an overall summary of the findings.

Before I present our findings, it may be helpful to provide an overview of the database that houses all the postmarketing adverse event reports received by the FDA. In the next two slides, I will discuss the strengths and limitations of the FAERS data.

FAERS is a computerized database, which contains over 11 million adverse event reports from consumers and drug manufacturers. It has many

strengths that allow the FDA to use it as a postmarketing drug safety surveillance tool. Reports in FAERS include all U.S.-marketed products and may include foreign products as well as all uses for both approved indications and off-label use.

While FAERS has many strengths, it does have limitations. For example, for reporting purposes, the FDA does not require a causal relationship between an event and a product to be proven. Some reports do not contain enough information or detail to fully evaluate an event. Further, the FDA does not receive all adverse event reports that occur with a product.

Many factors can influence whether or not an event will be reported such as the time the product has been marketed and publicity about a drug or event. Therefore, FAERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

The 2005 FDA guidance recommends epidemiological studies as the best method of

evaluating a causal relationship between a drug exposure and congenital anomalies whereas case reports can signal the need for further research. Also, given the fact that the background rate of birth defects is approximately 2 to 4 percent in the general population, it is not typically possible to establish causality for an isolated birth defect from a drug exposure.

A lack of spontaneous adverse events cannot establish that a drug is free of risk for any specific event, including teratogenicity.

Now that I've provided you with the strengths and limitations associated with the data, I will discuss the cases of congenital anomalies or adapalene used on a large body surface area that were received in the FAERS database.

This slide shows you the search parameters we used to identify cases from the FAERS database in two separate searches. In our current analysis, we searched the FAERS database for single ingredient adapalene products from January 1969 through November 2015 that involved patients of all

ages with a serious outcome with specific MedDRA-related terms to abnormal pregnancy outcomes.

In a separate search, we searched for single ingredient adapalene for the same period of time and reviewed all serious reports to identify cases of use on a large body surface area.

We also looked through the medical literature for any additional case reports, which may not have been reported in the FAERS database for the same events of interest. We were especially interested in cases that were consistent with the pattern typical of retinoic acid embryopathy, which includes features of craniofacial anomalies, cardiac defects, abnormalities in thymic development, and alterations in central nervous system development.

We identified a total of 237 reports associated with adapalene in FAERS for the dates specified. There were 11 cases associated with congenital anomaly of which one case was also published in the medical literature. There was one case of adapalene off-label use on a large body

surface area that was in FAERS and also published in the medical literature.

This table shows several descriptive characteristics of the 11 congenital anomaly cases that we identified. The maternal age had the same mean and median age of 30 years. Cases did not spike during any particular year, and the majority of cases were from foreign sources. Acne was the indication reported in the majority of cases as is reflected in the drug use data.

Most exposures occurred in the first trimester. Also, in 4 cases, an abortion was reported, and one case, it was considered at the time of reporting. From the MedWatch cases, we do not know other factors which may have contributed to that decision.

Listed in this table are the 11 cases and continued on the next slide are the 11 cases of congenital anomaly. Each number represents a separate case report in no particular order. And as you can see from these cases, there does not appear to be a pattern of congenital anomalies

consistent with retinoid embryopathy.

I will now discuss the one case we identified of off-label adapalene use on a large body surface area. This was a foreign case reported in a 55-year-old female with Darier disease, which is a rare inherited skin condition characterized by the loss of binding between skin surface cells with thickening of the skin, bumpy skin, and blisters.

She was treated with an oral retinoid and 10 months later, developed an acute mixed pattern hepatitis. Other causes were excluded, and the drug was discontinued, and she recovered.

Due to a relapse of the Darier's disease, she was then treated with adapalene 0.1 percent cream daily. She used 15 tubes of the 30 grams adapalene over 8 months on 15 percent of her body surface. Again, she developed an acute hepatitis. Other causes were excluded, and adapalene was discontinued, and she recovered 7 months later.

While it appears that there was a temporal relationship with adapalene, with factors such as

an increased amount of adapalene use and the potential increased absorption due to the lesions, the contribution of adapalene cannot be determined.

To summarize the FAERS data, DPV observed 11 cases which do not show a pattern consistent with retinoid embryopathy. These cases appear to be isolated malformations. The cases do not support a signal of adapalene-associated congenital anomalies at this time, and we did not identify any additional safety signals.

The Division of Epidemiology performed a PubMed search for postmarketing safety studies of adverse effects to topical retinoid therapy. A total of 15 studies were identified, 4 of which assessed reproductive outcomes. However, no studies of adverse reproductive outcomes or other serious events assessed adapalene specifically.

Findings from studies of other topical retinoids are inconclusive, and their extrapolation to adapalene may be inappropriate.

In summary, there appears to be a wide utilization of adapalene with the majority of use

in women of childbearing age. In the 20 years since approval, there have been approximately 11 cases of congenital anomalies observed with single ingredient adapalene use and there have been no epidemiological studies of reproductive outcomes or other adverse events, which assess adapalene specifically, and findings from other studies of other topical retinoids are inconclusive.

I'd like to acknowledge the contributors to my review, and invite Dr. Jane Filie to the podium.

FDA Presentation - Jane Filie

DR. FILIE: Thank you, Dr. Thambi.

Good morning, everyone. I'm Dr. Jane Filie, lead medical officer in the Division of Nonprescription Drug Products. I will present to you an overview of what we heard today from FDA to help you formulate your benefit-risk assessment before proceeding to the deliberations.

Adapalene 0.1 percent gel was approved for prescription use in 1996 for the treatment of acne vulgaris in patients 12 years and older. Acne affects an estimated 50 million individuals in the

United States of which 85 percent are teenagers and 12 percent are adult women.

It is a benign condition in the sense that no mortality is associated with it. But morbidity is, including scarring and psychological effects such as poor self-image, depression and anxiety.

The potential for teratogenicity is a concern in pregnant women, and the population likely to use the drug includes a large proportion of women of childbearing potential. Today we are interested in hearing your opinion whether the benefit of this drug in the over-the-counter setting outweighs any risks.

The application submitted to FDA does not contain new efficacy data, which was established for prescription use, and there's no reason to expect that the efficacy would be different in the over-the-counter setting. Retinoids are often recommended in guidelines as first-line therapy for acne of all severities, alone or in combination with other agents.

In the over-the-counter setting, treatment

options include the list shown. I would like to point out that these active ingredients are regulated and allowed in the market under the over-the-counter monograph topical acne drug products.

So let's recap the highlights of the information presented by FDA. In terms of toxicology, I would like to reiterate that teratogenicity is a known toxicity associated with retinoids. Preclinical studies did show congenital anomalies in animals when exposed to high doses of adapalene as observed with other drugs of this class.

The human maximum use trial showed that absorption occurred and plasma concentrations were quantifiable in all 24 subjects in the study by day 29. Based on the no adverse effects level in animals and the highest systemic exposure obtained in the human maximum use trial, the margin of exposure for adapalene is estimated to be at least 70-fold.

Although the margin of exposure is wide, we

heard from our nonclinical colleague, Dr. Li, that animal studies do not always predict effects in humans, and the human sensitivity to this drug is unknown. So let's look at the human data.

I will start with postmarketing safety data. We have the applicant's 20-year postmarketing safety data, safety data from FAERS, and an epidemiology literature review conducted by FDA. From the applicant's database, it is estimated that 40 million patients have been prescribed adapalene gel 0.1 percent and 0.3 percent.

Eight reports that contain information on pregnancies following exposure to adapalene were identified. According to the applicant's review of the cases, some of them did not show patterns that were consistent with retinoid exposure, and in some of the reports, the data was insufficient to draw definitive conclusions.

As noted in Dr. Thambi's presentation, an FDA review of FAERS from approval to November 2015, 11 cases of congenital anomalies were observed with adapalene. An epidemiology literature review by

FDA identified 5 publications related to pregnancy and retinoids with outcomes, but none of them assessed adapalene specifically.

The postmarketing data has limitations such as under-reporting, insufficient clinical data, and reporting biases. In addition, the postmarketing data of prescription use may not reflect the safety of this product in the over-the-counter setting.

In summary, FDA concluded that at this time, the safety data does not support a causal association between adapalene and congenital anomalies.

So let's look at key results from the consumer studies. In the label comprehension study, the pregnancy statement was not tested as recommended by FDA. On occasion, FDA may request that language that appears in other currently marketed products be retested if misunderstanding of such may cause safety concerns.

Although the pregnancy statement is often displayed in DFLs, in the case of this drug, the potential lack of understanding or acknowledgement

of the statement was of concern by FDA.

The self-selection study that followed the label comprehension failed to demonstrate that pregnant women would consult a healthcare provider before using the product. The self-selection study was conducted mostly in breastfeeding women rather than pregnant women.

The verbatims collected by questioning the women who incorrectly chose to use the product illustrate the lack of perception that an over-the-counter product could potentially harm their babies. The study also showed that 15 women did not see the warning on the label.

Lastly, the actual-use trial indicated that consumers will use the product as per directions once daily and that consumers will unlikely overuse the product. Nevertheless, of 9 pregnant women who enrolled in the study, 5 of them incorrectly chose to purchase the product without first asking a healthcare provider.

In addition, during a short period of 6 weeks, 4 pregnancies occurred. This indicates

that women may become pregnant while using this product. If available over the counter, we anticipate that the product will be used by pregnant women.

So these are the factors to consider for your benefit-risk assessment. Teratogenicity is a concern with retinoids as a class. Teratogenic effects were observed in animal studies, but there's a significant margin of exposure based on the preclinical data and data from the human maximum use trial.

The clinical significance of the margin of exposure is unclear as the human sensitivity to this drug is unknown.

FDA concluded that the available postmarketing safety data at this time does not support a causal association between adapalene and congenital anomalies, although you heard about the limitations of the data. Based on what we learned from the actual-use trial, it is clear that pregnant women will use the product.

We now leave to you the discussion of what

is an appropriate margin of exposure for such drug in the over-the-counter setting.

I thank you for your attention. That concludes the FDA presentations, and now I direct your attention to the chair of the committee.

Clarifying Questions

DR. ROUMIE: Okay. We're running a little bit behind, so we're going to limit clarifying questions to 10 minutes. Are there clarifying questions?

Dr. D'Agostino, we'll start with you.

DR. D'AGOSTINO: Ralph D'Agostino. The question I asked to the sponsor, I guess throw also to the FDA. I was concerned -- and as you point out very well in excellent presentations also. I was concerned that there weren't enough subjects in the right categories to make inferences. And I was concerned that there may have been exclusion criteria, but I take from your presentation, and possibly the sponsor's also, it's just that they didn't do sort of enough recruiting, that they stopped before they had all the bins filled and

what have you.

Am I missing something in terms of that we should have more? There should have been more pregnant women. There should have been more adolescents in these categories. We just can't really draw a lot of inferences from the actual-use studies and also the self-selection because we don't have enough individuals in those categories.

DR. FILIE: May I invite Ms. Cohen to answer these questions?

DR. BARBARA COHEN: I can speak to the label comp and the self-selection studies. I mean, in general, I agree with what the sponsor said in terms of the exclusions. In the self-selection study, I'm not sure I understand why there weren't more pregnant women or adolescents, so maybe they could address that.

DR. D'AGOSTINO: It would be nice to hear them, but we can do it later on. But taking what they said, that the exclusion criteria didn't do it, it just seems to me that there really hasn't been enough intense recruitment of the subjects.

So there are certain questions that we just don't answer with the studies.

DR. BARBARA COHEN: Right. Again, they would have to address those issues. I can't speak for them about why there weren't a lot of subjects in those categories.

DR. ROUMIE: Dr. Scialli.

DR. SCIALLI: I have a question for Dr. Shukla. It looked from your slide 9 that there might have been a difference in the distribution of adapalene between the gel and the lotion.

Do you think that's normal variation, or is there something different that we should know about between the gel and the lotion?

DR. SHUKLA: First of all, in this case, we are doing cross-trial comparison, and also, there are formulation factors which affect the drug absorption, which I have shown in the first slide, or the introductory slide, where formulation does affect absorption. So a head-to-head comparison should not be done in this case.

DR. SCIALLI: So it's okay if we ignore the

lotion since we have data with the gel?

DR. SHUKLA: For this particular case, the gel data will be the most relevant.

DR. SCIALLI: Okay. Thank you.

DR. ROUMIE: Dr. Katz?

DR. KATZ: My question is about adverse events or potential risks, and most have focused on cutaneous adverse effects and risk of teratogenicity. My question is not about that, but about the pregnant women, who according to the self-selection study, we see will choose to use the medicine.

I think a lot of dermatologists and other physicians don't recommend using this. So what happens to these women who then start using it, discuss with their doctor, and find that they're using a medicine that maybe their doctor doesn't recommend? What is the -- are they going to have anxiety? Are they going to have guilt?

I'm wondering if FDA thinks that we should factor that into the calculus as well, and is there a way of getting at that question?

DR. MICHELE: This is Terri Michele, FDA. So I think that's actually a very pertinent question and one that we have raised. The question of how to get at that in a clinical trial, I think would be exceedingly difficult. So unfortunately, I don't know that we have data that we can apply to that question per se.

I would rely on the committee in terms of those of you who have experience with this patient population and how you've dealt with them in your clinical practice.

DR. ROUMIE: Dr. Bigby?

DR. BIGBY: Michael Bigby. This question is for Dr. Li on her comparison of other topical retinoids. It's the table that she showed. It's slide 11.

What I want to know is how was the dermal dose delivered, and that will probably answer -- so my real question is, why is the lowest teratogenic dose so much lower for dermal delivery than for oral for adapalene?

DR. LI: Cindy Li, toxicologist from FDA.

The question is about if the dermal application will produce very low systemic exposure than oral systemic exposure?

DR. BIGBY: No. The question is how was the dermal dose delivered.

DR. LI: Topically.

DR. BIGBY: So topically, on top of the skin?

DR. LI: Right.

DR. BIGBY: So why is that number so much lower than the -- I mean, it seems like you need less topically than orally. To me, that's counterintuitive.

DR. LI: That's what we observed in the animal studies with adapalene used 25 mg per kg. With a dermal, you haven't observed any teratogenic effects, even at highest dose tested.

DR. BIGBY: I see.

DR. LI: Yes. For the other numbers from this table adapted from the labeling, we would like to have some systemic exposure data to have a better comparison, so we could have some margin of

exposure. However, if you can see, the product approved in early years, and we couldn't get all the available data.

DR. ROUMIE: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you. My question is for Dr. Li. I was wondering with the maximal-use study if you believe that the subject enrollment of 24 people is sufficient to draw conclusions from in terms of toxicology and maximal amounts.

DR. LI: Cindy Li, toxicology from FDA. I would defer the question to my clinical colleague, Dr. Shukla.

DR. SHUKLA: Well, the number of subjects being 24 is low in a sense. I mean, this is what we normally recommend from the agency, is that we like to see at least 18 subjects. But in order to draw any strong inferences where you do like some kind of a statistical significance, that number is not adequate for any strong inferences.

DR. ROUMIE: Dr. Pruchnicki?

DR. PRUCHNICKI: Yes, Maria Pruchnicki. It

was mentioned a few times in the FDA presentation that they had actually requested of the applicant some testing on that label statement regarding pregnancy, which they declined to do, the sponsor declined to do. And I'd like to hear more about why they decided not to do that. I don't know who's best to answer that, whether FDA can respond with what they heard or whether the sponsor has additional input.

DR. MICHELE: Hi. Terri Michele, FDA. The statement that the sponsor told us, which I think you heard them say here at the meeting, was that they did not feel that there was a significant risk here, but I defer to them as to why they chose not to test.

DR. ROUMIE: Let's finish with the FDA questions, and then we'll give you a moment to answer. This is the last question, Dr. Rasmussen.

DR. RASMUSSEN: Sonja Rasmussen. There were two cases of anophthalmia mentioned, and I wondered, are they the same case? There's one that Dr. DeSesso mentioned, and there was one that

Dr. Thambi mentioned. And the one that Dr. DeSesso mentioned, it said lots of other defects, but this one, it just says optic chiasma, which I don't know exactly what that means in this other one.

DR. THAMBI: Hi. Lopa Thambi from FDA. Yes, it is the same case, and it was also published in the literature. That is the same case.

DR. ROUMIE: We will now break for lunch. We will reconvene in this room in one hour, at about 1:00 p.m., at which time we will begin the open public hearing session. Please take any personal belongings that you brought with you.

Panel members, please remember there is no discussion of the meeting topic during lunch amongst yourselves or with any members of the audience. Thank you.

(Whereupon, at 12:07 p.m., a lunch recess was taken.)

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

(1:02 p.m.)

Open Public Hearing

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee

if you do not have 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.

The FDA and this committee places great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the Chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. SPANGLER: Good afternoon. I'm David

Spangler. I'm with the Consumer Healthcare Products Association. We represent approximately 80 manufacturers of OTC medicines. Galderma, however, is not a CHPA member.

I'm going to briefly go through five points: acne in the United States, talk a little bit about access and how that expands people's opportunity to treat, the value of access, people's demand for choice, and then last, responsibility and the choice and use of OTC medicines.

As you heard this morning, acne is the most common skin condition in the United States, and there are growing numbers of women with this condition. Treatment can do things like avoid scarring and can certainly have an impact on self-esteem.

I think it's important to think about when you have OTC medicines, this is providing access to people who in many instances would not be treating at all. Without access to OTC medicines, over 60 million people would not be seeking treatment for many of their common, average, everyday

illnesses.

That access translates to monetary value. OTC medicines provide about $102 billion in value to the U.S. healthcare system, and if you think about that said in a different way, for every dollar spent on OTC medicines, there's about a 6 to 7-dollar value to the healthcare system. And if you look at skin treatments, of which acne is one, certainly not all but one, that's even higher. About every dollar spent on OTC medicines provides about $9 in healthcare value.

Let's think of a different example. If the most frequently used decongestant for allergies and cold and flu was not available, we'd have well over a million more doctor visits. That would add costs to payers of around $200 million a year. That would add out-of-pocket costs to consumers of around $45 million a year.

It's not just about money. It's also about people's sense of empowerment. It's about their preferences. If you think of the availability of OTC medicines and when people prefer OTC to Rx,

yes, you get things like cost and time, but you also get things like I want more control or I want more options. Having options in and of itself has value to consumers.

Of course, none of this would really matter if people didn't choose and use OTC medicines responsibly, and the good news is that evidence supports that they do. Large majorities of Americans report that they're confident in their ability to use OTC medicines, that they know OTC medicines work for them from their experience, and that they let them take better care of themselves.

We also know in the main that people report reading labels widely. They report reading the label on things like the section on uses, on directions, its purpose, warnings. And overall, about 9 in 10 Americans report that they always or sometimes read the label when choosing and using an OTC medicine.

So in sum, access provides value, value to millions of Americans who would otherwise leave untreated many of their average, everyday

conditions. We know that people want choice, and that has a value in and of itself, and there's evidence that underscores people's responsibility in choosing and using nonprescription medicines. Thank you.

DR. ROUMIE: Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. FRIEDMAN: Hi. I'm Dr. Adam Friedman. I'm an associate professor of dermatology, residency program director and director of translation research at GW Medical School for Medicine and Health Sciences. I'm representing myself. I have worked with the company that's proposing this medication, but never in the acne arena, and I am here on my own time and dime because, no question, I think this is going to be a game changer in not only how we manage our patients but how our patients manage their own disease.

To kind of give some insight to where I'm coming from, I'd like to give you a little bit of

my background, I'm a full-time academic dermatologist, a physician scientist. As the physician element of that, I see about anywhere from 70 to 100 patients per week. A large percentage of those, no question, are acne, given it is the most common skin disease we see.

I see the impact both emotionally and physically of this disease. I also constantly hear the frustration, the frustration of getting to the dermatologist in time before permanent damage is done, but even more so the frustration with our current armament of current over-the-counter products.

The second part, the scientist, part of my research is focusing on the pathophysiology of acne, the underpinnings of its biology, and in understanding this chronic inflammatory disease. No question, I have a good understanding of how our current armament of OTC products really fail to meet the mark.

Without any doubt, retinoids are by far our best topical product for acne. So I have to ask

this question: Well, if you look at other disease states, inflammatory disease states like dermatitides, eczema, we have hydrocortisone over the counter and then prescription topical steroids. Look even further afar, antifungals, we have topical antifungals that are over the counter and then prescription. Why do we not have retinoids over the counter?

Now, I think the question that always comes up here is safety. That's why we're really all here, is safety. So retinoids, there is a theoretical risk of teratogenicity, meaning birth defects.

But let's look at what we already have out there. Benzoyl peroxide, salicylic acid, these are already over the counter. These are category C. We counsel our patients already that if they're going to become pregnant, if they are pregnant or breastfeeding, they should not be using these medications. This is already part of our lexicon. So how different is it with adapalene 0.1 percent?

In thinking of adapalene 0.1 percent, this

product, though initially in the Rx area, it was really designed for OTC in retrospect. This was the mildest of retinoids in terms of causing irritation. It was purposely designed to be lipophilic, meaning it likes fatty areas. It is preferentially going to go into the pilosebaceous unit, the hair follicle and oil gland unit. And the likelihood for systemic absorption, in my opinion, is nil.

But even so, playing devil's advocate, let's say there is a safety risk. Once again, we will counsel our patients on this. We are in a flexion point I think in dermatology. Acne is going up and up. It was just mentioned moments ago, female adult acne is a rising problem. Adults do get acne. This is not a myth, and there are plenty of them. I see more adults with acne than I even see teenagers with acne just because there are more adults around than teenagers.

So I think, really, this is an important flexion point in time. We have an opportunity to make history here, and I think we really need to

take this by the reins. Thank you so much for your attention.

DR. ROUMIE: The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. Before we address the task at hand, I think we're going to go back and spend some time with any other clarifying questions for either the FDA, and I believe the sponsor has a couple of clarifying comments based on this morning's questions.

DR. MARSH: This is Howard Marsh. I'm the vice president from medical affairs at Galderma U.S. Thank you for the opportunity of providing a few clarifying answers.

Dr. Harris had asked for the sites at which we conducted the preclinical toxicology studies. This is RR-1. Slide up, please.

So these are the -- all the studies were done at a site in England. You can see that the principal investigators in each study were different, but they were all done at the same site in the United Kingdom.

The next question I wanted to relate was a question raised by Dr. Li regarding comparison with other topical retinoids. I think it's actually Dr. Katz asked the question.

The reason for dermal administration top dose being 6 milligrams per kilogram, and that appeared to be a lower number than for the oral top dose is a practical matter. So getting more than 6 milligrams per kilogram into the animal was what the limiting factor was.

So in this situation, I think the slide that was presented actually said greater than 6. That's because 6 was the maximum dose that we could apply, and therefore, the likely lowest dose is 6 or above because that's what we could get in.

The next question, if I could have slide RR-3 up, please. So this was a question relating to the maximal-use PK study, and specifically, there was one outlier. You can see the individual PK profiles on this slide at days 1, 15 and 29. And at day 29 and day 15, you can clearly see the subject with a higher exposure levels. This was

the same subject at day 15 and day 29.

We didn't identify a cause for this high level exposure. However, what I do want to emphasize that it was this outlier that we used his data in calculating the highest systemic exposure. So the outlier created the actual safety margin. If we'd used the group mean of exposure, then the margin would have been 234. So we took a conservative approach in this by using that outlier.

The final point I wanted to make related to the question about the testing of the pregnancy warning "see a healthcare professional." We did discuss this with FDA. We decided not to test this warning. This was because we felt it was already FDA codified language. We did not consider the comprehension and compliance with this particular warning is essential to ensure safe use of the product because if you take the totality of the evidence, teratogenicity is not a human risk for this topical product.

The important point here is even if pregnant

women were to use the product, there is not a safety risk.

That's what I need to say at this point. Thank you very much for allowing me to speak.

DR. ROUMIE: The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments. We will now have the charge to the committee from the FDA.

Charge to the Committee- Valerie Pratt

DR. PRATT: Good afternoon. My name is Valerie Pratt. Today, I will provide the charge to the committee and introduce the questions for discussion. The key points discussed today include the following: Adapalene is a retinoid-like product. Teratogenic effects were seen in animal studies. Based upon the maximal usage trial, the margin of exposure is at least 70-fold. However, the human sensitivity to this drug is unknown.

The label comprehension study did not assess the pregnancy statement. Under 12 years of age, consult a physician tested well among males and

females ages 12 to 70. The self-selection study failed to demonstrate that pregnant women would consult a healthcare professional before use. And the actual-use trial demonstrated that most consumers with acne use the product as directed.

The most common reason for discontinuation was mild skin-related adverse events, which resolved. Five out of nine pregnant women inappropriately requested to use the product without seeking HCP advice. With the current labeling, it appears that pregnant women will not stop use and seek healthcare professional advice.

Seven children less than 12 years of age approached the pharmacy to access the product.

Question 1 for discussion, discuss the safety profile of adapalene gel 0.1 percent in the over-the-counter setting. In your discussion, please consider the following: A, use by females with reproductive potential, i.e., teratogenic risk; B, pediatric use, i.e., use by adolescents and/or younger children; and C, the potential for misuse, e.g., excessive use or use for non-acne

conditions and the consequences of such use.

Voting question 2, has the safety of adapalene gel 0.1 percent for OTC use for the treatment of acne been adequately demonstrated? If not, what additional data, if any, should be obtained to demonstrate the safety in the OTC setting?

Question 3 for discussion, discuss the proposed Drug Facts label and consumer information leaflet. If your review of the label and leaflet identifies concerns, please discuss ways in which the documents could be revised to encourage the safe and proper use of the product by consumers.

Voting question 4, the sponsor proposes OTC use of adapalene gel 0.1 percent for the treatment of acne in consumers ages 12 years and older.

Does the totality of the data support the use of this product OTC? If yes, do you have additional comments or recommendations for labeling? If not, what further data, if any, should be obtained to support such use?

Thank you for your time.

Questions to the Committee and Discussion

DR. ROUMIE: We now have the charge from the committee to the FDA, and I think we'll start with discussion 1, which is the safety profile of adapalene gel 0.1 percent in the over-the-counter setting. Dr. Scialli?

DR. SCIALLI: Tony Scialli. I'll start it off by saying I'm not at all concerned about the teratogenicity of retinoids as a group. I think, in fact, it's rather unfair to characterize a whole group of molecules at different doses as being teratogenic. That kind of generalization just leads to trouble.

I should note Dr. Thambi in her excellent presentation mentioned doing an evaluation of the epidemiology studies, and she found five. These are listed in the briefing document on page 37. And what I think is important is that these studies, although they didn't separate out adapalene largely at tretinoin, which is all-trans retinoic acid, which, in fact is believed to be in high enough doses quite teratogenic in human

beings, and yet these five studies, which certainly had some limitations did not show any increase in adverse pregnancy outcome, except for an increase in elective abortions in one of the studies, which is one of the hazards of labeling or might be one of the hazards of labeling.

So I think that to extend concerns about retinoids as a class to this particular product would be to ignore substantial evidence that topical use of the product will not increase the risk of birth defects.

DR. ROUMIE: Thank you.

I'm just thinking out loud and putting my two cents in. The part that has been, I suspect, most concerning for many of us is the self-selection study results and how the actual use actually kind of rolled out, and that many people who probably shouldn't have used it chose to use it. And I believe that's probably one of the biggest issues that I see for all of us to discuss, on whether or not that -- is more data necessary or needed to help us make an informative decision?

Dr. Scialli?

DR. SCIALLI: Well, I treat pregnant woman and make recommendations to pregnant women. There's no question that, regardless of the labeling, pregnant women will use this and every other product unless there's a particular program in place to require pregnancy testing and so on.

So the fact that pregnant women chose to use this product or that women became pregnant will using this product to me is a commentary on women and not on the product. And I don't mean that as disparaging to women, but they're the ones that get pregnant, at least last I checked.

So I would suggest that we just have to accept that pregnant women will use all products to which they have access, which by the way, includes ethanol, and that we're not going to prevent the exposure of pregnant women through different labeling.

So I'm not concerned. And actually, if a woman asked my advice on use of this product during pregnancy, I'd tell her to go right ahead, although

I probably would recommend she try something less expensive.

DR. ROUMIE: Dr. Katz?

DR. KATZ: Ken Katz. I remain a little bit concerned about pregnant women using it and then showing up at the doctor's office with a product that says talk to your doctor about it, because the other products I think were mentioned earlier in the discussion and by one of the speakers don't bear that same warning, at least as far as I can tell, on the package.

So I think it still raises some questions about how women will feel once they realize they're using a product that bears that label.

DR. ROUMIE: Dr. Scialli?

DR. SCIALLI: And were you suggesting not making the product available or changing the labeling to remove the sort of pseudo warning?

DR. KATZ: Ken Katz again. Yes, I agree with that I don't think the teratogenicity concerns are substantial. So then why have the label there? I think it just creates problems for consumers and

for their physicians later on down the line.

DR. ROUMIE: Dr. Gudas?

DR. GUDAS: I would just like to add that I think the product -- the data that has been presented indicate that the product is safe, and I think it would be a big boon to adolescents with acne. I think it's a very severe disease and that this would really help in the treatment, and I think the benefits greatly outweigh any minimal -- I don't really see any risk. I don't think the teratogenicity is a risk.

DR. ROUMIE: Dr. Harris, and then Dr. D'Agostino.

DR. HARRIS: Steve Harris. Can I just speak to the animal data? I cannot speak to the human data. When you look at this data, I agree with what Tony's saying and what Lorraine's saying, I don't believe there's any teratogenic risk in human exposure, pregnant women especially.

When you look at this animal data that's presented, Galderma went out of the way and did multiple reproduction studies. They did a

fertility study, general reproductive performance study in pregnant animals, and they used oral exposure. They did a peri, postnatal study of oral exposure, and they did a variety of developmental toxicology studies orally and topically.

When you look at the whole package of reproduction studies that they did, really, the only findings they found were in the oral embryo-fetal toxicity studies in rats and rabbits at -- I think it was 6 milligrams or 60 milligrams per kilogram. I think at the high dose levels of 25 and 60 milligrams per kilogram.

From the briefing document, it presented several observations consistent with teratogenic effects expected for systemic retinoids, including effects on bones, the urinary tract, and the palate.

Now, me as an animal person, I'll look at this data and say, all right, they have some findings, but I'm not certain it's specific to retinoids. But the point being is they went ahead and they were talking about a 0.1 percent topical

application, and this study was clean, meaning there were really no effects found. The reproduction in the perinatal studies, which were orally dosed, there was no problems found.

When you look at all the potential signals that we look for in developmental and reproductive toxicology studies to determine a human risk, I see none. And the only findings -- and I mean, I don't question the findings because I haven't seen the findings that -- at these high dose levels in the oral study, they saw some malformations. Don't know how many, but they saw some.

But when we push doses in our animal studies, push doses, and it can just be water, it can be some physiological saline -- we can push doses, and we can create problems when we go to excessive doses. And in this case, these studies satisfy my concern regarding reproductive risk.

DR. ROUMIE: Dr. D'Agostino?

DR. D'AGOSTINO: Ralph D'Agostino. During the questions to the sponsor and to the FDA, I was trying to get a sense of the completeness of the

studies and what have you and of the implications. Those of us who fussed with OTC products over the years, I can remember going, quite convinced, that weight reduction aids -- was it PPA, phenylpropanolamine -- was the greatest thing in the world, and then it attached stroke to it. And then with Tylenol and things of that nature, how much data do you need and how right can you be and how wrong can you be?

Because I got the material so early, I did read through a lot of it, and I also read a number of the articles that were involved. I think the data is quite substantial. I mean, I don't know how much more one would need.

So it being said, you could pick some studies, you could say drill in on the adolescents, which I think we might recommend if we go recommending approval, what else is needed. Drill in on the adolescents more, on the pregnancy issue more.

But I don't see anything that's tremendously compelling to say that we don't have enough know to

have a reasonable discussion that we don't see any signals. I think we have to sort of bite the bullet on do we think we really have enough and how much is enough. But anything that I've read, and as I said, I have read a substantial amount of this, it seems to find it very hard to pull something out and say this is really substantially bad and we have to really worry about it.

DR. ROUMIE: Dr. Pruchnicki?

DR. PRUCHNICKI: Maria Pruchnicki. I think I'll just jump onto the bandwagon and add my two cents that I agree that this is a safe medication. I don't think it poses risks for teratogenicity when used over the counter.

However, if I were to be counseling a patient on this medication, I think I would certainly mention at least the potential for the class to cause reproductive concerns and maybe even explain why this one is different and why this might be okay for use in a patient who becomes pregnant or is planning to become pregnant.

I also know from my own experience that

patients, that they will go out and seek information on the internet before talking to a healthcare provider or from other sources. And I worry that they may not be able to distinguish between a retinoic acid derivative like adapalene compared to something like other creams that are available.

So I do think being very specific in the labeling and making sure they're aware that pregnancy is something that they should be considering differently with this medication is important, and that probably speaks to our next discussion point, which is labeling changes. So I'll stop there.

DR. ROUMIE: Dr. Obican?

DR. OBICAN: Thank you. Sarah Obican. I guess I'm just going to get on the bandwagon as well. I wanted to respond to Dr. Katz, too.

The thing that bothers me the most is that pregnant and breastfeeding women ask a health professional. I guess I would just warn a little bit against that since we understand the safety

data a little bit better and people in this room have probably the most knowledge about the particular medication.

My colleagues and generalist OB/GYN and probably also maternal-fetal medicine probably do not have the same amount of data as you do, and I worry about the case scenario, women being exposed to medication knowing now that they're pregnant, coming to the physician, asking the question of the physician, who's supposed to be the knowledgeable professional -- here may actually say, oh, I'm concerned about that now.

Not in cases with particularly this medication, maybe even not this class of medication, but certainly some exposures in pregnancy that we consider relatively safe have been then routed to the point of having to have an abortion because the provider thought the risk was too high. And I think that's actually a bit of a concern.

So my recommendation would be actually not even to have that. And I understand there might be

other reasons to have this labeling present, but I do have concerns about that. Thank you.

DR. ROUMIE: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. I wanted to raise just a couple of considerations regarding pediatric and adolescent use. One thing that I thought was interesting in the data is that, overall, they were finding with the adolescents that they on average had a higher maximal plasma concentration than adults, almost double.

Also, in the 13 subjects that used at least 80 grams, 9 of them were between the ages of 12 to 29, and 17 percent of adolescents used more than 40 grams or more.

I think of the days of like being in college where people sort of slather things on, or in high school where if a little bit works, more is better, right? And does this have any consequences for considering safety? We don't have a lot of adolescents in the study, so I want us to just be mindful of that.

Also related to that, there was not really

as high as I would have liked responses in terms of comprehension if they were suffering irritation for people suffering irritation, going to see your doctor because of it and not using other medications at the same time. So while it's not teratogenic, it's still an adverse effect for people that would be getting perhaps issues with their skin.

Then finally, still related to that, the one thing I find really interesting is that if you have an adverse event that requires medical interventions, my question that I asked that was not answered is what do those medical interventions look like? And would being a certain age or being pregnant disallow you from getting that intervention that would be needed?

So those are my comments.

DR. ROUMIE: Dr. Katz?

DR. KATZ: Ken Katz. This is for point C, potential for misuse, and I guess this touches on labeling as well. And this has to do with the nonprescription proposed label, which says "acne

blemishes," and I think the term "blemishes" is sort of vague. The package insert for the prescription products just says "treatment of acne."

So I think the term blemishes raises -- maybe people will think that they'll be able to use it for skin lightening, for post-inflammatory hyperpigmentation, or for other conditions that cause darkening of the skin. So that's one potential for misuse.

I don't think it will be unsafe except for the cutaneous adverse events, but I think it's an issue.

DR. ROUMIE: Dr. Michele, do you feel like we have a good representation of the discussion?

DR. MICHELE: Yes. Thank you.

DR. ROUMIE: Okay. The next is a voting question. Has the safety of adapalene gel 0.1 percent for over-the-counter use for the treatment of acne been adequately demonstrated? If not, what additional data, if any, should be obtained to demonstrate safety in the OTC setting?

We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record.

Next, we will go around the room, and each individual who voted will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in that manner until all questions have been answered and discussed.

Before we go to the voting, does anybody have any additional questions that we need to discuss or answer?

(No response.)

DR. ROUMIE: Okay.

(Vote taken.)

DR. CHOI: For the record, we have 16 yes, zero no, and zero abstentions.

DR. ROUMIE: Let's go around the room and start with Dr. Engle.

DR. ENGLE: Janet Engle. Yes.

DR. GUDAS: Lorraine Gudas. Yes. I mentioned the reasons before. I think the company has done a very credible job in their research, and they also had quite a bit of experience with this drug in the prescription setting. So I think that those are the reasons for my yes vote.

DR. KATZ: Ken Katz. Yes.

DR. BIGBY: Michael Bigby. Yes.

DR. PISARIK: Paul Pisarik. Yes.

DR. ROUMIE: Christianne Roumie. Yes.

DR. SCIALLI: Tony Scialli. Yes.

DR. HARRIS: Steve Harris. Yes.

DR. WU: Victor Wu. Yes.

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. Yes.

MS. BERNSTEIN: Cheryl Bernstein. Yes.

DR. D'AGOSTINO: Ralph D'Agostino. Yes.

DR. PRUCHNICKI: Maria Pruchnicki. Yes.

DR. MICHAEL COHEN: Mike Cohen. Yes.

DR. OBICAN: Sarah Obican. Yes.

DR. RASMUSSEN: Sonja Rasmussen. Yes.

DR. ROUMIE: We'll now continue with the next discussion question, which is to discuss the proposed Drug Facts label and the consumer information leaflet. If your review of the label and the leaflet identifies concerns, please, we should discuss ways in which we should revise these documents to encourage the safe and proper use of the product by consumers.

Dr. Sultan?

DR. SULTAN: Thank you. Marla Sultan. I've heard different suggestions about what to do with the pregnancy label, and I'm just wondering if something that should be considered in frequently asked questions, is what do I do if I become pregnant while using the drug. And that question could be entertained in both directions, both for

the assistance of the patient and also in helping to provide that answer before the physician starts in on the answer.

DR. ROUMIE: I think that's an excellent suggestion and would really add value, I think, to both the frequently asked questions suggestion and could probably help patients navigate some of those issues that we brought out earlier, which were what to do if someone did become pregnant.

Dr. Bigby?

DR. BIGBY: I don't actually have a solution for this, but there is a little problem here. On the Drug Facts sheet it says, "If pregnant or breastfeeding, ask a health professional before use." And I know that the majority of dermatologists when asked will say you shouldn't use it while you're pregnant. Whether that's correct or not clearly is up for debate. But then in the product information sheet, it says, "Adapalene should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

So you have a problem, and I think you need to do something about it.

DR. ROUMIE: Can you point out where -- is that in the facts sheet or the label?

DR. BIGBY: It's on the same sheet as this under pregnancy. It's the last sentence under pregnancy, the product insert, the last page under pregnancy.

So you say ask. The doctor is going to say don't use it, and then in your instructions on your product label, emphasizes it should be only used if the potential justifies the risk -- and that there is a potential risk on the fetus.

So I mean, you've created a scenario here that doesn't make any sense.

DR. ROUMIE: Dr. Scialli?

DR. SCIALLI: This is Tony Scialli. I think Dr. Bigby's point was underscored by Dr. Katz and Dr. Obican, that when you have cautions in the label, they can create adverse effects on their own, which might argue to just take any mention of pregnancy and breastfeeding -- certainly

breastfeeding -- but might argue taking mentions of pregnancy out of the labeling, and I wouldn't be opposed to that. I frankly counsel lots of women who have been scared to death by things that have been written in product labeling.

DR. ROUMIE: Dr. Pruchnicki?

DR. PRUCHNICKI: Maria Pruchnicki. I think my point falls along the lines of my colleagues here. I think it is very typical to see a breastfeeding or a pregnancy warning on an over-the-counter drug label that may or may not be meaningful.

I think what is different in this scenario is that there is a concern, at least with the class of medications, that use during pregnancy could potentially be a problem. And therefore, I think what we saw in the consumer studies was that these warnings are often ignored. They always say that.

If there's truly a conversation that needs to be had, we need to identify it for consumers in a different way. If we don't need to have the conversation, then I'm not sure what limitations we

have on this label and what can be removed. But certainly, it needs to be decided and more consistently delivered so it's noticeable for consumers.

The second point that I wanted to make is that I think there is an additional problem on the label related to the sun sensitivity. There is a warning to avoid unnecessary sun exposure and tanning beds and using sunscreen. I wonder if that might be viewed by consumers in a similar way, that that's a pretty generic warning. And in this case, there is a specific reason for it.

So maybe adding a statement that this product could increase sensitivity to the sun very specifically might not have more benefit than sort of dancing around the issue by not providing that directive.

DR. ROUMIE: Dr. Bernstein -- or Ms. Bernstein. Sorry.

MS. BERNSTEIN: I'm enjoying today.

(Laughter.)

MS. BERNSTEIN: I'm just looking at the

information to the patients, and it's just a thought that comes to me as I read it. First of all, the definition of mild cleaner, I think most people here would understand what that means, but possibly not an adolescent or even an adult. So maybe something more specific, maybe an example of what is considered a mild cleaner for the skin.

Also the words "thin layer," I think thin is relatively -- could be misconstrued. So I don't know if there's a way to be a little bit more specific as to what that means because I've seen patients where they think a little bit, they need more.

So if you put more on, it's going to be more effective. And I've seen it with antihistamines where they'll take one pill, and they're still having symptoms, and they'll take another pill even though it's once-a-day dosing. So it's just a comment.

Then the other part that I think might be beneficial for the public is how to apply it, like apply once or once a day only, something a little

more specific so that they don't start mixing it up and using it more frequently than what is actually indicated from the medication.

DR. ROUMIE: I'll say in relation to that, that all of the studies that have been presented have never been longer than a year of duration, and majority of the data has been presented on 6 weeks and 12 weeks in study durations. And as you know, people tend to buy a bottle, and they may use it, and they may use it continuously, or they may stop and then keep going.

I think some potential limits in the duration of use would be beneficial or even something like if using longer than 6 weeks, consult your physician.

I think Dr. Wu was next.

DR. WU: Great. I'll address the pregnancy point second, but I think in terms of specific label changes for now, I wanted to call out in the sponsor's data they presented around the low literacy group that there were several questions around the severity of irritation and inflammation

that wasn't quite understood to the threshold of 85 for low literacy group.

So I'm concerned for that group, I think especially when you probably won't read the box until you have severe inflammation or irritation, at which point you probably will come back and look for more guidance.

So I would recommend that, at the very least, in the frequently asked questions, there be a little bit more guidance on what is considered irritation and when it becomes severe. Because I do think that across the three questions around what happens if it worsens when you put it on and around the question of what do you do whenever it becomes severe, and also around product irritation and the types of symptoms, the low literacy group specifically was unable to reach that threshold of understanding.

Then when it comes to the question around pregnancy and breastfeeding, I think it's a tricky one. I appreciate the discussion around unintended consequences of having that, and I think that's

what we're talking about today. So I'm torn in the sense of do you go further on the warning in order to have a discussion. If you were to increase language to something along the lines of do not use if you're pregnant until you've spoken to your physician, that's a much stronger, that I think people would probably pay attention.

But do we want to shift that conversation to the doctor's office or to a pharmacist's office versus if we take it off all together? So I think based on the information in the data, I would favor personally just taking it off all together, but I certainly understand that that would be kind of a paternalistic decision versus having a consumer make that for themselves and at least giving them the information.

So I appreciate the challenge in the labeling question on that point.

DR. ROUMIE: Dr. Gudas?

DR. GUDAS: I'm just going to follow up. Maybe you were going to bring it up again, Janet. I don't know, but I think Dr. Engle had a point

earlier about this first page, it says, "Cover the entire affected area," which seems reasonable, cover the area of acne. And then on the next page, it says -- as you pointed out -- I mean, I just want to make sure this gets in the record, that it says you "should apply to the entire face," and it says it can't be used for a single blemish.

But maybe just saying the entire affected area because there may be -- the entire face isn't always affected. So it just is a bit of a contradiction, the first page and the second page.

Maybe other people have better suggestions, but maybe just saying the entire affected area.

DR. ROUMIE: Dr. Engle?

DR. ENGLE: Jan Engle. That's exactly what I was going to say. I know it's hard. There's not much real estate in the label, but I think when it's an over-the-counter drug, patients get very confused how to use things, and the more direction we can give them, the better.

In my experience, these frequently asked questions as a separate entity, they're very useful

for the folks who actually read them and keep them, but they tend to get lost. So I like to see as much information as possible with the limitations of space on that label, the Drug Facts label.

DR. ROUMIE: Dr. Sultan?

DR. SULTAN: They covered it. I think that language should be aligned and as clear as possible, not contradicting itself.

DR. ROUMIE: Okay. Dr. Joniak-Grant?

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. I had several comments about the DFL label. One suggestion I was thinking, there seemed to be not a lot but a little bit of confusion with use once daily. It might help to put something in there, use once per 24-hour period. That's how people tend to think of time.

They could also do that in terms of -- because there was some misunderstanding with using only one topical acne medication at a time. Do they mean if you put one on in the morning and one on in the evening, you're okay? I can definitely see people taking it that way.

So again, saying not using other acne medication in a 24-hour period would give them sort of more specific parameters.

One thing I also thought there was some confusion with was in one of the items, it says "to clean skin thoroughly." And that says it on the DLF. And for me at least, this implies sort of scrubbing, more abrasiveness. Again, I think of younger people and sort of the scrubbing is better approach, where on the frequently asked questions, it says to "use a mild cleanser and pat dry."

So that's sort of very different connotations in terms of what you're asking of the people. Also, if we have something that is a little bit -- sort of focuses more on this mild approach, that may help. I don't know, but that may help with lowering irritation for certain individuals.

For the using a moisturizer, there's a lot of moisturizers on the market now that contain chemicals that can be irritating, especially if someone goes and uses their mother's moisturizer

that's used to eliminate fine lines and wrinkles. So I think clarification about perhaps moisturizers that do not contain these ingredients could be worthwhile.

I agree with Dr. Wu about there needing to be more information about how to manage irritation, what does sever mean, what signs should you be looking for.

Then finally, it says, "Do not use wax to remove hair." There are many types of hair removal approaches. There's depilatory. There's electrolysis. There's laser hair removal. They're very common. I teach at the university. A lot of the university students are getting them. Would those be something to be avoided? That's something that Galderma would have to discuss and decide if that should be included under that instruction.

DR. ROUMIE: I think I'm going to go back to a point that Dr. Wu raised and have us kind of discuss a little more the two spectrums of the label under the pregnancy category.

So there have been calls to remove it, and

there have been calls to make it stronger. And I have to say I lean a little more on the stronger side just because when you see a patient and you counsel a patient who is going to start this in the office, often there is a counseling of, if you get pregnant, you need to call us, and we'd prefer that you not use these medications.

Despite the safety profile, that's typically how I would conduct myself in practice. So I think having us kind of chat a little more about should we unpack the pregnancy from the breastfeeding issue and whether or not there are ways to either make it stronger or to have some internal consistency with the product label.

Dr. Katz?

DR. KATZ: Ken Katz. I think that we often do say things like that, to talk to us before using medicines or not to use medicines. I think probably all of us strive to practice evidence-based medicine, and I think we saw how the committee felt about the safety of this product. I think a lot of us were probably informed by the

briefing document and the other data that were presented.

So I think if I had to stick to evidence-based medicine, a reflexive sort of caution, I think we should move more towards evidence-based medicine. If we're comfortable with the safety profile, we should put our nickel down on that.

DR. ROUMIE: Dr. Scialli first.

DR. SCIALLI: If this chemical didn't look superficially like all-trans retinoic acid, we wouldn't be having this conversation because its profile in the safety studies looks very good. And I would just like to come back to this boogeyman of class labeling or class thinking.

In fact, as I pointed out before, even all-trans retinoic acid, which is marketed as Retin-A, which intravenously or orally in experimental animals produces congenital malformations but topically does not, and for which there are epidemiology studies that are reassuring, it comes back to something that we as toxicologists

grew up on, which is that the dose makes the poison. So if the systemic exposure is low enough, even all-trans retinoic acid becomes safe to use during pregnancy.

I would recommend, therefore, that we just not get too wound up in the class labeling of this compound that might lead us to disregard the substantial safety information.

DR. ROUMIE: Dr. Cohen?

DR. MICHAEL COHEN: When you said stronger, you mean more of an explanation or a question and answer --

DR. ROUMIE: I think having something in there like what to do if I get pregnant, should I stop this medication. I think more knowledge is power for the patient, especially when there's not a physician who is right there who you can ask. If they can get information either through the Drug Facts label or the insert, that's only a plus.

DR. MICHAEL COHEN: And this would affect -- I can't say obviously, but there's a prescription product. Is there a similar warning

right now on the prescription product label? I'm not sure if there is. I didn't read the label, I'd have to confess, for the prescription product. But when people look things up on the internet, they might, in fact, see that. And that would be a cause for concern if that's going to remain in the prescription product, too. You could have the same thing happen when they find out they're taking something that has a pregnancy warning or whatever.

DR. ROUMIE: Dr. Wu?

DR. WU: As I mentioned earlier, I would favor actually removing the label, and a couple of the reasons I think I would go there, I think of myself as a primary care doc. When I get a call from a patient about a drug that I'm mildly familiar with but do not know all the details, I will myself Google it and give them a quick answer.

So I think you'll see that this is a class C, and so I think that as a result will then begin to lead a physician down a different route of discussion.

So to me, what tips me over the edge is the

fact that we're talking specifically about 0.1 percent. We're not talking at a higher level. And the efficacy data and the safety data at this point to me feels compelling enough, and I think about other over-the-counter drugs like an NSAID, that I would not counsel a patient of mine who might have a cardiac disease or a GI bleed disease in the past, that would be a discussion.

But as a whole, at the 0.1 percent level, to me it feels safe enough that I'm willing to remove some of the ambiguity that a physician might feel when looking it up if they're not familiar with it on a regular basis.

Anything beyond that that requires prescription level, I think becomes a much different reason and discussion at that point. That's why it's prescription. So to me, that's why I would favor removing that label in this case. I'm comfortable standing on the data that we've seen at this drug level.

DR. ROUMIE: But just to play devil's advocate, even on NSAIDs, the bottle says consult a

physician if you've had stomach issues or heart disease. I mean, I think it is very forthright with if you have this medical history, you do need to talk to somebody.

Removing that from this label doesn't give anybody any information. It just basically says, oh, this is okay. If you're 14 years old, a little is good, then a lot is better, and then, oh, I get pregnant. Oh, well, it's fine, it's just for my face.

I don't know. Again, that's just my opinion that it's very dismissive of the potential that may be there.

Dr. Pruchnicki?

DR. PRUCHNICKI: I'm just going to add my support of the more knowledge is better because there is information out there, and it may not be from a reputable drug information or product label that someone has looked up. It may be from a testimonial. It may be from a magazine article. So it's very difficult for consumers, in my experience, to sort through what is good

information and what is not good information.

One of the most common scenarios that I encounter is where they are frustrated by conflicting information. So I think addressing the fact that, in fact, this is very safe based on the product label would be very helpful and especially if that could be specific.

I also think that general practitioners, folks who haven't had the benefit of the presentation that we have here, may also have misconceptions. Addressing that in some way, it gives them at least a prompt to look into it more deeply.

I think there's also sort of a public service component in that if we are putting information on a package in a strong way for consumers who maybe for the first time are looking at an OTC product -- young teenagers, this may be the first time they're going and selecting or using an OTC product -- to start hearing that message that if you become pregnant for a topical product or not, this is something you need to talk to a

healthcare provider about.

Again, I think this language that is standard on the label is sort of generic and perhaps overused in a way that we don't pay much attention to it, so maybe it is time to switch that up, but I think it's a good message to deliver at a young age, so it might be an opportunity.

DR. ROUMIE: Ms. Bernstein?

MS. BERNSTEIN: I guess I'm a little confused, so I'll admit that. I think I can see where it's safe with the data that was presented. My only concern is what if patients overuse the drug. Doesn't that change the dosage, and would that then be a potential health risk?

Like if they took it more than once a day or dabbed on a tremendous volume of it -- I have seen patients where you do a lot of teaching, you train them. I always say to a patient, I say, "Repeat back what you understood." And I just don't even know where they got that information. Sometimes I'm in there for an hour, and everyone's screaming at me that we have to hurry up.

So that's my only concern, is that I think it's completely safe, and from what I understand, everything seems reasonable. But what if, because it's out in the population, they don't follow the prescribed recommendations?

Somebody made a comment about cleaning your face. I agree with that. What if you rub too hard and now you have scratches or you cause abrasion, and then you apply it, and how is that absorbed? And what is the dosage if you prick the skin, so to speak, and then you put the cream on or gel and then it's absorbed?

So that's my only concern. I'm not really too keen on taking out the warning about if you're pregnant or breastfeeding, ask a professional. At least that's, hey, wait a minute, maybe I -- if somebody actually read that and thought about it, maybe they'll consider are there any risks, and then making sure that they're putting on.

Because I thought maybe it would be nice to have something highlighted or once a day dosing only, or like your comment, every 24 hours or

whatever, and then highlight a thin layer, or if you could specify what is the definition of thin because thin to me might be different to somebody else. So that's just my thoughts.

DR. ROUMIE: Dr. Gudas?

DR. GUDAS: I would just like to agree with the last two speakers. I think saying something on the label like use only once per 24-hour period and one time per day just to make it a little bit stronger.

Then I agree with Dr. Pruchnicki that I think that it is good to have the terminology in there about if you're pregnant, talk to your health professional because it does make people think, and I think that's an important point, even though I think the drug is safe at the dose. We've already went through that in the discussion today.

But I think I would not favor taking out any warning about talk to your doctor if you're pregnant. Thank you.

DR. ROUMIE: Dr. Katz?

DR. KATZ: I am in favor of probably taking

out the warning, and given the choice of bringing the new Drug Facts label in line with the package insert for the prescription product, which it doesn't seem to be supported by the evidence. I don't like the idea of that. I'd rather do it the other way around, and bring the package insert for the prescription product in line with what we see is the data for this product that we're considering right now.

The other thing I wanted to say is that this label is sort of double -- this warning is now double-barreled, and we've been talking a lot about pregnancy. I haven't heard any concerns I think from my fellow committee members, or from the sponsor, or from the FDA about safety in breastfeeding.

It exists in the package insert, but I think we're creating -- if we keep that in, creating anxiety for women and a discussion that's going to involve a doctor, where maybe other things more important to someone's health could be discussed.

DR. ROUMIE: Well, that was actually one of

my questions. Should it be uncoupled from the breastfeeding warning?

DR. KATZ: I would uncouple or couple them and toss them.

(Laughter.)

DR. KATZ: But yes, I understand your question.

DR. ROUMIE: Dr. Rasmussen?

DR. RASMUSSEN: I just want to put in my two cents for the take it out of the label completely. If we were referring them to somebody who actually might have the benefit of this safety information here, that would be one thing, if they were being referred to a teratogen information service or something.

But going to their general healthcare provider, who might not know this information and might give them more scary -- I think all of us that have been sometime involved in teratogen counseling have all been in a situation where somebody's general practitioner has told them to terminate their pregnancy because they read

something on the internet about something, and fortunately, the woman gets to one of us before that happens.

I just really am concerned about that. I think we have good information here that suggests safety. Why put something on there that's just going to scare people? And scaring people isn't good, either.

There is a 70-fold margin. Right? Isn't that what we saw? I mean, how could you get 70 times the amount on you? Even if you did it every moment of the day.

DR. ROUMIE: Dr. D'Agostino?

DR. D'AGOSTINO: Ralph D'Agostino. I lived through the period with the OTC of designing these labels and so forth, and I have to admit that most of the time when I take an OTC drug, I can't find out what the directions are because there's so many damn other things on it.

(Laughter.)

DR. D'AGOSTINO: But in this case, I would argue to keep it on there. I think that there is

biologically the possibility of overdosing and things of this nature, and I think we would make a mistake by making it sound so clean.

DR. ROUMIE: Dr. Obican?

DR. OBICAN: I'm sorry. I'm the same with Dr. Katz and Dr. Rasmussen. I'm of the same opinion. As a clinician, first and foremost here, this is what I have real concerns about.

I have also concerns about scientifically kind of having a double-edged sword. We either say it's safe, or we say it's not safe. If we vote that it's safe, then I don't like giving our pregnant moms misinformation. And I really have a concern about that. I want to be very, very clear to my patients, safety yes or safety no. And if there's ever a concern with any medication, it should be discussed.

But if we feel and we have voted, then I feel like we have to go one way or the other. So going back and forth seems like it'd be really tough for our patients.

DR. ROUMIE: Dr. Pisarik?

DR. PISARIK: Paul Pisarik. I also agree with Dr. Katz and Dr. Rasmussen. I think if we're going to say that it's safe to be used in pregnancy, I think we need to take off that label that says warning if you're pregnant or if you're lactating, discuss with your clinician. We're giving mixed signals, and if we think it's really safe like the data suggests that it is, I think we need to take that labeling off.

The other issue is women may read that, and they're pregnant and they're using it, and think oh, my goodness, my baby's going to have problems, so I'm going to have an abortion. So I'm concerned about that aspect, too, not talking to a healthcare provider, having an abortion just because they're scared about possible side effects.

DR. ROUMIE: So let's summarize. The committee felt that the adapalene 0.1 percent gel was safe with a good margin of error. There were differences in opinion on the Drug Facts label and what should be included. In particular, the pregnancy warning is pretty evenly split on the

pregnancy and breastfeeding, whether it should be included or not included in the Drug Facts label.

There was a call for some clarification on the once-daily dosing as well the skin cleaning and how you apply the product and the amount of product that should be applied.

Those were the main issues I heard unless somebody has --

DR. KATZ: Blemishes.

DR. ROUMIE: Blemishes. Blemishes are not a clear -- they're not clear, ha.

DR. WU: And the word "severe" as well, severe irritation --

DR. ROUMIE: Yes, clarification on the severity of adverse effects and when to seek physician assistance regarding severity of the adverse effects.

Dr. Michele?

DR. MICHELE: That was very nice. Thank you.

Since we do have a little bit of time, I was wondering if the committee could perhaps go back to

the safety question for just a moment and opine upon what is an appropriate exposure margin for something like this in the OTC setting.

Here, we clearly have a fairly substantial exposure margin. If we were to see other products come along the pike that had perhaps different exposure margins, does anyone have a feel for where to set that bar in the OTC setting, recognizing that that is beyond the scope of this particular product?

But since this would be the first product that's on the market that does have any kind of a teratogenicity signal, if this were to be approved, it kind of opens the door and gives -- oh, I'm told that we are not allowed to discuss that. Okay.

So we did not screen for a general topic, but if anyone does wish to opine on safety margins in general.

DR. ROUMIE: Dr. Katz?

DR. KATZ: Ken Katz. Just to speak about this product, I think the safety margin is important, but in my view, the safety profile here

is much more than the margin of safety. It also reflects the pharmacovigilance and the decades of experience and millions of prescriptions that have been written for this product.

DR. ROUMIE: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. I don't have specific numbers, but I think one thing that's good to be mindful of is perhaps the smaller the sample size, the larger I would want that safety margin to be, especially when you have a sample size that's 25, 30 people.

DR. ROUMIE: Dr. Bigby.

DR. BIGBY: Michael Bigby. This is not addressing that question, but I think that there was unanimity about not putting in any warning about breastfeeding. I mean, there was some disagreement about the warning about pregnancy. But I didn't hear anybody at the table say that we should keep the warning about breastfeeding because there is really no reason to have that.

DR. ROUMIE: Dr. Pruchnicki.

DR. PRUCHNICKI: Maria Pruchnicki. I'm

going to go back to the safety question just a little bit and bring up my earlier point that I'm worried that skin sensitivity, that there are certain behaviors that users need to follow to ensure that they aren't having untoward adverse effects and particularly the sun sensitivity; especially when we're approving or considering a product that is going to be used by teenagers who may or may not consult anyone in using this.

I can expect as a mom that maybe the first time I'm going to know that my daughter is using a product like this, that she's able to buy on her own, could be when we do have this severe sunburn, when we do have a situation where she's not maybe treated her skin appropriately in using the product, and thinking about the implications of that, so maybe not the severity of something like a teratogenic effect during a pregnancy, but certainly a very significant health situation with a youngster who might be very uninformed and not able to make decisions well on their own.

So I think that's something to consider as

well that we really have not talked about in this meeting.

DR. ROUMIE: Dr. Gudas?

DR. GUDAS: Lorraine Gudas. I wanted to bring up one other point that hasn't been discussed. So the reason I feel that the -- I don't know if you call it warning but the statement about seeing a health professional if you're pregnant, I think it should stay in there. While I feel pretty comfortable about the safety of this product, I think it is important -- we don't know with adolescents what other drugs they might be taking, and we also don't know if this product could become dangerous in conjunction with other drugs that a person could be taking.

So I think that the pregnancy -- not the nursing, but the pregnancy statement, see a health professional is worth keeping in for that reason, too, so that then the adolescent can be monitored for other kinds of -- just to be asked what other drugs are you on, what other things are going on in your life when you're pregnant.

DR. ROUMIE: Do you know, from the FDA's standpoint, whether or not adapalene gel is over-the-counter in any other country?

DR. MICHELE: The sponsor has noted that it's available in Russia in our briefing package.

DR. ROUMIE: Yes.

DR. SULTAN: Marla Sultan. I saw that note about it being available in Russia. I was wondering if there was any specific data about Russia available on the use of the drug.

DR. ROUMIE: Can the sponsor answer that question?

DR. MARSH: Howard Marsh. I'm the vice president of medical affairs at Galderma. The product has been available as a nonprescription product in Russia for many years. We believe the exposure in terms of number of patients that have been exposed to the product is about 500,000.

had a relatively small number of adverse events reported in Russia. The safety profile in the OTC in Russia is very similar to the safety profile that we've seen in the prescription market

all over the world. So there's been no safety concerns since the product's been available in Russia without a prescription.

DR. SULTAN: Hi. Marla Sultan. Just to follow up on that, is there any specific information about pregnancy or live births in Russia?

DR. MARSH: Sean Griffin, can you answer that question, please?

MR. GRIFFIN: Absolutely.

Good afternoon. I'm Sean Griffin, director of regulatory affairs. So yes, if I could get slide 1 on screen, please.

This is the statement that appears in the nonprescription label in Russia, and essentially it states that it's not recommended for use during pregnancy. It may be used during breastfeeding and to avoid contact effects on the child, Differin should not be applied to the skin of the breast, so similar to a lot of the discussion today.

DR. ROUMIE: Thank you.

Are there any other comments, discussion?

(No response.)

DR. ROUMIE: Okay. So again, we will be using an electronic voting system for the meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you had entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all questions have been answered and discussed.

The question at hand is the sponsor proposes over-the-counter use of adapalene gel 0.1 percent

for the treatment of acne in consumers age 12 and older. Does that totality of the data support the use of this product OTC? If yes, do you have additional comments or recommendations for labeling? If not, what further data, if any, should be obtained to support such use?

(Vote taken.)

DR. CHOI: For the record, we have 16 yes, zero no, and zero abstention.

DR. ROUMIE: Dr. Engle. Please state your reasons for your vote.

DR. ENGLE: Jan Engle. Yes, I agreed with what we discussed. I think if the changes to the labeling are made that we collectively just had a conversation about, I'm very comfortable with this being OTC.

DR. ROUMIE: If you can also make a comment on if any further data should be obtained to support such use. Sorry, I'm putting you on the spot.

DR. ENGLE: The only question that came up for me in my head was other uses of the product

because when they did the actual use study, the flier actually said if you have acne, come in. So I'm not sure that it captured people who would use if off label. I'm not saying there's necessarily a huge issue with that, but we don't really know based on the data. So that's something I'd be interested in is a more generic approach.

I'm not really sure how you would do that, but something that says what the product is versus if you have acne because that sort of self-selected people that specifically were concerned about acne.

DR. ROUMIE: Dr. Gudas.

DR. GUDAS: Lorraine Gudas. I voted yes, again, for all the -- I stated some points in the discussion, and I agree with the general discussion.

I'll just make the point again that I do think there should be some statement left in about if you're pregnant, to go see a physician or healthcare provider mainly for the point I made at the very end about just you don't know what other drugs, what other things a teenager might be -- or

woman might be taking, and I think that's important for the healthcare provider to provide counseling. But other than that, I think I'm in favor of this going forward.

DR. ROUMIE: Dr. Katz?

DR. KATZ: Ken Katz. I voted yes. I think the risk-benefit profile is very favorable and appropriate for OTC or nonprescription product. My comments on labeling were to limit the use to acne and take out the blemishes and remove the warnings on pregnancy and breastfeeding. And I don't think any additional data are needed.

DR. ROUMIE: Dr. Bigby.

DR. BIGBY: Michael Bigby, I voted yes, and I think I've already said everything I have to say.

DR. PISARIK: Paul Pisarik, and I voted yes, too, for all the reasons that people have mentioned already.

One other thing that I would have on the Drug Facts label that's in the prescription but not in the OTC setting, is for uses. In the prescription setting, it says, "Helps prevent new

acne pimples and acne blemishes from forming." I'm a stitch-in-time-saves-nine type of person, and if people start using this and they stop when their blemishes go away and they come back again, they're going to be on a seesaw of using the medicine and not using it, using it, not using it.

But if they use it on a regular basis, it might keep the acne from coming on, and I think it'd be a little better for the patient and for the company that more medication would be used.

DR. ROUMIE: Christianne Roumie. I voted yes, but with multiple caveats. So I actually liked the labeling that was in the Russian over-the-counter version, which uncoupled pregnancy from breastfeeding and really stated not to be used during pregnancy.

I also believe that labeling changes that limit the total duration of use, given that there is currently no long-term data on the use of the medication. Also as previously discussed, cleaning up some of the adverse effect reporting as well as the directions for patients. And I think I'll stop

there.

Dr. Scialli.

DR. SCIALLI: Tony Scialli. I voted yes. With respect to labeling, breastfeeding clearly has to come out. I would take pregnancy out. I would not send patients to a healthcare professional unless I had good reason to think that that healthcare professional would be equipped with good information to guide an appropriate recommendation.

DR. HARRIS: Steve Harris, and I vote yes with no further comment.

DR. WU: Victor Wu. I vote yes as well. I agree with the comments of the committee so far. Specifically, we should clean up and make sure that the duration and the use instructions are as crystal clear as possible. I agree that we should clarify the adverse events and irritation so that folks can understand when to seek further medical professional help. And I do endorse taking off the label pregnancy and breastfeeding as well. Thank you.

DR. JONIAK-GRANT: Elizabeth Joniak-Grant.

I voted yes. I agree with the general discussion. I already discussed my suggestions for the label and leaflet, particularly pertaining to youths and mitigating irritation.

I would like to see that breastfeeding uncoupled from pregnancy. I think that there should be some consideration as was in the Russian directions about not applying it to the breasts or perhaps other body areas that babies, perhaps eyes, nose, mouth, may be coming into direct contact with. I think that's something that should be considered.

MS. BERNSTEIN: This is Cheryl Bernstein. I voted yes also. I double agree with your comments. I thought that was very clear about where not to put it on where the baby would be in contact. So I am in agreement with putting information on to give people a clearer idea of how to use the product and what to avoid in terms of contact with the baby. I agree with that. And I agree with the general statements that everybody made.

DR. D'AGOSTINO: Ralph D'Agostino. I voted

yes. I think the pregnancy should stay. The breastfeeding I think should go out. There is a switch -- when you have a switch from Rx to OTC, I think one has to be aware that there may be a whole new population that is going to start taking this, and I think there should be some mechanism for following up with adverse events and things of that nature. But I think that's hopefully pretty standard as you make these switches.

DR. PRUCHNICKI: Maria Pruchnicki. I voted yes. I think the safety profile of this drug with all of the information provided to us certainly makes it a very compelling yes. I don't think anyone here on the committee is in doubt of that.

One point that I want to bring up, the question for vote asks if the totality of data supports the use of the product. And although I think the sponsor did a very nice job of providing a good bit of data, what they didn't provide to us maybe was enough consumer information or consumer data regarding how they would use this product, particularly pregnant women regarding some of the

pregnancy questions and others. And because this drug is safe, because we have a lot of data encouraging us that the margin of safety is large, I think we felt okay about that, about voting regardless of that little data or the lack of data.

I'm not sure that that's a good precedent for others to follow. If the FDA is requesting more information, I personally would like to see that information. So I do think we in terms of the process or in terms of the totality of data, in other situations would need more to be able to make that assessment.

It's a little bit, I think, like having to fill out the tax form even though you're not needing to send in any money at the end of the day, you still have to go through the process. The IRS doesn't give you the buy, I don't think. So I would just state that even though in this case, it was fine because the sponsor felt like it was really safe, I would like to see the proof in the pudding.

DR. MICHAEL COHEN: Mike Cohen. I also

voted yes. One of the thoughts that I always go through as far as safety is comparing it to other products, other OTC products. And unfortunately, sometimes other OTC products are not used correctly.

I didn't get to see the packaging here. That would be a consideration. We weren't able to look at that, I guess, because maybe it doesn't exist yet. But we've had people drink gels. We had numerous patients drink it, and it relates to the way the product is packaged, so that's something that should be kept in mind.

DR. OBICAN: Sarah Obican. Also my vote is yes because I think the science that was presented here is both sound and reasonable and sufficient. It is my opinion that we should remove from the labeling regarding pregnancy, or if it does remain, to actually have somebody on the other end of the line for that patient who has significant information in regards to teratology and exposure in pregnancy that may actually help that patient appropriately and actually decrease the harm to

both the mother and the fetus.

DR. RASMUSSEN: Sonja Rasmussen. I vote yes, and I agree with exactly what Sarah just said. Thanks.

DR. ROUMIE: Are there any questions or comments?

(No response.)

DR. ROUMIE: Before we adjourn, last comments from FDA?

DR. MICHELE: Just to say thank you to the committee. We do appreciate all of your efforts on this case.

DR. ROUMIE: Dr. Sultan, as the industry representative, do you have any questions or comments?

DR. SULTAN: Marla Sultan, I have nothing more to add.

Adjournment

DR. ROUMIE: All right. We will now adjourn this meeting. Panel members, please take all personal belongings with you as the room is cleaned at the end of the meeting day. All materials left

on the table will be disposed of. Please remember to drop off your name badge at the registration table on your way out so that they may be recycled. Thank you.

(Whereupon, at 2:35 p.m., the meeting was adjourned.)