Consideration of adapalene gel 0.1% for over-the-counter use for the treatment of acne in consumers 12 years and older
Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the issue of the safety of adapalene 0.1% for over-the-counter (OTC) use for the treatment of acne in consumers 12 years of age and older to this Advisory Committee in order to gain the Committee’s insights and opinions. If approved, this will be the first drug in the class of topical retinoids available for OTC use. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.
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1 Division Director Memorandum

Date: March 13, 2016
From: Theresa M. Michele, MD
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To: Members,
Nonprescription Drugs Advisory Committee

Subject: Overview of the FDA background materials for supplemental New Drug Application (sNDA) 20380 S-10, adapalene 0.1% gel for the over the counter (OTC) use for the treatment of acne

1 INTRODUCTION

Thank you for your participation in the Nonprescription Drugs Advisory Committee (NDAC) meeting to be held on April 15, 2016. As members of the Advisory Committee (AC) you provide important expert scientific advice and recommendations to the US Food and Drug Administration (the Agency) on the regulatory decision making process related to the approval of a drug for over-the-counter (OTC) marketing in the United States. The upcoming meeting is to discuss the supplemental New Drug Application (sNDA) from Galderma Laboratories, L.P. (Galderma), seeking approval for a full prescription to OTC switch of adapalene gel 0.1% (prescription trade name Differin®) for the treatment of acne vulgaris as a once daily topical administration.

Adapalene is approved as a prescription product for the topical treatment of acne vulgaris in adults and children 12 years of age and older in a variety of different formulations, including a 0.1% solution, 0.1% gel, 0.1% cream, 0.3% gel, and 0.1% lotion. It is also available in combination with benzoyl peroxide as a topical gel for the treatment of acne in adults and children 9 years of age and older. The subject of this AC is adapalene gel 0.1% (adapalene), not any of the other formulations, although comparisons to other formulations will be provided as appropriate. The proposed OTC dosing is the same as the approved prescription dosing. If approved, this would be a first-in-class prescription to OTC switch for a topical retinoid.

The indication that the sponsor is proposing “for the treatment of acne” is consistent with other OTC products available for treatment of this condition. Galderma is also proposing “clears up
acne pimples and acne blemishes,” which would be a new indication in the OTC setting. Because there were no new efficacy data submitted as part of this application, we intend to discuss efficacy only in relation to the benefit-risk determination for the drug in the OTC setting. As such, a discussion of the exact labeled indication is beyond the scope of this meeting.

Galderma’s OTC development program for adapalene relies on the safety and efficacy established for the prescription product, since the acne indication is considered to be similar for both prescription and OTC use. To support the full switch of this product, Galderma submitted the results of a maximal use pharmacokinetic trial (MUsT). In addition, the OTC indication is supported by three consumer studies—a label comprehension study, a self-selection study focusing on pregnant and lactating women, and an actual use study. A review of safety data was submitted including clinical trial data and post-marketing data from the time of first worldwide marketing approval in 1995 through December of 2014; a more comprehensive review was provided from August 2010 to July 2014.

This memorandum provides an overview of the original sNDA submission. The content of this document and the materials prepared by the Agency contain findings and opinions based on reviews of information submitted by Galderma. These represent preliminary findings and do not represent the final position of the Agency. An important piece in our decision on this application will be the opinions and input that we receive at this AC meeting.

The materials to be discussed at this AC meeting and the opinions we are seeking are primarily related to the overall benefit to risk ratio of adapalene for the treatment of acne in the OTC setting. Factors to consider for this discussion include the potential for teratogenic effects including the safety margin, human absorption data, potential for use by pregnant women, post-marketing safety data related to pregnancy, and implications for the pediatric population. In the regulatory decision making process to determine approvability of a product, the Agency takes into consideration various other factors in addition to clinical and toxicology issues, including chemistry, manufacturing and controls of a product. These will not be the focus of this AC meeting.

This package includes the background materials for this meeting. In addition to this memorandum, the FDA background materials include reviews of the non-clinical data for adapalene, MUsT pharmacokinetic trial, post-marketing safety (clinical, pharmacovigilance epidemiology, and drug use data), and consumer studies. The approved prescription label, proposed Drug Facts Label, the proposed Consumer Information Leaflet, the proposed carton label, and a description of the drug utilization databases are also included.
2 BACKGROUND

2.1 Acne

Acne vulgaris is a common inflammatory skin disease characterized by open or closed comedones (blackheads and whiteheads) and inflammatory lesions, including papules, pustules, or nodules, particularly affecting pilosebaceous follicles of the face, chest, and upper back. Acne may have significant physical and psychological morbidity, such as permanent scarring, poor self-image, depression, and anxiety.\(^1\) Although it may affect any age group, acne occurs most frequently in teenagers, with up to 85% being affected, and may persist into adulthood.\(^2\) The prevalence of acne in adult women is about 12\%.\(^3\)

Therapy for acne consists of both topical and oral products. Although there is no standardized grading system for acne, it is generally divided into mild, moderate and severe, with therapy escalated in a step-wise fashion. Mild acne is generally treated with topical products, including benzoyl peroxide, topical retinoids, or a variety of different combinations of benzoyl peroxide, topical retinoids, and topical antibiotics. Additional oral agents are added for moderate to severe acne including oral antibiotics, oral contraceptives, spironolactone, or oral isotretinoin.\(^4\)

Topical retinoids are vitamin A derivatives that include various formulations of tretinoin, adapalene, and tazarotene. Isotretinoin is an oral retinoid. Professional guidelines recommend these agents as first line therapy for all severities of acne either alone or in combination with other topical or oral agents for more severe disease due to their comedolytic and anti-inflammatory effects.\(^5\) All retinoids are known to have teratogenic effects in animals, with tazarotene and isotretinoin known to cause birth defects in humans. Oral isotretinoin is available only with a Risk Evaluation and Mitigation Strategy (REMS) consisting of a medication guide and a pregnancy prevention program and registry.

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In the OTC setting, acne is a well-established indication. Topical acne products are marketed under the final OTC Drug Monograph for Topical Antimicrobial Products 21CFR Part 333.310 for the treatment of acne. Under this monograph, the following ingredients have been found to be Generally Recognized as Safe and Effective (GRASE) for OTC use under the conditions established in the monograph: benzoyl peroxide 2.5-10%, resorcinol 2% when combined with sulfur, resorcinol monoacetate 3% when combined with sulfur, salicylic acid 0.5-2%, sulfur 3-10%, and sulfur 3-8% when combined with resorcinol.

2.2 Relevant Regulatory History for Adapalene

Adapalene is registered worldwide in 82 countries as of July 2014, primarily as a prescription product. The 0.1% gel formulation is the most extensively prescribed, and is available in 28 countries, including the European Union, Canada, Japan, and Australia. Russia is the only country which currently permits OTC marketing of adapalene, where it is available OTC as the 0.1% gel.

Adapalene gel 0.1% was originally approved in the U.S. in 1996 as a prescription product under NDA 20380. For the OTC switch of adapalene, two major milestone meetings were held between Galderma and FDA [Division of Nonprescription Clinical Evaluation (DNCE, now Division of Nonprescription Drug Products (DNDP)) and Division of Dermatology and Dental Products (DDDP)] regarding the development program. These included a pre-IND meeting in March 2013 and a pre-NDA meeting in June 2015. In addition to these, FDA also provided written advice on several occasions regarding consumer study design. Key interactions are summarized below.

March 12, 2013: Pre-IND meeting

- Concerns raised related to potential for teratogenicity and carcinogenicity
- For label comprehension study recommended testing pregnancy warning to ensure that the warning would prevent use in pregnant women, and testing sun exposure warning
- Recommendation for self-selection study to determine if adapalene would be used by pregnant women or women looking to become pregnant
- Recommendation for pharmacokinetic study under conditions of maximal use (MUsT)
- Recommendation to provide information on reproductive counseling practices by health care professionals for the prescription product

January 6, 2014: Type C Written Response Only meeting
• Recommendation for self-selection study to determine if adapalene would be used by pregnant women and if adapalene would be discontinued by women who became pregnant while using the product
• Recommendation for actual use study to evaluate off-label use and amount applied; also recommended evaluating self-selection related to pregnancy as part of the actual use study
• Recommendation for a pharmacokinetic study under conditions of maximal use (MUst); may not extrapolate data from one adapalene formulation to another
• Discussed design of MUst; recommendation to include an adequate number of adolescent subjects aged 12 to 17 years

June 30, 2014: Written feedback provided on MUst

July 10, 2014: Galderma submitted IND 116,864

October 22, 2014: Advice letter regarding actual use study
• Recommendation to address self-selection during pregnancy, off-label use (misuse), application amount, and duration of use in actual use study

June 10, 2015: Pre-NDA meeting
• Recommendation to address impact of OTC availability on reproductive risks to women of child-bearing potential
• Recommendation to address potential for off-label use
• Recommendation to evaluate self-selection related to use in pregnancy

3 NON-CLINICAL INFORMATION
No new non-clinical data were submitted with this sNDA. A comprehensive non-clinical program for adapalene was conducted in support of the prescription approval. While non-clinical issues are not typically discussed in an AC meeting, this package will review pertinent findings necessary for discussion of the benefit risk profile of the product in the OTC setting.

3.1 Teratogens and Teratogenic Potential
A teratogen is a drug, chemical, or exposure that has the capacity under certain conditions to produce abnormal development in an embryo or fetus. Whether a drug is considered a teratogen depends on several factors, including the physical and chemical nature of the drug (e.g., whether

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the drug crosses the placenta); the fetal exposure resulting from the maternal dose as well as the duration, frequency, and route of administration of that dose; maternal and fetal metabolic integrity; and gestational timing of fetal exposure. A teratogen generally increases the rate of specific malformations above the background rate for that malformation when the embryo or fetus is exposed to the drug at specific times during gestation.\(^7\) These factors are evaluated along with other available relevant information. The evidence must be biologically plausible when determining whether a drug or exposure is a human teratogen.

The first trimester of pregnancy is considered a sensitive time for the embryo and developing fetus, as it is the time of many key developmental processes of organogenesis. Exposure to a teratogen during the first trimester of pregnancy may result in spontaneous abortion (i.e., miscarriage) or major structural congenital malformation (e.g., orofacial cleft, neural tube defect, heart defect).\(^8\) Exposure to a teratogen during the late first trimester, second trimester, and/or third trimester may also lead to abnormal organ differentiation, growth and function.

Major congenital malformations are defined as those that are life-threatening, require treatment or major surgery, present significant disability, or have significant cosmetic impact. In the United States, the estimated annual rate of major congenital malformations is approximately 2-4% of live births.\(^9,10,11\) The etiologies of most congenital malformations are unknown. However, maternal medical conditions, such as diabetes and hypertension, contribute to the development of some congenital malformations.\(^12\)


Chemically-induced congenital malformations, including those associated with drug products, probably account for less than 1% of all congenital malformations, but are important because they are potentially preventable.\textsuperscript{13} Prenatal exposures to drugs or other chemicals can also lead to damage that impacts the normal development of function. For example, developmental neurotoxic effects may cause changes in brain structure and chemistry (i.e., neurotransmitter signaling) which produce long-lasting effects on the developing brain. Studies in humans and animals have documented impaired intellectual function and various behavioral abnormalities that resulted from prenatal exposure to drugs.\textsuperscript{14} Drugs are evaluated for their teratogenic potential during the drug development process in a series of animal reproductive and developmental toxicity studies. By design, these studies cover all aspects of reproduction.\textsuperscript{15} Typically, one of the studies performed is the embryofetal toxicity study that assesses the potential for teratogenicity. This study consists of multiple dose groups that are administered the study drug during the period of organogenesis (implantation through palate closure). The data from these dose groups are compared to data from an internal control group of animals. Usually, three doses are studied and selected to provide exposures that, at the low dose, at or near the exposure of the anticipated human therapeutic range and at the high dose, are an exposure sufficient to elicit some maternal toxicity in the pregnant female animal. This provides a dose response that allows for an evaluation of teratogenic risk (potential) for the drug. Based on an integrated review of data that includes the reproductive and developmental toxicity data, the general toxicity data, and available pharmacokinetic data, a drug may be determined to have teratogenic potential in humans.

For drugs with known teratogenic potential based on animal data, the anticipated level of risk may be quantified using a safety margin calculation. A margin of safety is a calculation that takes the highest animal no observed adverse effect level and estimates a maximum safe level of exposure for humans. One caveat is that animal studies do not always predict effects in humans, and the actual threshold for an effect in humans may be different (higher or lower) than the species tested. The human sensitivity to a drug is often unknown, as is the case with adapalene.


\textsuperscript{15} See ICH SS for a complete discussion of the reproductive and developmental studies.
3.2 Developmental and Reproductive Toxicity Data

Reproductive and developmental toxicity studies were conducted in rats and rabbits via both the oral and topical route. When given orally, adapalene is teratogenic in both rats and rabbits at doses of 25 mg/kg or greater. Findings in the rat include cleft palate, microphthalmia, encephalocele and skeletal abnormalities. Findings in the rabbit include umbilical hernia, exophthalmos, and kidney and skeletal abnormalities. No teratogenic effect was seen in rats and rabbits at an oral dose of 5.0 mg/kg/day of adapalene. When given topically, adapalene did not induce malformations, but there were increases in supernumerary ribs in both species and delayed ossification in rabbits. A dermal No-Adverse-Effect-Level (NOAEL) of 36 and 72mg/m²/day was established in rat and rabbit embryo-toxicity studies, respectively.

These findings are generally consistent with the known adverse reproductive effects of retinoids, although adapalene is generally believed to be a less potent teratogen than other drugs in this class due to a lower binding capacity for some retinoid receptors. Using the highest observed dermal absorption from the human MUsT conducted for this OTC switch application, the margin of safety for teratogenic effects of adapalene is estimated to be approximately 70 times for rats and 357 times for rabbits. Because this value was calculated using the highest blood levels observed under maximal use conditions rather than average values, the safety margin represents a conservative estimate. Whether this safety margin represents an appropriate risk in light of the benefits of adapalene for the treatment of acne in the OTC setting, we leave to your discussion.

3.3 Other Pertinent Non-Clinical Data

Adapalene did not demonstrate genotoxicity or clastogenic effects from in vitro or in vivo testing. The carcinogenicity of adapalene was tested in a rat oral study and a mouse dermal study. The rat oral study demonstrated an increased incidence of benign and malignant pheochromocytomas, with a safety margin of approximately 7.5 times the human dose based on a body surface area comparison, assuming 100% systemic absorption as a conservative estimate. This finding is also observed with other retinoids in rodent studies. However, given the differences between rat and human adrenal glands, the findings are not considered to represent a risk in humans. The mouse dermal carcinogenicity study demonstrated no drug-related neoplastic tumors.

4 PRODUCT AND PHARMACOLOGY INFORMATION

Adapalene is a retinoid-like compound that modulates cellular differentiation, keratinization, and inflammatory processes, all of which represent important features in the pathology of acne. Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene may normalize the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. Excretion is primarily by the biliary route.
To support OTC use, Galderma conducted a multiple-dose pharmacokinetic study under maximal use conditions to evaluate absorption through the skin in an adolescent and adult population. Although PK data were provided as part of the original application, pharmacokinetics for adapalene 0.1% gel were assessed over a limited body surface area and were not assessed in adolescents. Given the wide exposure expected with OTC availability and the need to establish a clear safety margin for potential teratogenic effects observed in animal studies in order to guide the benefit-risk determination for adapalene, FDA recommended a MUsT consistent with current guidance for acne products.\textsuperscript{16,17} A MUsT is designed to capture the effect of maximal use on absorption into the blood with standard pharmacokinetic assessments (e.g., $C_{\text{max}}$, $T_{\text{max}}$, area under the curve, half-life, clearance, and volume of distribution).

Study RD.06.SRE.18254 was a multi-center, open-label study to assess the systemic exposure to adapalene 0.1% topical gel in adolescents and adults with moderate to severe acne under maximal use conditions over 4 weeks. Twenty-four subjects including 18 adolescents (10 males and 8 females, 13-17 years of age) and 6 adult subjects (3 males and 3 females) were treated with adapalene daily for 29 days, applied as a thin layer to the face, shoulders, upper chest and upper back. Three 24-hour PK profiles were performed on Day 1, Day 15, and Day 29. Adapalene plasma concentrations were determined by HPLC coupled with tandem mass-spectrometry, providing a limit of quantification (LOQ) of the assay of 0.02 ng/mL.

All 24 subjects completed the trial. The mean daily medication usage was 1.95 g (range 1.21 to 2.92 g), with a mean percent treated body surface area of 9.2% (range 6.8% to 13.0%). By Day 29, adapalene plasma concentrations were quantifiable in all subjects, and steady state appears to have been achieved by Day 15. The highest individual human exposure was 2.9 ng·h/mL expressed as AUC$_{0-24h}$ by one subject (a 16-year-old male) at Day 24, with a mean value of 0.83 ng·h/mL. In order to provide the most conservative safety margin calculation, the highest individual human exposure (2.9 ng·h/mL) was used for the calculation rather than the mean value.

\textsuperscript{16} See the draft guidance for industry \textit{Acne Vulgaris: Developing Drugs for Treatment}. When final, this guidance will represent the FDA’s current thinking on this topic.

5 CLINICAL AND STATISTICAL EFFICACY

No new efficacy data were submitted for this sNDA. The efficacy of adapalene for the treatment of acne has been previously established in the prescription setting. Since the acne indication is similar between OTC and prescription use, efficacy will be summarized only briefly here.

A total of five controlled clinical trials were conducted with adapalene gel 0.1% in subjects with mild to moderate acne vulgaris, two of which were vehicle-controlled. The remaining three trials included Retin-A (topical tretinoin) as an active control. One of the vehicle-controlled trials also included an active control arm with Retin-A. Primary assessments were at 12 weeks, and included an assessment of non-inflammatory lesions, inflammatory lesions, and/or a global grade. One placebo-controlled trial demonstrated a statistically significant benefit over vehicle for both inflammatory and non-inflammatory lesions, while the other placebo-controlled trial demonstrated a numerical improvement over vehicle. The three active-controlled trials were also generally supportive of a favorable benefit-risk ratio, with the totality of the data supporting approval.

6 SAFETY FINDINGS

The safety profile of adapalene is well-characterized, including a safety database of 5414 subjects exposed to adapalene gel (0.1% and 0.3%) in clinical trials and 20 years of marketing history in the United States and worldwide. The prescription label for adapalene states that some adverse effects such as erythema, scaling, dryness, pruritus, and burning will occur in 10-40% of patients. Pruritus or burning immediately after application also occurs in approximately 20% of patients. Adapalene is contraindicated in individuals who are hypersensitive to adapalene. There is also a warning not to use on sunburned skin, cuts, abrasions, or eczematous skin and to minimize sun exposure while using the product.

6.1 Safety in Clinical Trials

Adverse events seen in the MUsT and the 6-week actual use trial performed for this application were consistent with the product label for adapalene. There were no serious AEs in either trial. In the MUsT, 33% of subjects reported one or more AEs; the most frequently reported events were skin irritation, pruritus, and headache. In the actual use trial, 50% of patients reported one or more AEs; the most frequently reported events were headache, dry skin, and erythema. There were 4 pregnancies during the trial, one of which was terminated for personal reasons. There is no information on outcomes of the other 3 pregnancies. Of note, none of these women spoke to their doctors about adapalene use as instructed on the product label.

6.2 Consumer Studies

Galderma conducted three consumer studies in support of the OTC use of adapalene: a label comprehension study, a self-selection study in pregnant and lactating women, and an actual use study.
**Label comprehension study**

A label comprehension study in adults and adolescents ages 12 to 70 years (Study 100544) was conducted in 586 respondents divided into a general population cohort and an augmented low literacy cohort. Overall, 515 were of normal literacy and 130 (22%) were low literacy. Adolescents aged 12 to 17 years were well represented, with 282 adolescents and 304 adults, although there was limited enrollment of adults in the 18-24 year old age group [N=33 (5.6%)]. The primary objective was to test the instruction “Use once daily,” and the secondary objective was to test “Do not use on damaged skin.” Unfortunately, warnings regarding use in pregnancy and sun avoidance (other than tanning bed use) were not tested, which substantially limits the utility of the study.

Respondents did reasonably well for both objectives, although subjects with low literacy did worse on the primary objective. For “Use once daily,” 96.5% of normal literacy [Lower Bound of the Confidence Interval (LCB) 94.4%] and 86.9% of low literacy (LCB 79.9%) subjects answered correctly. For “Do not use on damaged skin,” 97.4% (LCB 95.5%) of normal literacy and 99.2% (LCB 95.8%) of low literacy subjects answered correctly. In general, the adolescent population had a comparable level of understanding of these objectives as adults.

**Self-selection study**

Study 103439 was a single visit, targeted self-selection study in 293 pregnant and breastfeeding women ages 13 to 54. In the general population cohort of 242 women, against which the a priori target threshold was measured, 91 (37%) were pregnant, the remainder were breastfeeding. An additional low literacy cohort was recruited, with 51 (17%) subjects. The vast majority of subjects were adults, with only 2 adolescent subjects. The primary objective of the study was to assess whether pregnant or breastfeeding women with acne would ask a health care professional prior to use of adapalene, as per the directions on the Drug Facts Label (DFL). Women were recruited for the study at 25 different malls across the country based on the appearance of being visibly pregnant or accompanied by an infant under 18 months of age. Trimester of pregnancy was not recorded; however, given the method of recruitment it is likely that most were in later stages of pregnancy. The majority of women were breastfeeding; there were only 80 subjects (27%) who were pregnant and not breastfeeding, with an additional 11 subjects who were both pregnant and breastfeeding.

Overall, women generally did poorly when asked if they would consult a doctor prior to use of adapalene. In the pregnant only group, 70% of women (LCB 58.7%) said they would ask a doctor before use. Rationales given by subjects for incorrect self-selection suggest that women believe that topical products cannot hurt a developing infant and that OTC products are safe to use during pregnancy. In addition, a subgroup (N=15) stated that they did not see the warning on the label.
Actual use study

Study 13049 (JUNO) was a 6-week, open label, multi-center trial in 947 adolescent and adult subjects with self-reported acne. All women were tested for pregnancy before being allowed to purchase study drug; subjects were also pregnancy tested at completion of the 6-week study period. Enrollment included 203 (21.4%) adolescents aged 12 to 17 years, and approximately two thirds of the subjects were female. The population included 125 (13.2%) subjects of low literacy.

Of subjects who chose to purchase the product based on reading the product label but were excluded from participation after screening, 7 subjects were younger than 12 years of age. Of these, 5 were within 12 months of their 12th birthday. Nine subjects reported they did not have acne; most of these wanted to prevent acne or unclog pores. None wished to use the product for non-acne skin conditions. Fourteen subjects chose to use the product while pregnant or breast feeding. Similar to the self-selection study, the stated reasons for this suggest that women perceive a low risk with topical products, lack of perception of the seriousness of the warning, or not seeing the warning.

The primary objectives of the trial were to evaluate the frequency of use and to determine off-label use for non-acne conditions. Because subjects were excluded at screening if they did not self-report acne, off-label use was based on reported use for another skin condition in addition to acne. A secondary objective was to evaluate whether subjects used the product inappropriately near eyes, mouth, or lips, or used it on damaged skin.

Overall, 89.1% (LCB 87.1%) of subjects used the product once daily. Results in subjects with low literacy and in adolescents were generally comparable. Most subjects using the product more than once daily reported reapplying after showering or washing, or used the product twice daily per routine or in an attempt to obtain greater or faster benefit. Almost all subjects in the trial [99.3%, (LCB 98.5%)] used the product for acne and not for other skin conditions. Subjects also did very well using the product on the correct body area [97.5% (LCB 96.2%)].

6.3 Post-Marketing Data

As part of this application, post-marketing safety data related to carcinogenic and teratogenic potential in humans for adapalene were submitted and reviewed from the following sources: the sponsor’s pharmacovigilance database, FDA’s Adverse Event Reporting System (FAERS), the World Health Organization (WHO Vigibase), and the published literature. All of these sources are subject to a number of limitations, primarily due to issues inherent in spontaneous reporting. In addition to data submitted by the sponsor, FDA conducted separate reviews of the FAERS data, post-marketing drug use, and epidemiology data available in the literature, with a focus on pregnancy outcomes. Key issues are reviewed here; additional primary discipline reviews are provided in the background package.
**Galderma pharmacovigilance database**

The sponsor’s pharmacovigilance database includes data from first worldwide market introduction in 1992 through August 2013. During this time period, the sponsor estimates that over 40 million patients have been prescribed adapalene gel (0.1% and 0.3%) and there were 4,176 adverse events. Of these, only 21 cases (0.5%) included serious adverse events (SAEs). Over 70% of the adverse events were skin-related, with the most commonly reported events being dry skin and erythema. There were also 15 cases of local hypersensitivity confirmed by patch testing.

A specific review investigating pregnancy cases with all adapalene formulations (including the combination adapalene/benzoyl peroxide products) revealed 276 cases as of September 2014. Of these, adverse outcomes were reported in 17, with varied outcomes that the applicant concluded did not describe patterns consistent with retinoid exposure or there were insufficient data to draw conclusions.

**FDA Adverse Event Database (FAERS)**

FDA review of the FAERS database from time of approval (May 1996) through November 2015 revealed 127 serious, unduplicated cases associated with adapalene gel (65 cases with 0.1% and 23 with 0.3%). No approved strength was reported for the remaining cases. With one exception, all of the adverse events reported in these cases were consistent with those listed in the label for prescription adapalene. The one exception involves a cases of hepatitis associated with off-label use of adapalene over a large body surface area for Darier disease. Hepatitis is a known adverse event with oral retinoids.

FDA review of the FAERS database from April 2006 through November 2015 identified a total of 18 cases of abnormal pregnancy outcomes in women who used adapalene. These cases included reports of miscarriage (9), congenital anomalies (5), abortion (2), preterm birth (1), and hemorrhage (1). The five cases of congenital anomalies included two isolated limb malformations, one VACTERL Syndrome (vertebral anomalies, anal atresia, cardiovascular anomalies, tracheoesophageal fistula, esophageal atresia, renal and/or radial anomalies, and limb defects), one 2q37 deletion, and one case of Dandy Walker Syndrome (brain malformation). Of these, only Dandy Walker Syndrome has any known association with retinoids, but the overall range of malformations of the fetus were inconsistent with retinoid exposure. Given the background rate of birth defects (~4%) in the general population, it is typically not possible to establish causality for an isolated birth defect (e.g., heart defect) from a drug exposure based on spontaneous adverse event reports alone. FDA also identified one additional case from the literature that described adapalene-associated anophthalmia and agenesis of the optic chiasma in the fetus of a mother using adapalene 0.3% gel from the month before pregnancy until 13 weeks gestational age. The authors did not report whether the mother was using concomitant
medications. The five cases of congenital anomaly associated with adapalene in FAERS appear to be isolated malformations and do not support a causal association between adapalene and these events.

**Literature review**

FDA performed a literature review for epidemiological studies related to adverse events from topical retinoids. Fifteen publications were reviewed in detail, including five related to pregnancy outcomes, two with other serious adverse events, and eight on local skin reactions. The most common adverse effects of topical retinoids including adapalene reported in the literature are related to local skin irritation, including erythema, dryness, scaling, pruritus, burning, and post inflammatory hyperpigmentation. The majority of these adverse events are generally transient and mild to moderate in severity. The studies related to pregnancy outcomes did not assess adapalene-related risk specifically.

**Drug use data**

FDA analysis of United States outpatient retail prescription data for single-ingredient adapalene products demonstrated that the overall number of prescriptions has decreased by 16% from 1.2 million prescriptions dispensed in the 12-month period ending in November 2011 to approximately 974,000 prescriptions in the 12-month period ending in November 2015. Of these, patients 12-45 years old accounted for 91% of patients, followed by patients aged 46 years and older at 5-6% of total patients; patients 0-11 years old accounted for 3% of the total patients. Among females 12-45 years of age, 99% of the use was for a diagnosis of acne according to office-based physician surveys.

### 7 BENEFIT RISK ASSESSMENT

The efficacy of adapalene for the treatment of acne has been established for prescription use. It is expected that the product would have similar efficacy in the OTC setting, as the acne indication is similar and acne is a well-established OTC indication. Further, professional guidelines recommend topical retinoids, such as adapalene, as first line-therapy for all severities of acne either alone or in combination with other topical or oral agents for more severe disease.

The primary consideration for this application is whether the benefits of OTC availability outweigh any potential risk for teratogenic effects on the developing fetus. It is apparent from

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the data provided by the sponsor that if adapalene were available OTC, the product would be used by pregnant women due to the low perceived risk of OTC products in general and topical products in particular. The sponsor did not investigate whether strengthening the proposed Drug Facts Label or other labeling options for adapalene OTC would change this consumer perception.

Toxicology data clearly demonstrate a teratogenic signal with oral adapalene, with findings consistent with other drugs in the retinoid class. Congenital anomalies seen in animal studies include cleft palate, microphthalmia, encephalocele, umbilical hernia, exophthalmos, kidney abnormalities, and skeletal abnormalities. However, using data from the human pharmacokinetic study performed using maximal topical administration according to the product label gives a safety margin of at least 70-fold for these effects. Although the margin could potentially be somewhat lower if consumers were to use the product over more than 10% of the body surface area or apply it multiple times per day, data from the actual use study suggest that consumers are likely to apply the product appropriately.

One additional caveat to the calculation of safety margins, particularly for teratogenic effects such as these, is that the actual threshold for an effect in humans is unknown and may be different than in the species tested. One way to evaluate this caveat is to look at available human data on pregnancy outcomes. Post-marketing safety data from 20 years of prescription use demonstrate few cases of abnormal pregnancy outcomes with no clear-cut cases of teratogenic effects due to adapalene. Given the high likelihood of significant underreporting, the absence of reports does not necessarily translate to an absence of events, but nonetheless does provide some information regarding the level of potential risk.

Input from the AC panel is needed to help determine the appropriate benefit-risk equation to apply to adapalene in the OTC setting, assessing whether the safety margin related to teratogenicity and the post-marketing safety database provide adequate reassurance that the product may be used safely across a broad population of consumers, including pregnant women, without the intervention of a health care professional.

8 SUMMARY
The purpose of the NDAC meeting is to discuss the adequacy of the data submitted by Galderma to support approval for adapalene 0.1% gel for OTC use for the treatment of acne in adults and children 12 years of age and older. The major issue for discussion is the overall benefit to risk ratio of adapalene for the treatment of acne in the OTC setting. Factors to consider for this discussion include the potential for teratogenic effects including the safety margin, human absorption data, potential for use by pregnant women, post-marketing safety data related to pregnancy, and implications for the pediatric population. Points for discussion, which we ask you to keep in mind during the AC presentations, are provided in this briefing document.
2 Topics for Advisory Committee Discussion

1. Discuss the safety profile of adapalene gel 0.1% in the over-the-counter (OTC) setting. In your discussion, please consider the following:
   a. *use by females of reproductive potential (i.e., teratogenic risk),*
   b. *pediatric use (i.e., use by adolescents and/or younger children), and*
   c. *potential for misuse (e.g., excessive use or use for non-acne conditions) and the consequences of such use.*

2. Has the safety of adapalene gel 0.1% for OTC use for the treatment of acne been adequately demonstrated?
   a. *If not, what additional data, if any, should be obtained to demonstrate safety in the OTC setting?*

3. Discuss the proposed Drug Facts Label and Consumer Information Leaflet.
   a. *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.*

4. The sponsor proposes OTC use of adapalene gel 0.1% 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?
   a. *If yes, do you have additional comments or recommendations for labeling?*
   b. *If not, what further data, if any, should be obtained to support such use?*
3 Review Findings

3.1 Overview of Regulatory Background

3.1.1 Prescription Regulatory Background

The Agency initially approved adapalene as a new molecular entity in 1996, under the trade name Differin®. Five topical dosage forms containing adapalene at two different strengths (0.1% and 0.3%) are currently being marketed in the United States. Adapalene is approved as a single agent for the topical treatment of acne vulgaris in patients 12 years of age and older as:

- 0.1% solution (NDA 20-338), approved 5/31/1996, now discontinued
- 0.1% gel (NDA 20-380), approved 5/31/1996
- 0.1% cream (NDA 20-748) approved 5/26/2000
- 0.3% gel (NDA 21-753), approved 6/19/2007
- 0.1% lotion (NDA 22-502) approved 3/7/2010

Adapalene 0.1% is also approved in combination with benzoyl peroxide 2.5% as a topical gel (Epiduo®, NDA 22-320). It was approved on 12/8/2008 for the topical treatment of acne vulgaris in patients 12 years of age and older and the indication was revised to include patients 9 years of age and older in February 2013, based on clinical studies conducted in this pediatric population.

3.1.2 OTC Regulatory Background

Galderma (the Applicant) and FDA have interacted on several occasions to discuss the development of adapalene for OTC marketing status. Those interactions are summarized below.

On March 12, 2013, FDA held an early development meeting with the Applicant to discuss the overall development. FDA advised the Applicant to conduct several studies including label comprehension, self-selection, actual use and a pharmacokinetics assessment under maximal usage conditions, also known as Maximal Usage Trial (MUsT).

FDA specifically requested that warnings against use in pregnancy and for sun avoidance be tested in label comprehension. FDA expressed concerns about teratogenic and carcinogenic potential as identified in animal studies and postmarketing experience for retinoid drug products. As part of the overall consumer behavior program, we advised the Applicant, in their overall consumer behavior studies program, to assess decisions by pregnant women, women seeking to become pregnant and women of child-bearing age to use or potentially use the product. We requested information on usage and counseling of these women in clinical practice. We wished to understand if healthcare providers, for example, co-prescribe oral contraceptive drugs, advise women to stop use if they become pregnant, or avoid prescribing if a patient is pregnant. We advised the Applicant to primarily test adherence to the approved indication, thus identifying extent of possible off-label use for wrinkles or other skin lesions, for example. We recommended they address concerns about overuse, by quantity used, body site, frequency of use
and duration of use. FDA also requested data from postmarketing experience from various sources [e.g., the Applicant’s safety database, safety databases from FDA and World Health Organization (WHO), scientific literature] with particular focus on teratogenicity, fetotoxicity and carcinogenicity.

On January 6, June 30, and October 22, 2014, FDA offered further advice on studies. The Applicant was encouraged to enroll enough women of reproductive age, including adolescents, and pregnant women so that conclusions from consumer behavior studies could be interpreted adequately.

We advised that off-label usage would need to be a primary objective in the actual use trial (AUT). Therefore, we recommended the protocol incorporate an ‘all-comers’ recruitment approach, versus targeting only acne patients, and adequate documentation procedures on the extent of application, frequency, duration and reasons for use. We recommended recruiting a cohort of eczema patients as well.

At a pre-NDA meeting, the Applicant was tasked with providing a very strong, well-supported rationale that the product could be used safely and properly in the over-the-counter (OTC) setting. FDA recommended that some additional key safety language be translated from the prescription (Rx) label to the OTC label. Finally, FDA noted that the acceptability of mitigations in the endpoint assessments would be a review issue.

### 3.2 Overview of Nonclinical Data

Comprehensive nonclinical characterization of the pharmacological and toxicological effects of adapalene was conducted during the development of currently marketed adapalene products. The characterization included studies of pharmacology, pharmacokinetics/toxicokinetics, safety pharmacology, general toxicity, genetic toxicity, reproductive and developmental toxicity, and carcinogenicity of adapalene. These studies have been previously reviewed by FDA in the relevant applications. Below is a brief summary of the toxicity profile of adapalene.

1. **Genetic toxicity**: Adapalene did not exhibit any genotoxic or clastogenic effects in both in vitro (Ames test, Chinese hamster ovary cell assay, and mouse lymphoma TK assay) and in vivo (mouse micronucleus test) studies.
2. **Carcinogenicity of adapalene** was evaluated in rats and mice.
   a. In a rat oral carcinogenicity study, increased incidence of benign and malignant pheochromocytomas in the adrenal medullas was observed in high dose male rats at 1.5 mg/kg/day. This dose is about 7.5 times higher than the human dose based on a body surface area comparison. Pheochromocytoma is a finding that has been associated with other retinoid compounds in rodents. There are morphological and biochemical differences between the adrenal glands of the rat and man. The incidence of pheochromocytoma in humans is very low (0.005 to 0.09%). As such, the relevance of these animal findings to humans is unknown, but the findings are not considered to represent a risk in humans.
   b. In a mouse dermal carcinogenicity study, no drug-related neoplastic lesions were observed at topical doses of 1.3, 3.9, and 12 mg/m².
(3) Reproductive and developmental toxicity studies showed that adapalene is teratogenic in animals dependent on route of administration.

a. When administered orally at doses ≥ 25 mg/kg, adapalene has been shown to be teratogenic in rats and rabbits. Findings include cleft palate, microphthalmia, encephalocele and skeletal abnormalities in the rat and umbilical hernia, exophthalmos and kidney and skeletal abnormalities in the rabbit. No teratogenic effect was seen in rats and rabbits at an oral dose of 5.0 mg/kg/day of adapalene.

b. When administered topically in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day, adapalene showed no evidence of teratogenicity, but there were variations in fetuses: increases in supernumerary ribs in both species and delayed ossification in rabbits. A dermal No-Adverse-Effect-Level (NOAEL) of 36 and 72 mg/m^2/day was established in rat and rabbit embryo-toxicity studies, respectively.

One major concern regarding the OTC switch of adapalene products is the teratogenicity associated with the retinoid class of drugs. Although the risk of teratogenicity due to topical exposure in humans is unknown, concerns about the teratogenicity of adapalene appear to be lower than that of other retinoids.

Retinoids exert their pharmacological activities by binding to specific retinoic acid nuclear receptors (e.g., RAR α, β, γ) and cellular retinoid binding proteins (CRABP I and CRABP II). Compared to other retinoids, adapalene has much lower binding capacity to RARα. It does not bind to CRABII at all. The impact of these differences in binding are not entirely clear although could result in potentially different biological activities.

One caveat is that, animal studies do not always predict effects in humans and the human sensitivity to this drug is unknown. With certain retinoid compounds, the human appears to be a sensitive species for drug-related teratogenicity. To date, there are no adequate and well-controlled studies in pregnant woman. The level of exposure required to cause teratogenicity in humans is unclear.

**Margin of safety calculation for adapalene-induced teratogenicity:** A margin of safety is a calculation that takes the highest animal no observed adverse effect level and estimates a maximum safe level of exposure for humans. Based on the newly-conducted human maximal use trial with 0.1% adapalene gel, the highest individual human exposure was 2.9 ng·h/mL expressed as AUC0-24h value. In 10-day animal dermal toxicology studies with 6 mg/kg/day adapalene gel, the mean AUC0-24h values of 204 and 1036 ng·h/mL were achieved in rats and rabbits, respectively. When comparing the exposures of animals at the NOAEL for teratogenicity to human maximum use exposure, the margin of safety for adapalene is estimated to be approximately 70 times (204/2.9) for rats and 357 times (1036/2.9) for rabbits.

In summary, adapalene, as well as other retinoids, can induce teratogenicity in animals at sufficiently high systemic doses (oral doses from 25 mg/kg/day). However, the margin of safety for adapalene-induced teratogenic effects is estimated to be over 70-fold. Based on this
calculated safety margin, the risk for adapalene-induced teratogenicity appears to be relatively low from the nonclinical perspective.

3.3 Overview of Postmarketing Experience

3.3.1 Drug Utilization Data

Proprietary drug utilization databases available to the Agency were used to conduct this analysis. Detailed descriptions of the databases used are included in the Section 4.5, Appendix 5. The National Prescription Audit (NPA™) database was used to obtain the nationally estimated number of dispensed prescriptions for single-ingredient adapalene from U.S. outpatient retail pharmacies, from December 2010 through November 2015, annually. The number of dispensed prescriptions stratified by the top 10 prescribing specialties for the study period were also examined.

The IMS, Vector One®: Total Patient Tracker database was used to provide the nationally estimated number of unique patients, stratified by patient age (0-11, 12-45, and 46 years and older) and sex, who received a dispensed prescription for single-ingredient adapalene from U.S. outpatient retail pharmacies, from December 2010 through November 2015, annually.

The Encuity Research, LLC, Treatment Answers™ with Pain Panel database was used to examine diagnoses associated with the use of single-ingredient adapalene from a U.S. office-based physician surveys database, from December 2010 to November 2015, cumulative. Mentions of drugs in association with a diagnosis during a patient visit to an office-based physician were captured from this database.

Drug Utilization Results: U.S. Outpatient Retail Pharmacy Utilization Data

U.S. Dispensed Prescriptions

Figure 1 displays the nationally estimated number of dispensed prescriptions for single-ingredient adapalene and combination adapalene/benzoyl peroxide products from U.S. outpatient retail pharmacies from December 2010 through November 2015, annually. The total number of dispensed prescriptions increased from approximately 2.0 million prescriptions in the 12-month period ending in November 2011 to 2.2 million prescriptions in the 12-month period ending in November 2015, accounting for a 7% increase overall.

Single-ingredient adapalene products decreased by 16% from 1.2 million prescriptions dispensed in the 12-month period ending in November 2011 to approximately 974,000 prescriptions dispensed in the 12-month period ending in November 2015. Conversely, combination adapalene/benzoyl peroxide products increased by 37% from approximately 867,000 prescriptions dispensed in the 12-month period ending in November 2011 to 1.2 million prescriptions dispensed in the 12-month period ending in November 2015.
Figure 1: Nationally estimated number of dispensed prescriptions for all adapalene products, stratified by combination and single-ingredient products, from U.S. outpatient retail pharmacies, December 2010 - November 2015


**U.S. Dispensed Prescriptions by Prescribing Specialty**

Of the estimated 5.4 million single-ingredient adapalene prescriptions dispensed from December 2010 to November 2015, dermatologists accounted for 49%, followed by physician assistants at 15% and pediatricians at 10% of the total dispensed prescriptions.

**U.S. Patients by Age and Sex**

Figure 2 shows the nationally estimated number of patients who received a dispensed prescription for single-ingredient adapalene products from U.S. outpatient retail pharmacies. The total number of patients decreased by 16% from approximately 673,000 patients in the 12-month period ending in November 2011 to 563,000 patients in the 12-month period ending in November 2015.

Patients 12-45 years old accounted for 91% of patients, followed by patients aged 46 years and older at 5-6% of total patients; patients 0-11 years old accounted for 3% of total patients who received single-ingredient adapalene prescription dispensed during the entire review period.
The largest proportion of use for single-ingredient adapalene products was among females 12-45 years old. Of the 12-45 years old age group, female patients accounted for approximately 74% of patients using single-ingredient adapalene products in the 12-month period ending in November 2015.

**Diagnosis Data by Patient Sex and Age**

We also examined the top diagnosis code associated with a drug use mention\(^{20}\) for single-ingredient adapalene products based on U.S. office-based physician surveys from December 2010 to November 2015. The majority of drug use mentions were associated with patients 12-45 years old. Among females 12-45 years old, “Acne, Not Elsewhere Classified (NEC)” (ICD-9 code 706.1) was the top diagnosis code associated with the use of single-ingredient adapalene containing products at 99% of drug use mentions, followed by “Rosacea” (ICD-9 code 695.3) at 1% of drug use mentions. Of note, the number of drug use mentions for single-ingredient adapalene as reported by office-based physician surveys for use by pediatric patients 0-11 years old and adults 46 years or older were below the acceptable count allowable to provide a reliable estimate of national use.

\(^{20}\) The term "drug uses" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.
3.3.2 Pharmacovigilance Data

The Applicant addressed the potential toxicity of adapalene on reproduction and fetal development with focus on teratogenicity and fetotoxicity. It also addressed carcinogenicity and analyzed postmarketing reports of skin-related toxicity and drug interactions. The Applicant estimates that over 40 million patients have been prescribed adapalene gel at strengths of 0.1% or 0.3% since its international birthdate in 1992. From 1998 through 2014, 4,176 postmarketing safety reports have been submitted by users (~235 reports/year), with skin-related adverse events (AEs) accounting for 70% of those reports. Only 21 reports (0.5%) were serious. In the entire postmarketing period (from 1992 through July 1, 2014), the Applicant received 239 reports of pregnancy exposure to adapalene. The Applicant also provided an assessment of the teratogenicity risk including a review of the characteristics of the adapalene molecule, its retinoid-like properties, a summary of retinoid-related teratogenicity with animal toxicity data and a review of the safety margin based on systemic exposure.

The Applicant commissioned a review of their pharmacovigilance data to investigate pregnancy cases²¹. Dr. E. Gnansia, an expert in medical genetics and teratology, highlighted 276 pregnancy cases found in the Applicant’s database through September 2014 and including use of both adapalene single ingredient products and Epiduo® (adapalene/benzoyl peroxide). The reported outcomes were varied and none appeared to describe patterns of anomalies consistent with retinoid syndrome or contained adequate information to support any significant association with the use of adapalene (Table 1). Because postmarketing data relies on spontaneous reporting, the author notes that it is unlikely that the number of pregnancy exposures reflects the actual number of exposures. In addition, there is likely bias towards untoward outcomes since normal pregnancies are unlikely to be reported to great extent. The circumstances resulting in “lost to follow-up” outcomes are not elucidated further.

Table 1: Pregnancy Outcomes from Galderma’s Pharmacovigilance Database

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Postmarketing surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing at time of report</td>
<td>27</td>
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<tr>
<td>Lost to follow-up</td>
<td>126</td>
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<tr>
<td>Healthy baby</td>
<td>83</td>
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<tr>
<td>Elective termination</td>
<td>7</td>
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<tr>
<td>Miscarriage</td>
<td>16</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>276</td>
</tr>
</tbody>
</table>

Source: Applicant’s submission, Footnote 21, Table 1.

The Applicant searched for cases using the following Standardized MedDRA Queries (SMQ): Normal Pregnancy Conditions and Outcomes, Pregnancy and Neonatal Topics, Neonatal

²¹ Gnansia E, 2015, Review of Exposures to Topical Adapalene Gel, Cream, Lotion During Pregnancy.
Exposures via Breast Milk, Pregnancy and Neonatal Topics, and Pregnancy-related Hepatic Disorders. The Applicant identified eight cases that contained information on pregnancies following exposure to adapalene. One case was of an adult female who appeared to have a history of congenital anomalies (micrognathia, kidney malformation) rather than a neonate following maternal exposure. The second case described adapalene as one of 44 drugs mentioned where the suspect drug, associated with autism, craniosynostosis and strabismus in a newborn, was sertraline. A third case described various cardiac anomalies and adapalene and sertraline were included in a list of 11 medications. It was unclear to the Applicant whether the subject was a neonate following maternal exposure. Three cases reported exposures only, and two reported only fetal growth restriction and induced abortion, without further details.

The Applicant noted that postmarketing reports of skin-related AEs mirrored the findings from the JUNO trial (see Section 3.4.5 Actual Use Study) and the well-established safety profile of topical retinoids and other topical products indicated for treatment of acne. Regarding photosensitivity, the Applicant points to only a single case of sun-exposure sensitization in all clinical trials conducted to support the original approval. In postmarketing data, the most frequently reported skin-related AEs are “dry skin” and “erythema” (25-30% of AEs). In 15 total cases of overdose, or use of adapalene more than once daily, users generally reported local skin effects, mostly erythema, exfoliation and worsening acne. The Applicant notes that in a few cases (N=15), dermatitis was confirmed as local hypersensitivity by positive patch testing to adapalene or the final formulation. Another small number of cases (N=48) suggested some degree of possible photosensitivity. These included skin irritations or burns following sun exposure. The events were generally local, mild and, where reported, resolved on their own. Nine cases reported concomitant use of tetracyclines, common inducers of photosensitivity. Presumably due to limited data in the reports, it is unclear in several of the cases describing sun exposure what role adapalene played in potentially increasing sensitivity. There were no reports of adapalene and photosensitization found in the scientific literature. The Applicant conducted a search of possible drug interactions between adapalene and acne drug products containing sulfur, resorcinol or salicylic acid, since caution, in adapalene Rx labeling, is recommended with concomitant use. The Applicant identified 50 cases of exposure. As expected, cases included frequently reported events such as dry skin, irritation and erythema. None were serious and no AEs raised any safety issues.

The Applicant submitted a Periodic Safety Update Report covering the period from August 2013 through July 2014. In it, 215 medically-confirmed AEs were reported following over two million presumed patient exposures. Of these, two were serious (congenital anomalies – clubfeet and miscarriage) and the most frequent AEs were skin-related. The Applicant notes that 71 serious, unlisted AE reports have been collected since marketing of adapalene began (over 40 million patient users). Skin-related AEs are most expected compared to other events that may be seen following use of oral retinoids since systemic exposure following topical application is minimal (see Section 3.4.1 Maximal Usage Study). There were 34 reports of off-label use with the most frequent number of reports for use to “brighten,” “lighten,” or “whiten” the skin (N=8). Three of these cases included skin irritation as an AE. There were no apparent safety concerns, raised over the reporting period, that prompted the Applicant to revise the Core Data Sheet or the labeling of marketed adapalene 0.1% products.
As part of a pediatric-focused safety review of Differin® lotion 0.1% presented at the May 7, 2012 Pediatric Advisory Committee (PAC) meeting, the Office of Surveillance and Epidemiology (OSE) identified three serious, non-fatal unlabeled AEs of intracranial hypertension (IH) in pediatric patients from the date of approval of the first Differin® formulation (gel; May 31, 1996) through January 3, 2012. While these three cases did not lead to modification of adapalene labeling at the time, they did prompt FDA to conduct a review of IH associated with the use of topical retinoids in all ages. A follow-up review by OSE identified ten cases reported to FDA’s Adverse Events Reporting System (FAERS) database and three literature cases of IH reported in association with two of the topical retinoids, tretinoin and adapalene. The FAERS cases lacked information about height, weight, cerebrospinal fluid pressure, medical history, concomitant drug use, and age. The literature cases were confounded by concomitant tetracycline derivative use, possible excess dietary vitamin A intake, or patient weight greater than 20% above ideal body weight, all of which are associated with IH. Based on the limited number of cases, most of which were poorly documented, OSE concluded that there was insufficient evidence to suggest an association between the topical retinoids and IH.

**FDA Adverse Events Reporting System Review**

A review of FAERS was performed to characterize abnormal pregnancy outcomes that had been observed during FDA monitoring of adapalene safety reports and adapalene use on large BSA.

**CASE DEFINITION FOR ABNORMAL PREGNANCY OUTCOMES**

CDER standards for assessment of embryofetal toxicity studies were outlined in ICH CICH5A 1993. This Guidance includes study design elements (dosing, group size, species selection, etc.). In 2005, the Agency outlined a human specific guidance in *FDA Reviewer Guidance on Evaluating the Risks of Drug Exposure in Human Pregnancies*. This Guidance document recommends epidemiological studies as the best method of evaluating a causal relationship between a drug exposure during pregnancy and congenital anomalies. Discussion regarding the utility of “Case Reports” and “Epidemiologic Studies” in the assessment of teratogenic risk with drug exposure during pregnancy in this FDA Guidance is provided below.

Case Reports: Although an individual case report, by itself, can never prove causality, a series of similar reports of a distinct abnormality or group of abnormalities can establish a strong association or signal the need for further research. Most signals based on case reports will need to be further investigated using other pharmacoepidemiologic studies.

Epidemiologic Studies: Formal epidemiology studies provide the best means of evaluating whether a gestational exposure adversely affects the developing infant. Epidemiology studies can identify associations between a given drug exposure and abnormalities in the newborn, and they can quantify the strength of such associations.
As noted in the Guidance and the literature - including the overview of drug-induced teratogenicity provided by Motherisk Program\(^\text{22}\), most proven human teratogens result in a spectrum - or syndrome – of adverse effects and not one isolated birth defect. Thus, with interest in a new signal for teratogenic risk with adapalene or any other agent, any review of spontaneous reports would include an assessment for a known or unique clustering of birth defects.

Importantly, a review of spontaneous reports can only provide an assessment of risk, not apparent safety. An analysis of spontaneous AE reports cannot establish that a drug is free of risk for any specific event, including teratogenicity. Spontaneous case reporting systems are designed for the detection of rare, serious, and unknown risks of drugs. Spontaneous reports have limited utility in assessment of events that are common in the recipient population background. In addition, spontaneous reports have several well-known limitations including under-reporting, reporting biases, and variable case information.

Given the estimated background rate of birth defects (2-4%) in the general population, it is typically not possible to establish causality for an isolated birth defect (e.g., heart defect) from a drug exposure using spontaneous adverse event reports alone. However, as noted above, the identification of cases with drug exposure and 1) a rare birth defect or, 2) a cluster of birth defects, or 3) birth defects consistent with a previously described syndrome, could establish a strong potential association or signal the need for further research. In an effort to assess the apparent risk of teratogenicity of adapalene, spontaneous AE reports (also called MedWatch reports) submitted to the Agency in association with adapalene were reviewed.

Spontaneous AE reports submitted to the Agency are collated and accessed via the FAERS database. Since adapalene is a retinoid and a specific retinoid embryopathy has been described\(^\text{23}\), reports were reviewed not only for a rare event in the newborn population but also the clinical features of retinoid embryopathy: craniofacial anomalies (microtia or anotia, accessory parietal sutures, narrow sloping forehead, micrognathia, flat nasal bridge, cleft lip and palate, and ocular hypertelorism), cardiac defects (primarily conotruncal malformations), abnormalities in thymic development, and alterations in central nervous system development.

**Inclusion Criteria**

- Temporal relationship in a patient using single ingredient topical adapalene
- Use in a female exposed to adapalene while pregnant regardless of duration of exposure


• Any abnormal pregnancy outcome [reports of pregnancy with one or more of the following outcomes: spontaneous abortion, induced abortion, premature or post-term birth (regardless of fetal outcome, congenital anomaly, peri-natal or post-perinatal complication), stillbirth (intrauterine death), or ectopic pregnancy] reported regardless of cause or potential confounding factors

**Exclusion Criteria**

• None

**FAERS SEARCH STRATEGY FOR ADAPALENE AND ABNORMAL PREGNANCY OUTCOMES**

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<td></td>
<td>• Congenital, familial, and genetic disorders</td>
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<td></td>
<td>• Pregnancy, puerperium and prenatal conditions</td>
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<td></td>
<td>SMQ (standardized MedDRA Queries)</td>
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<tr>
<td></td>
<td>• Congenital and neonatal arrhythmias</td>
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<td></td>
<td>• Congenital biliary disorders</td>
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<td></td>
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<td>• Congenital, familial, neonatal, and genetic disorders of the liver</td>
</tr>
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<td></td>
<td>• Foetal disorders</td>
</tr>
</tbody>
</table>

* See Appendix 6 for a description of the FAERS database.
†reports of adapalene were searched from 04/01/2006 - November 17, 2015 as an update from two previous reviews by FDA (Brinker 2004, Pitts 2006)
FAERS SEARCH STRATEGY FOR ALL ADAPALENE EVENTS

In addition to the search strategy above, the FAERS database was searched to identify all serious cases of adapalene associated AEs.

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<th>FAERS Search Strategy*</th>
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<tr>
<td>Product Terms</td>
</tr>
<tr>
<td>Outcome</td>
</tr>
</tbody>
</table>

* See Appendix 6 for a description of the FAERS database.

PHARMACOVIGILANCE LITERATURE SEARCH STRATEGY

The medical literature was searched with the strategy described below to identify any additional case reports not reported in FAERS.

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RESULTS

FAERS CASE SELECTION

ADAPALENE AND ABNORMAL PREGNANCY OUTCOMES (n=18)

The OSE Division of Pharmacovigilance (DPV) identified 18 cases of adapalene associated abnormal pregnancy outcomes in FAERS reported from May 2006 through November 17, 2015. These cases included reports of miscarriage (9), congenital anomalies (5), abortion (2), preterm birth (1), and hemorrhage (1). The five cases of congenital anomalies are described in detail below.

Congenital Anomalies (n=5)

Case# 7014857 Switzerland 2009
A mother used adapalene, azelaic acid, and erythromycin 50 mg for 7 days during the first trimester for acne. Her fetus was diagnosed with an anomaly of the left hand with brachydactyly, oligodactyly, and overlapping fingers. She had a negative history of smoking and drinking. No additional information was provided.

Reviewer’s comments: Isolated limb malformations are a well-described birth defect. Azelaic acid and erythromycin are considered FDA pregnancy category B.

Case# 10084260 Netherlands 2014
A female patient with a history of high blood pressure, one previous abortion, previous healthy child, and tobacco user gave birth to a baby with club foot on both sides. Amniocentesis did not show any chromosomal defects. Concomitant medications included folic acid, ferrous sulphate, and adapalene 0.1% gel for acne during the first 14 weeks of pregnancy. No additional information was provided.

Reviewer’s comments: Isolated limb malformations are a well-described birth defect. Additionally, club foot is associated with tobacco use during pregnancy.

Case# 6636807 France 2008
A pregnant woman (age unknown) was exposed to adapalene, doxycycline, and topical erythromycin when it was discovered the fetus had VACTERL Syndrome (vertebral anomalies, anal atresia, cardiovascular anomalies, tracheoesophageal fistula, esophageal atresia, renal and/or radial anomalies, and limb defects). She was also exposed to the following products in a “professional context”: acetone, methanol, l-propanol, benzene, dichlorethylene, and vinyl chloride. As a result, she had an abortion. No additional information was provided.

Reviewer’s comments: The case lacks specific information regarding time and duration of exposure to the numerous medications and products. VACTERL Syndrome is not known to be associated with retinoid exposure and may be genetic. Based on the information provided, the contribution of adapalene to VACTERL Syndrome cannot be determined.
Case#7059072 US 2009
A 28-year-old female with a history of penicillin and seasonal allergies, gestational diabetes, and five previous pregnancies, one child, had a fetus with a genetic defect, 2q37 deletion. The pregnancy was terminated. She used adapalene gel 0.3% for 21 weeks into her pregnancy.

Reviewer’s comments: The genetic defect 2q37 deletion case is not known to be associated with retinoid exposure.

Case#7703133 AUT 2010
A 34-year-old female was pregnant and a 22-week organ screen revealed malformation of the aorta and brain. Magnetic resonance imaging (MRI) and magnetic resonance tomography were performed and malformations of the fetus were identified as Dandy Walker (DW) Syndrome. As a result, she had an abortion. She used adapalene 0.1% QOD for mucinosis follicularis seven weeks into her pregnancy. No other concomitant medications were reported.

Reviewer’s comments: Dandy Walker Malformation is a congenital human brain malformation involving the cerebellum and the fluid-filled spaces around it. The etiology of DW malformation is poorly understood but is presumed to be multifactorial, with genetic forms accounting for the majority of patients. DW has not been associated with a teratogenic treatment in the literature, except for one article which describes two newborns with multiple malformations including a DW malformation with oral isotretinoin. The malformation is isolated and a very rare manifestation of retinoid embryopathy. The only congenital anomaly case identified in a prior safety review conducted in 2006 described a DW malformation. It was concluded that there were some cardiac and brain anomalies; however, the overall range of anomalies identified were inconsistent with those known to be associated with retinoid exposure.

Reviewer Comments on Severity and Frequency of Adverse Events

From the time of approval (May 31, 1996) through November 17, 2015, there were 237 serious reports associated with adapalene in FAERS. A review of the 237 reports identified 127 serious, unduplicated cases associated with adapalene. The majority of the reports describe use with the 0.1% strength (n=65), followed by 0.3% (n=23), 0.01% (n=1), 0.2%, (n=1), and 0.05% (n=1) (one patient used two strengths consecutively). When known (n=102), the majority of indications were for acne (n=96). Three cases reported more than one indication. Off-label indications (n=9) were reported as keratosis follicularis (1), pigmentation disorder (1), skin rejuvenation (1), therapeutic skin care (1), skin discoloration (1), whitening freckles (1), hyperpigmentation (1), follicular mucinosis (1), or skin aging (1). In the hyperpigmentation case, the patient reported using adapalene “rarely” on the upper part of the body. No new safety signals were identified. The one case of adapalene for off-label use on a large BSA is described below.

Off-label use on a large body surface area (n=1)

Case#9067293, France 2015, Literature Report (Lerisson, 2014)\textsuperscript{25}  
A 55-year-old female with Darier disease and no other medical history or other treatment was treated with acitretin (oral retinoid) long term. In May 2010, her liver tests were normal. In March 2011 (10 months later), she developed an acute mixed pattern hepatitis characterized by ALT 107 IU/L, AST 67 IU/L, alkaline phosphatase 319 IU/L, gamma-glutamyltransferase 81 IU/L, and bilirubin 7.1 micromol/L. The hepatitis was attributed to acitretin because it was her sole medication, other causes of hepatitis were excluded (negative tests for recent viral hepatitis A, B, C, E and auto-antibodies), an ultrasound showed normal liver and biliary tract, and she had a positive dechallenge. Approximately 10 months later, she was treated with adapalene 0.1% cream daily for the relapse of Darier disease. Overall, 15 tubes of 30 g adapalene were applied on approximately 15% of her body surface from January 2012 to September 2012 (8 months). She developed asthenia, nausea, and dyspepsia. The clinical exam was normal and there was no jaundice or other manifestations of liver disease. Liver tests were: ALT 403 IU/L, AST 205 IU/L, alkaline phosphatase 203 IU/L, gamma-glutamyltransferase 105 IU/L, serum bilirubin 11.8 micromol/L. Serum albumin was 34.5 g/l, gammaglobulin 14 g/l, INR 1.00, prothrombin time 100% of normal value and blood cell counts were normal. Tests were negative for recent infections (hepatitis virus A, B, C, E, cytomegalovirus, Epstein-Barr virus and Herpes simplex virus, antibodies to mitochondria, smooth muscle and nuclei, transglutaminase). Serum levels of iron, copper and ceruloplasmin were normal. Ultrasonographic and MRI tests showed normal liver and biliary tract patterns. A liver biopsy was performed because liver tests improved slowly. Histological examination revealed a normal architecture without fibrosis, inflammation, steatosis, hepatosiderosis, cholangitis, or endothelial lesion. Her liver tests progressively improved upon discontinuation of adapalene and returned to near normal seven months later.

Reviewer’s comment: Hepatitis is an unlabeled event for adapalene, but labeled for oral retinoids. This case supports a probable association between adapalene and hepatitis based on temporality, clinical presentation, laboratory values, positive dechallenge, and absence of other causes of hepatitis. The use of a large dose of adapalene on her lesions may have resulted in an increased absorption of adapalene resulting in toxicity. Studies enroll patients who have approximately 5-6% BSA involvement whereas this patient had 15% involvement.

PHARMACOVIGILANCE LITERATURE SEARCH

Literature report (Autret 1997)
A female treated with adapalene gel 0.3 mg daily from the month before pregnancy until 13 weeks gestational age. At 22 weeks, a scan showed fetal growth retardation and anophthalmia. Agenesis of optic chiasma was found after a medical abortion.

Reviewer’s comment: The article did not report whether or not the mother was using concomitant medications. The authors stated that microphthalmia had been observed among 81 rabbit fetuses exposed to very high doses of topical adapalene, and that tretinoin is known to cause microphthalmia and anophthalmia in mice. Additionally, they concluded that this was the first published observation of a severe malformation in a fetus of a woman who used adapalene gel in early pregnancy. This case was described in a prior OSE-DPV review.

FAERS ANALYSIS

Adapalene associated abnormal pregnancy outcomes

OSE-DPV identified 18 serious cases of adapalene-associated abnormal pregnancy outcomes. These cases included miscarriage (9), congenital anomalies (5), abortion (2), preterm birth (1), and hemorrhage (1). Three of the five congenital anomaly cases reported one isolated anomaly [limb malformation, club feet, and Dandy Walker (DW) malformation]. Additionally, there was one case of a congenital anomaly in the literature which described adapalene-associated anophthalmia and agenesis of the optic chiasma. This case was described in a previous OSE-DPV review (Brinker 2004). Of the five congenital anomaly cases, three fetuses were aborted. The five cases of congenital anomaly associated with adapalene (FAERS-5) appear to be isolated malformations. Based on the previous review by OSE-DPV of six cases and the current review of five additional cases, OSE does not find reasonable evidence to support a causal association between adapalene and these events. There was one possible case of adapalene associated hepatitis in a patient using adapalene off-label for Darier disease which was published in the literature and reported to FAERS. However, there was an insufficient basis for concluding that adapalene caused the episode of hepatitis, therefore FDA did not identify any new adapalene-associated safety signals. FDA will continue routine monitoring of FAERS and the medical literature for additional cases of hepatitis and unlabeled events associated with adapalene.


CONCLUSION

Spontaneous reporting of MedWatch reports in the FAERS database is one of the available tools that can be used to detect serious, rare AEs. However, due to limitations such as under-reporting, lack of clinical data in individual cases, and reporting biases, FAERS is not the ideal database to detect adverse events that have a latency period of expression, such as congenital anomalies. A focused pregnancy registry may be a better tool to assess congenital anomalies.

Since the approximately 20 years since adapalene has been approved and in the context of the wide utilization of adapalene-containing products, there is little information in FAERS and the medical literature that support a causal association between adapalene and retinoid embryopathy. Additionally, OSE- DPV did not identify any new safety signals associated with adapalene at this time and will continue routine surveillance.

3.3.3 Literature and Epidemiological Data

PHARMACOEPIDEMIOLOGY EVALUATION METHODS

A PubMed search for epidemiological studies was conducted using a combination of generic drug names of topical retinoids and subheadings for drug adverse effects, and restricted to articles with full text and published in English. The search algorithm is described in the table below:

<table>
<thead>
<tr>
<th>Literature Search Strategy for Epidemiological Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Refresh Date</td>
</tr>
<tr>
<td>Database</td>
</tr>
<tr>
<td>Years included in search</td>
</tr>
<tr>
<td>Types of studies retrieved for further review</td>
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</tbody>
</table>

Initially, 1,120 publications were retrieved from PubMed. After reading the abstracts and then full texts when necessary and excluding the studies that are reviews, case reports or case series, and those without the interest of exposures (topical retinoids) or outcomes (adverse effects), the FDA reviewer identified five studies on pregnancy outcomes, two studies on other serious...
adverse effects, and eight on local skin adverse effects. In total, 15 studies were included in this review.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design</th>
<th>Exposure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregnancy Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jick (1993)</td>
<td>retrospective cohort</td>
<td>topical tretinoin</td>
<td>RR=0.7 (0.2-2.3)</td>
</tr>
<tr>
<td>Shapiro (1997)</td>
<td>prospective cohort</td>
<td>topical tretinoin</td>
<td>1. No significance difference in the rates of live births, miscarriages, elective terminations of pregnancy, and major malformations. 2. Mean birthweight which was borderline modestly but statistically lower in cases exposed women ($P=0.05$).</td>
</tr>
<tr>
<td>Loureiro (2005)</td>
<td>prospective cohort</td>
<td>topical tretinoin</td>
<td>No difference</td>
</tr>
<tr>
<td>Kaplan (2015)</td>
<td>meta-analysis</td>
<td>topical tretinoin</td>
<td>major congenital malformations: OR=1.22 (0.65-2.29) spontaneous abortions: OR=1.02 (0.64-1.63) stillbirth: OR=2.06 (0.43-9.86) elective termination: OR=1.89 (0.52-6.80) low birthweight: OR=1.01 (0.31-3.27) prematurity: OR=0.69 (0.39-1.23)</td>
</tr>
<tr>
<td>Panchaud (2012)</td>
<td>prospective cohort</td>
<td>topical retinoids</td>
<td>spontaneous abortion: OR=1.5 (0.8-2.7) minor birth defects: OR=1.3 (0.4-2.7) major birth defects OR=1.8 (0.6-5.4) elective termination: $OR=3.4 (1.5-7.8)$</td>
</tr>
<tr>
<td><strong>Other Serious Adverse Effects</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Alhusayen (2013)</td>
<td>retrospective cohort</td>
<td><em>oral isotretinoin</em> <em>topical acne medication (benzoyl peroxide, erythromycin, clindamycin, retinoic acid, or adapalene)</em></td>
<td>1. oral isotretinoin and IBD: all patients: RR=1.14 (0.99-1.24) patients aged 12-19: $RR=1.39 (1.03-1.87)$ 2. topical acne medication and IBD RR=1.11 (0.99-1.24) 3. topical acne medication and Ulcerative Colitis $RR=1.19 (1.00-1.42)$</td>
</tr>
<tr>
<td>Weinstock (2009)</td>
<td>RCT</td>
<td>topical tretinoin</td>
<td>$OR=1.54 (1.10-2.15)$</td>
</tr>
<tr>
<td><strong>Cutaneous Adverse Effects</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tirado-Sanchez (2013)</td>
<td>RCT</td>
<td>adapalene 0.1% and 0.3%, tretinoin 0.05%</td>
<td>adapalene 0.1% vs adapalene 0.3% and tretinoin 0.05%: skin irritation (dermatitis): $P&lt;0.05$ scaling: $P&lt;0.05$ dry skin: $P&lt;0.05$ pruritus: $P&lt;0.05$ burning: $P&lt;0.05$ post-inflammatory hyperpigmentation: $P=0.001$ total adverse events: $P&lt;0.05$ patients reporting adverse events: $P&lt;0.05$</td>
</tr>
<tr>
<td>Feldman (2013)</td>
<td>RCT</td>
<td>tazarotene 0.1%</td>
<td>Only application-site skin irritation and dryness were reported by &gt;5% of participants in active treatment groups in both studies</td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Design</td>
<td>Treatment</td>
<td>Findings</td>
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<tr>
<td>Goh (2009)</td>
<td>RCT</td>
<td>adapalene 0.1%, tretinoin 0.025%</td>
<td>The irritation potential of adapalene gel 0.1% was significantly lower than that of tretinoin gel 0.025% in all tolerability assessment</td>
</tr>
<tr>
<td>Kawashima (2008)</td>
<td>RCT</td>
<td>adapalene 0.1%</td>
<td>Well tolerated. Adverse events were mostly mild-to-moderate and transient in nature compared with gel vehicle.</td>
</tr>
<tr>
<td>Ioannides (2002)</td>
<td>RCT</td>
<td>adapalene 0.1%, isotretinoin gel 0.05%</td>
<td>adapalene 0.1% vs isotretinoin gel 0.05% at week 12: erythema 27.8% vs 41.9%, ( P&lt;0.05 ) scaling 25.0% vs 41.9%, ( P&lt;0.05 ) pruritus-burning 30.6% vs 45.2%, ( P&lt;0.05 )</td>
</tr>
<tr>
<td>Dunlap (1998)</td>
<td>RCT</td>
<td>adapalene 0.1%</td>
<td>compared to tretinoin 0.025% cream: 1. 64-68% of patients found adapalene 0.1% gel more tolerable than tretinoin 0.025% cream, ( P&lt;0.05 ) 2. 65% of patients preferred adapalene 0.1% gel, ( P=0.003 ) 3. adapalene 0.1% gel was significantly less irritating to the skin in terms of producing erythema, dryness, desquamation and burning/stinging, ( P&lt;0.02 )</td>
</tr>
<tr>
<td>Rao (2009)</td>
<td>RCT</td>
<td>microsphere adapalene 0.1%, conventional adapalene 0.1%</td>
<td>microsphere adapalene vs conventional adapalene: 1. reported side effect: 50% vs 71.3%, ( P&lt;0.05 ) 2. dryness: 7.9% vs 32.2%, ( P&lt;0.01 ) 3. erythema: 7.9% vs 25.3%, ( P&lt;0.01 )</td>
</tr>
<tr>
<td>Ellis (1998)</td>
<td>RCT</td>
<td>adapalene 0.1%, tretinoin 0.025%</td>
<td>1. No serious adverse events reported. 2. Skin reactions (burning, pruritus, scaling, dryness and erythema) were similar between adapalene and tretinoin treatment.</td>
</tr>
</tbody>
</table>

**RESULTS**

**Pregnancy Outcomes**

The first epidemiologic study investigating topical retinoid therapy and pregnancy outcomes was conducted by Jick and her colleagues in 1993\(^{28} \). Using an automated data source (Group Health Cooperative of Puget Sound, Washington, USA), the investigators compared the prevalence of major congenital disorders among the newborns born to the 212 women exposed to topical tretinoin in the first trimester of pregnancy to the prevalence among 427 age-matched unexposed controls (no adjustment for other covariates). No statistically significant increase in malformations was observed among exposed women compared to unexposed (RR=0.7, 95% CI 0.2-2.3).

Two subsequent studies also investigated the effect of topical tretinoin on pregnancy outcomes, and neither observed a positive association. Using a prospective cohort design, Shapiro et al.\(^{29}\) compared 94 first-trimester tretinoin-exposed women to 133 unexposed controls with similar maternal age, patterns of smoking, and alcohol use and reported no significant differences in the rates of live births, miscarriages, elective terminations of pregnancy, and major malformations between exposed and unexposed. However, mean birth weight was lower in exposed women compared to unexposed (3355g vs 3502g, \(P=0.05\)). Another prospective study conducted by Loureiro et al.\(^{30}\) compared pregnancy outcomes in 106 pregnant women with first-trimester exposure to tretinoin to 389 similar controls. No significant difference was reported between the two groups for spontaneous abortion (6.6% vs. 8.5%, \(P=0.53\)), major structural defects (2.2% vs. 1.2%, \(P=0.62\)), and the prevalence of one or more retinoic acid-specific minor malformations (12.9% vs. 9.9%, \(P=0.51\)).

More recently, Panchaud and colleagues prospectively studied 235 pregnant women exposed to any topical retinoid including tretinoin (n=143), isotretinoin (n=52), adapalene (n=24), retinoic acid (n=10), or their combinations and 444 controls for pregnancy outcomes from 1992 to 2006\(^{31}\). Although they observed a higher risk of spontaneous abortion (OR 1.5, 95% CI: 0.8-2.7), minor birth defects (OR 1.3, 95% CI: 0.4-3.7), and major birth defects (OR 1.8, 95% CI: 0.6-5.4) in the exposed group compared to unexposed, these increases were not statistically significant. The investigators did find a 3-fold increased risk of elective termination (OR 3.4, 95% CI: 1.5-7.8) among the exposed compared to unexposed. The authors did not adjust for any confounding variables. The authors suggest their findings are reassuring in cases of inadvertent exposure but that the use of topical retinoids during pregnancy remains questionable.

Kaplan et al. performed a meta-analysis based on the above four published studies\(^{32}\) to better understand any potential association between topical retinoids and adverse pregnancy outcomes. They did not detect significant increases in risks of major congenital malformations [OR=1.22, 95% CI 0.65–2.29], spontaneous abortions (OR=1.02, 95% CI 0.64–1.63), stillbirth (OR=2.06, 95% CI 0.43–9.86), elective termination of pregnancy (OR=1.89, 95% CI 0.52–6.80), low birth weight (OR=1.01, 95% CI, 0.31–3.27) or prematurity (OR=0.69, 95% CI 0.39–1.23). However,


the authors pointed out the inadequate statistical power and concluded that their results do not justify the use of topical retinoids during pregnancy.

**Other Serious Adverse Effects**

**Inflammatory Bowel Disease**

In a large retrospective cohort study Alhusayen et al. compared 184,824 patients ages 12-29 years treated with a topical acne medication (benzoyl peroxide, erythromycin, clindamycin, retinoic acid, or adapalene) to 1,526,946 non-exposed controls. After up to 12 years of follow-up, the authors observed a borderline statistically significant increased risk of ulcerative colitis, a type of inflammatory bowel disease (IBD), in those exposed to a topical acne medication (RR 1.19; 95% CI 1.00-1.42). While further analysis on topical retinoids specifically was unavailable, the investigators suggested a possible association between IBD and acne itself but did not rule out the possibility of topical acne medications, including retinoids, as a cause of IBD.

**All-Cause Mortality**

In 2009, Weinstock et al. reported an unexpected increased risk of all-cause mortality associated with topical tretinoin therapy, which led to the premature halt of their randomized placebo-controlled trial. The Veterans Affairs Topical Tretinoin Chemoprevention Trial (VATTC) was originally designed to determine whether topical tretinoin, 0.1% cream, prevented basal and squamous cell skin cancer. Six months before the planned 2-6 year follow-up of 1,131 U.S. veterans with an average age of 71 years, the investigators noticed a statistically significant increased risk of death after the adjustment for age, sex, smoking status, and Charlson index in those who received topical tretinoin up to twice daily applied to face and ears (OR 1.54, 95% CI 1.10-2.15) compared to placebo. This result led to the premature termination of the trial. The investigators were unable to fully explain the result but claimed a casual association is unlikely. They assert that respiratory and vascular disorders as causes of death in the trial deserve further scrutiny.

**Cutaneous Adverse Effects**

The most common adverse effects of topical retinoid therapy reported in the literature are related to local skin irritations including erythema, dryness, scaling, pruritus, burning, and post


inflammatory hyperpigmentation\textsuperscript{35}, \textsuperscript{36}, \textsuperscript{37}, \textsuperscript{38}, \textsuperscript{39}, \textsuperscript{40}. Although common and usually observed in the majority of treated patients\textsuperscript{35}, \textsuperscript{41} the local adverse effects are in general mild to moderate, and often transient\textsuperscript{35}, \textsuperscript{37}, \textsuperscript{38}, \textsuperscript{40}, \textsuperscript{42}. Among the three topical retinoid agents, adapalene is better tolerated than tretinoin and tazarotene with respect to both frequency and severity of local cutaneous adverse effects\textsuperscript{43}.

CONCLUSIONS

Findings from population-based studies of topical retinoids do not suggest an increased risk of birth defects among women exposed in early pregnancy. However, none of the reviewed studies assessed adapalene-specific risks. These pregnancy studies had small sample sizes and other methodologic limitations that prevent conclusions regarding the safety of adapalene and other

\textsuperscript{35} Tirado-Sanchez, A., Espindola, Y.S., Ponce-Olivera, R.M. & Bonifaz, A. Efficacy and safety of adapalene gel 0.1% and 0.3% and tretinoin gel 0.05% for acne vulgaris: results of a single-center, randomized, double-blinded, placebo-controlled clinical trial on Mexican patients (skin type III-IV). J Cosmet. Dermatol 12, 103-107 (2013).


\textsuperscript{37} Goh, C.L., Tang, M.B., Briantais, P., Kaoukhov, A. & Soto, P. Adapalene gel 0.1% is better tolerated than tretinoin gel 0.025% among healthy volunteers of various ethnic origins. J Dermatolog. Treat 20, 282-288 (2009).


\textsuperscript{39} Ioannides, D., Rigopoulos, D. & Katsambas, A. Topical adapalene gel 0.1% vs. isotretinoin gel 0.05% in the treatment of acne vulgaris: a randomized open-label clinical trial. Br. J Dermatol 147, 523-527 (2002).


topical retinoids. Findings of an increased risk of ulcerative colitis and all-cause mortality are difficult to interpret.

3.4 Overview of Studies to Support the Proposed OTC Switch

A consumer who uses an OTC product is making his or her own healthcare decision without a healthcare provider intermediary. Consumer studies can support OTC approval of a drug product by showing that consumers are able to understand the product label and can appropriately self-select, and self-medicate for a particular condition in an OTC environment using only the OTC drug label.

This overview will summarize the general characteristics of three types of consumer behavior studies: Label Comprehension Studies (LCS), Self-Selection Studies (SSS) and Actual Use Trials (AUT). Data from these studies provide information about how well an OTC product label can inform the nonprescription drug consumer about the drug and whether the consumer can appropriately use the information on the label. Thus, these data play a major role in the regulatory decision whether a product can be marketed without a prescription.

When a drug that has been previously available only by Rx is switched to OTC status, the healthcare provider is no longer a gatekeeper to drug access. Thus, drug labeling must communicate directly to the consumer. The consumer must understand and act appropriately based on the information available in OTC labeling.

While the general structure of the OTC drug label is codified in the Code of Federal Regulations, the text used to communicate to consumers undergoes iterative study and optimization (see Appendix 2 – Proposed Drug Facts Label for an example of a “Drug Facts” OTC label). Labeling used in LCSs, SSSs, and AUTs evolves, and the final product labeling ideally reflects the lessons learned from consumers following a careful label development program. The development program for Differin Gel was an iterative process that involved LCS, SSS and AUT. Proposed labeling, including Drug Facts, the Principal Display Panel and a Consumer Information Leaflet are included in the Appendices below.

In addition to the consumer studies described, the development program of Differin® Gel for OTC use included a MUsT. Since Differin® Gel, 0.1% is topically applied, and given the concerns regarding teratogenic effects of the retinoid class of drugs, FDA considers an important safety consideration as to whether dermal application of this product results in skin penetration and systemic exposure to the active ingredient and, if so, to what extent.

3.4.1 Maximal Usage Study

The principal barrier to cutaneous drug penetration is the multiple-layered lipid-rich stratum corneum. The passage of any drug through this layer is influenced by many factors, including the drug's physicochemical features, molecular size, formulation/vehicle properties, and the level of integrity of the skin barrier properties due to disease conditions.
Many methods for the assessment of topical or dermal in vivo bioavailability (BA) have been proposed and presented at a number of scientific forums. Most of these methods, however, focus on either a small assessment area or a limited duration of exposure. Since the mid-1990s, FDA has required sponsors to conduct a MUsT as part of the clinical pharmacology and bioavailability assessment of a topical product New Drug Application (NDA). This study is conducted in subjects with the disease of interest applied at the upper limit of surface area involvement that is studied in the phase 3 clinical trials and is proposed for labeling. That is to say, if an NDA applicant desires labeling of up to 30% BSA, then the MUsT is conducted in subjects with this same degree of body surface coverage. The study is thus designed to capture the effect of "maximal use" on absorption into the blood with standard pharmacokinetic (PK) assessments.

The duration of the MUsT should be sufficient to reach steady-state levels of absorption, i.e., the concentration of active ingredient is unchanged by further application of the product because the amount of active ingredient being absorbed is equal to the amount being eliminated by the body. For a steady-state study, the measurement of total exposure would be the area under the concentration-time curve (AUC) for plasma, serum, or blood over the length of the dosing interval at steady-state.

The PK information obtained from the MUsT can help identify potential safety concerns and help determine whether an adequate safety margin exists for an active ingredient based on toxic effects seen in animal studies. The safety margin is used to predict a safe exposure level in humans below that where toxicities were seen in animals.

Differin® Gel, 0.1% was approved in 1996 and PK assessment in the original NDA was conducted in adults. There is no PK information available in subjects 12 to 17 years of age under maximal use conditions. Hence, the Applicant conducted a maximal use PK trial (RD.06.SRE.18254) in 24 subjects 12 years of age and older with moderate to severe acne vulgaris. Differin® Gel, 0.1% was applied as a thin layer once daily for 29 days on the face, shoulders, upper chest, and upper back. PK assessment via serial plasma sampling was done on Days 1, 15 and 29. All 24 subjects (18 adolescents – 12 to 17 years old and 6 adults) completed this trial.

By Day 29, adapalene plasma concentrations were quantifiable in all 24 subjects and steady state appears to have been achieved by Day 15. The mean concentration versus time profile for adapalene systemic concentrations is shown in Figure 3 and the summary of PK parameters is shown in Table 2. The available data did not permit reliable estimation of terminal half-life ($T_{1/2}$).

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Figure 3: Mean concentration versus time profile of adapalene on Day 1, Day 15 and Day 29

Source: Applicant’s NDA submission

Table 2: Mean PK parameters on Day 1, Day 15 and Day 29

<table>
<thead>
<tr>
<th></th>
<th>C_{max} (ng/mL)</th>
<th>T_{max} (h)</th>
<th>AUC_{0-24h} (ng.h/mL)</th>
<th>AUC_{0-t} (ng.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=24, N quantifiable (%): 15 (63%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>0.033±0.015</td>
<td>14.3±5.4</td>
<td>0.57±0.14</td>
<td>0.41±0.27</td>
</tr>
<tr>
<td>CV%</td>
<td>45%</td>
<td>38%</td>
<td>25%</td>
<td>66%</td>
</tr>
<tr>
<td>Min, Max</td>
<td>-0.020, 0.066</td>
<td>8, 24</td>
<td>0.48, 0.96</td>
<td>0.15, 0.96</td>
</tr>
<tr>
<td>Median</td>
<td>0.031</td>
<td>14</td>
<td>0.52</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Day 15</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=22, N quantifiable (%): 21 (95%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>0.054±0.032</td>
<td>12.8±5.3</td>
<td>0.87±0.43</td>
<td>0.77±0.51</td>
</tr>
<tr>
<td>CV%</td>
<td>59%</td>
<td>42%</td>
<td>50%</td>
<td>67%</td>
</tr>
<tr>
<td>Min, Max</td>
<td>-0.020, 0.144</td>
<td>8, 24</td>
<td>0.48, 1.99</td>
<td>0.16, 2.00</td>
</tr>
<tr>
<td>Median</td>
<td>0.044</td>
<td>12</td>
<td>0.73</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Day 29</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=24, N quantifiable (%): 24 (100%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>0.049±0.030</td>
<td>11.9±4.5</td>
<td>0.83±0.49</td>
<td>0.85±0.86</td>
</tr>
<tr>
<td>CV%</td>
<td>62%</td>
<td>38%</td>
<td>59%</td>
<td>101%</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0.025, 0.171</td>
<td>0, 24</td>
<td>0.50, 2.90</td>
<td>0.17, 4.46</td>
</tr>
<tr>
<td>Median</td>
<td>0.042</td>
<td>12</td>
<td>0.68</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Source: Applicant’s NDA submission
The highest individual human exposure was 2.9 ng·h/mL expressed as AUC₀-₂₄h value by one subject at Day 24. This was the value utilized for the calculation of the safety margin as a conservative measure, instead of utilizing the mean AUC₀-₂₄h of 0.83 ng·h/mL (see Section 3.2 Overview of Nonclinical Data- Margin of Safety). The 70-fold safety margin represents the safety margin assuming this maximum human exposure. The summary of PK data for all approved adapalene products is provided in Table 3. The purpose of the data summarized in Table 3 is for qualitative comparison of the systemic concentrations of adapalene in the maximal use PK trial (RD.06.SRE.18254) submitted with this application and other approved products. The reader is advised that the cross-trial comparison of PK data is for qualitative purposes only due to the fact that trials have been conducted in different populations using different study designs, different formulations and different bioanalytical validation methods.

Based on the information in Table 3, qualitatively, the mean ± SD Cₘₐₓ and AUC₀-₂₄h following application of Differin® Gel, 0.1% (see PK data in Table 2) on Day 15 (0.054 ± 0.032 ng/mL and 0.87 ± 0.43 ng.h/mL, respectively) and on Day 29 (0.049 ± 0.030 ng/mL and 0.83 ± 0.49 ng.h/mL, respectively), appear to be within the systemic concentration range observed with the adapalene 0.1% strength products.
Table 3: Summary of PK data for all approved adapalene products for the treatment of acne vulgaris

<table>
<thead>
<tr>
<th>NDA # and approval date (age approved)</th>
<th>Trade Name</th>
<th>Active ingredients</th>
<th>PK data in the label</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA 020380 05/31/1996 (≥ 12 years)</td>
<td>Differin® Gel</td>
<td>Adapalene 0.1%</td>
<td>Trace amounts in the plasma (&lt; 0.25 ng/mL)</td>
</tr>
<tr>
<td>NDA 020748 05/26/2000 (≥ 12 years)</td>
<td>Differin® Cream</td>
<td>Adapalene 0.1%</td>
<td>No quantifiable conc. (LLOQ = 0.35 ng/mL)</td>
</tr>
<tr>
<td>NDA 021753 06/19/2007 (≥ 12 years)</td>
<td>Differin® Gel</td>
<td>Adapalene 0.3%</td>
<td>15/16 patients had quantifiable conc. (LLOQ = 0.1 ng/mL), mean $C_{\text{max}} = 0.55 \pm 0.46$ ng/mL and mean $\text{AUC}_{0-24} = 8.37 \pm 8.46$ ng*h/mL</td>
</tr>
<tr>
<td>NDA 022320 12/08/2008 (≥ 9 years)</td>
<td>Epiduo® Gel</td>
<td>Adapalene 0.1%/Benzoyl peroxide 2.5%</td>
<td>2/10 subjects had quantifiable conc. (LLOQ = 0.1 ng/mL) of adapalene with maximum $C_{\text{max}} = 0.21$ ng/mL and $\text{AUC}_{0-24} = 1.99$ ng*h/mL</td>
</tr>
<tr>
<td>NDA 022502 03/17/2010 (≥ 12 years)</td>
<td>Differin® Lotion</td>
<td>Adapalene 0.1%</td>
<td>2/14 adult subjects had quantifiable conc. (LLOQ = 0.1 ng/mL), ranged from 0.102 to 0.131 ng/mL. 5/14 pediatric subjects aged 12 – 17 years had quantifiable conc. LLOQ = 0.1 ng/mL, mean $C_{\text{max}} = 0.13 \pm 0.05$ ng/mL and mean $\text{AUC}_{0-24} = 3.07 \pm 1.21$ ng*h/mL.</td>
</tr>
<tr>
<td>NDA 207917 07/15/2015 (≥ 12 years)</td>
<td>Epiduo Forte® Gel</td>
<td>Adapalene 0.3%/Benzoyl peroxide 2.5%</td>
<td>16/26 subjects aged 12 to 33 years had quantifiable conc.(LLOQ = 0.1 ng/mL), mean $C_{\text{max}} = 0.16 \pm 0.08$ ng/mL and mean $\text{AUC}<em>{0-24} = 2.49 \pm 1.21$ ng*h/mL.  The most exposed subject had adapalene $C</em>{\text{max}} = 0.35$ ng/mL and $\text{AUC}_{0-24} = 6.41$ ng*h/mL.</td>
</tr>
</tbody>
</table>

NOTE: All PK data in the table above were obtained from trials in adult subjects unless specified otherwise.

Safety in Maximal Use PK Trial

There were no significant trends compared to baseline, in laboratory values (hematology and biochemistry) over the duration of the trial. While subjects reported some skin changes in the tolerability assessments, none were severe and none resulted in discontinuation. No subjects
became pregnant during the MUst and all enrolled women of childbearing potential committed to abstinence or use of approved contraceptive drugs during the trial. Eight subjects (33.3%) reported 17 AEs. None were serious and all were mild to moderate in severity. The most frequently reported AEs (N=3 each) were “skin irritation,” “pruritis,” and “headache.”

3.4.2 Label Comprehension Study

What is a Label Comprehension Study?

Label comprehension studies (LCS) are conducted for virtually all Rx-to-OTC switch products. If consumers cannot understand – or are not even aware of – what the label says relative to safe and effective use, chances are they will not correctly self-select and self-medicate, and they may not even be able to self-diagnose a condition.

Therefore, label comprehension is both ideally and typically the first consumer study in an OTC drug development program, to determine if the Drug Facts Label (DFL) successfully communicates important information about a drug to ultimately ensure the safe use of the drug.

FDA asks applicants to conduct LCS to address questions such as:

- Is the wording understandable to the average consumer?
- Does it contain technical or medical jargon, or terms that are unfamiliar to the average person?
- Does it convey the key concepts for the safe use of the product?

For instance, it is important for consumers to be aware of and understand statements such as “ask a doctor or pharmacist before use.” Sometimes applicants will question the need for retesting such a statement when it appears on so many other products and it has been tested before. In fact, sometimes they do not need to. However, if FDA believes that the warning is more critical to the safe use of a particular new product than it may have been for existing products, the applicant will be asked to retest it.

In a LCS, applicants need to identify the most important communication objectives that need to be assessed as primary objectives. These are the most important concepts, from the viewpoint of safety, that need to be understood by consumers. Target thresholds are established \textit{a priori}, and are based on clinical implications if consumers fail to adequately understand the labeled items. Therefore, applicants are to provide the clinical justifications for the thresholds. For instance, for a hypothetical OTC product, a target threshold for comprehension of “do not use if you have liver disease” could be established at 90%, because there would be serious medical consequences for the consumer with liver disease if the consumer were to use the product.

Adequate comprehension is assessed by comparing the established threshold with the lower bound of the 2-sided exact 95% confidence interval (CI) for the comprehension rate. For example, if the lower bound of the confidence interval is 92% and the target threshold is 90%,
adequate comprehension would be demonstrated. The lower bound is utilized because it accounts for the uncertainty in the estimate of the comprehension rate. Studies typically have a general population cohort and an augmented low literacy (LL) cohort; the threshold is typically applied to the general population cohort, but sub-analyses of these cohorts are also run and analyzed. FDA typically asks applicants to have a minimum of 22-28% LL representation in their consumer studies. Generally participants in consumer studies are administered the Rapid Estimate of Adult Literacy in Medicine (REALM) test, which is a validated literary assessment tool. For the purposes of nonprescription regulatory consumer studies, LL is defined as scoring <60 on the REALM, which represents a health literacy level of 8th grade or below.

If within their standard recruiting methods the applicants anticipate that they will be unable to recruit the target percentage of low literates into the general population cohort against which the target threshold is measured, they will simultaneously field an augmented LL cohort. This augmented cohort is typically fielded in research sites that have greater availability to recruit LL subpopulations. Therefore adequate comparisons can still be made overall in the study between normal literate and low literate subjects, across the two cohorts.

Secondary communication objectives are intended to address areas less critical to safe and appropriate use, yet clinically relevant. Secondary communication objectives typically are not assessed against target thresholds.

Label comprehension studies usually enroll as demographically diverse a population as possible. Generally, the studies include from 300-600 subjects from a variety of testing sites across the United States. Typically, LCSs are conducted with “all comers”; they are usually intentionally not limited to sufferers of a condition, because anyone should be able to pick up a DFL and understand what it says. For instance, caregivers are often involved in administering drugs to people who have conditions that they, the caregivers, don’t have. Also, anyone can newly develop a medical condition; therefore, almost anyone can be considered to be a potential user of an OTC product.

In a LCS, consumers are given the DFL to read at their own pace. They are then asked questions about the label, and can refer back to it as much as they want. It is not a test of memory, but rather an “open book” test to assess whether consumers are aware of and can understand key elements presented in the DFL. Questionnaires need to be constructed targeting the communications objectives in an unbiased way. Label comprehension studies typically employ many scenario questions, describing hypothetical consumers and their medical situations in order to test the ability of the consumer to apply the information from the label.

Ultimately, LCSs assess comprehension, and not behavior. Therefore LCSs are usually necessary as the foundation of successful OTC development programs. If a proposed label does not facilitate sufficient comprehension by consumers, it is far less likely that consumers would then be able to correctly self-select and use the product in a safe and efficacious manner. Therefore, ideally LCS provides a foundational opportunity to optimize the label before any other necessary studies are conducted.
**Label Comprehension Study # 100544**

**Objectives**

FDA informed the Applicant during the product development that the labeled statement on pregnancy needed to be assessed as a primary objective, and that ideally the most stringent possible warning should be tested. However, the Applicant did not test any pregnancy warning or statement in this study, either as a primary or secondary objective.

The primary objectives of the LCS assessed comprehension of the DFL phrases “Use once daily” and “Do not use on damaged skin.” The primary objectives were assessed at a lower bound threshold of 85%. The Applicant stated that these objectives did not represent serious safety concerns, but increased irritation could occur if the product was used on damaged skin or more than once daily; therefore, the labeled statements provided important information about proper use. Ten secondary objectives were also assessed.

**Design and Conduct of Study**

The LCS was conducted in April 2014 with a total of 586 unique respondents. The study population included males and females, ages 12-70, in eight geographically dispersed sites in the United States. Below is the study population:

- **Cohort 1:** The general population cohort against which the primary objectives were measured had 515 respondents, with only 59 (11%) LL respondents.

- **Cohort 2:** The augmented LL cohort had 130 respondents (71 recruited in targeted LL recruitment at separate sites, plus 59 subjects from the general population who tested as low literate).

Due to the small percentage of low literacy respondents in Cohort 1, FDA focused on both cohorts in its analyses. Both cohorts had a good representation of adolescents in the sample; in total, there were 282 adolescents and 304 adults. However, both cohorts had relatively poor representation among the 18-24 year old age group. As Table 4 illustrates, only 33 respondents (5.6%) in the entire study were between the ages of 18 and 24. FDA believes that this low percentage is not representative of the user population of acne products.
Table 4: Label Comprehension Study Distribution by Age and Gender

<table>
<thead>
<tr>
<th>Age</th>
<th>Total n (%)</th>
<th>Cohort</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cohort 1 n (%)</td>
<td>Cohort 2 n (%)</td>
</tr>
<tr>
<td>12</td>
<td>32 (5.5)</td>
<td>29 (5.6)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>13</td>
<td>53 (9.0)</td>
<td>46 (8.9)</td>
<td>7 (9.9)</td>
</tr>
<tr>
<td>14</td>
<td>50 (8.5)</td>
<td>41 (8.0)</td>
<td>9 (12.7)</td>
</tr>
<tr>
<td>15</td>
<td>42 (7.2)</td>
<td>38 (7.4)</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>16</td>
<td>44 (7.5)</td>
<td>41 (8.0)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>17</td>
<td>61 (10.4)</td>
<td>55 (10.7)</td>
<td>6 (8.5)</td>
</tr>
<tr>
<td>18-24</td>
<td>33 (5.6)</td>
<td>27 (5.2)</td>
<td>6 (8.5)</td>
</tr>
<tr>
<td>25-34</td>
<td>51 (8.7)</td>
<td>47 (9.1)</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>35-44</td>
<td>65 (11.1)</td>
<td>60 (11.7)</td>
<td>5 (7.0)</td>
</tr>
<tr>
<td>45-54</td>
<td>78 (13.3)</td>
<td>68 (13.2)</td>
<td>10 (14.1)</td>
</tr>
<tr>
<td>55-64</td>
<td>51 (8.7)</td>
<td>42 (8.2)</td>
<td>9 (12.7)</td>
</tr>
<tr>
<td>65+</td>
<td>26 (4.4)</td>
<td>21 (4.1)</td>
<td>5 (7.0)</td>
</tr>
</tbody>
</table>

Source: FDA Statistics

Results

Comprehension of the primary objective of “Use once daily” for the general population was 95.9%, with a 2-sided 95% exact lower confidence bound (LCB) of 93.8%. This LCB met the target threshold of 85%, but as previously noted, Cohort 1 had relatively few LL respondents (11%).

Comprehension of the primary objective “Do not use on damaged skin” for the general population was 97.5% with a 2-sided 95% exact LCB of 95.7%, which met the established threshold of 85%. Again, Cohort 1 had relatively few LL respondents.

In order to fully assess low literacy comprehension due to the small percentage of low literates in Cohort 1, FDA examined the comprehension results for these two objectives across both cohorts by normal literacy (NL) and LL. Results are shown in Table 5.
For “Use once daily,” comparing the NL vs LL scores across the two cohorts, NL respondents had a comprehension rate of 96.5% and LL respondents had a comprehension rate of 86.9%. Comprehension rates differed significantly between literacy groups (Fisher’s exact p-value<0.0001). This is not atypical in consumer studies, but the clinical implications of these comprehension differences do vary by product studied. For “Do not use on damaged skin”, NL respondents had a comprehension rate of 97.4% and LL respondents had a comprehension rate of 99.2%. Comprehension rates for this objective did not differ significantly between literacy groups (Fisher’s exact p-value=0.32). This lack of difference in the comprehension rates demonstrates that low literates were able to understand some key aspects of the label as well as normal literates, and therefore it may underscore the issues of concern where they did not understand other aspects as well as normal literates.

Table 5: Label Comprehension Study Results – Primary Objectives

<table>
<thead>
<tr>
<th>Primary Objective</th>
<th>Normal Literacy % (n/N) (LCB)</th>
<th>Low Literacy % (n/N) (LCB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directions: Use once daily</td>
<td>96.5 (440/456) (94.4)</td>
<td>86.9 (113/130) (79.9)</td>
</tr>
<tr>
<td>Do Not Use: On damaged skin (cuts, abrasions, eczema, sunburned)</td>
<td>97.4 (444/456) (95.5)</td>
<td>99.2 (129/130) (95.8)</td>
</tr>
</tbody>
</table>

LCB = 2-sided exact 95% lower confidence bounds
Source: Adapted from the Applicant’s study report Table 10-6 Includes subjects from the general population who tested as low literate (n=59) as well as low literate subjects enrolled through targeted recruitment (n=71)

Comprehension rates by gender and literacy level for the primary objectives are presented in Table 6. The comprehension rates for the objective “Use once daily” did not differ significantly between genders (Fisher’s exact p-value=0.86), but did differ significantly between literacy levels (Fisher’s exact p-value<0.0001). A subject’s gender did not affect these literacy differences (Zelen test p-value=1.00).

For the objective “Do no use on damaged skin”, the comprehension rates did not differ significantly between genders (Fisher’s exact p-value=0.78). For this objective, there were no significant differences in comprehension rates between literacy levels (Fisher’s exact p-value=0.32).
Table 6: Comprehension for the Primary Objectives by Gender and Literacy – All Ages

<table>
<thead>
<tr>
<th>Primary Objective</th>
<th>Normal Literacy % (n/N) (LCB)</th>
<th>Low Literacy % (n/N) (LCB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Directions: Use once daily</td>
<td>96.0 (267/278) (93.0)</td>
<td>97.2 (173/178) (93.6)</td>
</tr>
<tr>
<td>Do Not Use: On damaged skin (cuts, abrasions, eczema, sunburned)</td>
<td>97.5 (271/278) (94.9)</td>
<td>97.2 (173/178) (93.6)</td>
</tr>
</tbody>
</table>

LCB = 2-sided exact 95% lower confidence bound
Source: FDA Statistics

As noted above, LL respondents had significantly lower comprehension rates than NL respondents for the “Use once daily” objective. This difference did not vary by age group (Zelen test p-value=0.40). FDA is more concerned about use frequency among younger women of childbearing age; however, as already discussed, there were relatively few participants 18-24 years old in the study.

A key subgroup of concern to FDA is adolescents, since it is possible that they might use products more frequently due to the cosmetic concerns that are prevalent at that age. Here, Table 7 shows comprehension rates for “Use Once Daily” by literacy level and gender for adolescents. There was a significant difference (Fisher’s exact p-value=0.006) in comprehension between normal literacy adolescents (95.7%) and low literacy adolescents (84.9%). It should be noted that there was not a significant difference overall in comprehension rates between males and females (Fisher’s exact p-value=0.65), nor was there a significant difference in comprehension between males and females within each literacy group (Fisher’s exact p-value=1.00). The differences that did exist by literacy level were similar across genders (Zelen test p-value=1.00).

Table 7: Comprehension of Primary Objective “Use Once Daily”: NL vs LL Adolescents (Age 12-17)

<table>
<thead>
<tr>
<th></th>
<th>Normal Literacy % (n/N) (LCB)</th>
<th>Low Literacy % (n/N) (LCB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total NL</td>
<td>Female NL</td>
</tr>
<tr>
<td></td>
<td>95.7 (200/209) (92.0)</td>
<td>96.0 (119/124) (90.8)</td>
</tr>
</tbody>
</table>

*LBB = 2-sided exact 95% lower confidence bound
Source: FDA Statistics

Results for secondary objectives for the general population cohort are displayed in Table 8. Regarding the secondary objective of “Avoid unnecessary sun exposure, including tanning beds, and use sunscreen when going outdoors”, FDA had advised that the sunlight exposure
component of the warning be tested but the Applicant declined to do so, on the premise that this is labeling language consistent with the monograph and therefore did not need to be assessed. Because this product’s active ingredient, adapalene, is not generally recognized as safe and effective under the OTC monograph and because the effects of sun exposure while using this product would be of particular concern, FDA recommended the testing of this warning. The Applicant only tested the component of the warning regarding avoidance of tanning beds, by utilizing a scenario that only mentioned tanning beds: “Melissa has acne and has been using this product. She is planning to go to the tanning bed today. What, if anything, does the label say about this?” This tested very well among both NL and LL, but again, the tested labeling did not encompass sunlight exposure. There were no significant differences in comprehension between adults and adolescents.

Another secondary objective of potential interest is “Under 12 years old, consult a physician”. This tested well among both NL and LL. There were also no significant differences in comprehension between adults and adolescents.
### Table 8: Label Comprehension Study Results: Secondary Objectives

**Analysis of Secondary Communication Objectives: Normal Health Literacy Population vs. Low Health Literacy Population**

<table>
<thead>
<tr>
<th>Secondary Objectives</th>
<th>N</th>
<th>P.E.</th>
<th>N</th>
<th>P.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Use of the medication:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For the treatment of acne, clears up acne pimpls and acne blemishes, helps prevent new acne pimpls and acne blemishes from forming</td>
<td>456</td>
<td>100.0</td>
<td>128</td>
<td>98.5</td>
</tr>
<tr>
<td><strong>Directions:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ages 12 and older</td>
<td>453</td>
<td>99.3</td>
<td>122</td>
<td>93.8</td>
</tr>
<tr>
<td><strong>When using this product</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do not use wax to remove hair in the areas where the product has been applied</td>
<td>450</td>
<td>98.7</td>
<td>126</td>
<td>96.9</td>
</tr>
<tr>
<td><strong>When using this product</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoid unnecessary sun exposure, including tanning beds, and use a sunscreen when going outdoors (only tested the “including tanning beds” portion of this warning; all other wording is monograph)</td>
<td>444</td>
<td>97.4</td>
<td>124</td>
<td>95.4</td>
</tr>
<tr>
<td><strong>When using this product</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moisturizers may be used to relieve dry skin</td>
<td>443</td>
<td>97.1</td>
<td>112</td>
<td>86.2</td>
</tr>
<tr>
<td><strong>When using this product</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritation (redness, itching, dryness, burning) is more likely to occur in the first few weeks of use</td>
<td>431</td>
<td>94.5</td>
<td>112</td>
<td>86.2</td>
</tr>
<tr>
<td><strong>Directions:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under 12 years of age, consult a physician</td>
<td>430</td>
<td>94.3</td>
<td>111</td>
<td>85.4</td>
</tr>
<tr>
<td><strong>When using this product</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During the early weeks of use your acne may appear to worsen before it improves. This is not a reason to stop using</td>
<td>407</td>
<td>89.3</td>
<td>98</td>
<td>75.4</td>
</tr>
<tr>
<td><strong>Stop use and ask a doctor if irritation becomes severe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>439</td>
<td>78.7</td>
<td>79</td>
<td>71.5</td>
<td></td>
</tr>
<tr>
<td><strong>When using this product</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritation (redness, itching, dryness, burning) is more likely to occur if using more than one topical acne medication at a time</td>
<td>294</td>
<td>64.5</td>
<td>67</td>
<td>51.5</td>
</tr>
</tbody>
</table>
Source: Applicant’s Report
Includes subjects from the General Population who tested as low literate (n=59) as well as low literate subjects enrolled through targeted recruitment (n=71).

**Conclusions of the Label Comprehension Study**

The two primary objectives of this study - “Use once daily” and “Do not use on damaged skin” - tested well among normal literacy participants. One of these primary objectives “Use once daily”, did not test as well among low literacy participants, although this type of difference between NL and LL is not uncommon. The differences between NL and LL for comprehension of this primary objective were fairly consistent across gender and age groups, including adolescents. However, due to the lack of adequate representation of participants 18-24 years old in the sample, we cannot draw definitive conclusions about either the overall comprehension of this key subgroup or the differences between its NL and LL participants. Awareness of the need to avoid tanning beds and the need to consult a physician for potential users under age 12 tested well. Nevertheless, a key aspect of the sunlight warning was not tested. The major drawback of this study however, is that the awareness of the pregnancy statement was not assessed at all, despite FDA’s advice to the Sponsor to do so. Therefore, there is no evidence that can be obtained from this study that most women of childbearing age will understand that a healthcare professional should be consulted before use of the product.

**3.4.3 Targeted Self-Selection Study**

What is a Self-Selection Study?
Self-selection studies (SSS) assess whether consumers can apply their understanding of the label to their own personal medical situation for making a drug use decision. Typically, FDA might require a self-selection study when a potential Rx-to-OTC switch represents a new OTC indication, or when there is a potential concern about a specific subpopulation using the product, as for instance, in the case of Differin® OTC. FDA is interested in consumer research demonstrating that this subpopulation would not self-select to use the product at all, or would only do so after asking a healthcare professional first.

Self-selection studies are important because some consumers might “understand” a label in the abstract but not always understand, for instance, that they personally have a contraindicated medication or condition that could either preclude them from using the drug, or at a minimum require them to first consult with a healthcare professional. Without the healthcare professional writing a prescription for the drug, applicants need to assess the extent to which the relevant consumers can understand this on their own. Therefore, self-selection is a way of validating the label. Ideally this research is conducted after the label comprehension study, in order to ensure that an optimized label helps lead to safe use of the product. The target population for a self-selection study can be a generally representative sample of potential product users and nonusers, or a targeted study focusing on specific populations of interest. Target thresholds, or endpoints, are established by the sponsor *a priori* based on the clinical implications of failure of users to correctly self-select.
In self-selection studies, consumers are recruited for a specific contraindicated condition or medication, or another specific “do not use” category, such as minimum age or gender. The subjects themselves are usually “blinded” to why they are being recruited. Recruitment may take place through advertisements, shopping malls, research site facility databases, medical offices, or other kinds of treatment centers.

Self-selection studies typically involve in total from 400-800 subjects. FDA expects to see adequate LL representation in the SSSs, similar to that of LCSs, which is generally 22%-28%. When subjects arrive at the testing site, they are given the proposed product package with the DFL, asked to look at it as if they would do if seeking a drug for purchase, and then tell the interviewer whether the drug would be appropriate or not for them personally to use. Next they are probed to assess the reasons why they gave particular answers. They are not actually given the opportunity to use the product.

Often in order to validate that subjects have selected appropriately with respect to contraindicated medical conditions or other drugs, subjects are interviewed after their selection decision by a physician or other health care professional. The health care professional may administer tests, as well as obtain a detailed medical history in order to assess the appropriateness of a selection decision.

Self-Selection Study #103439

Objectives of the Targeted Self-Selection Study

The primary objective of the targeted SSS was to assess whether pregnant or breastfeeding women would ask a health care professional prior to use, as per the directions on the DFL. During development discussions, FDA had asked the Applicant to conduct self-selection research among pregnant women.

Design and Conduct of the Targeted Self-Selection Study

The SSS was conducted from November 2013-January 2014 among 293 unique pregnant/breastfeeding females ages 13-54. There were two cohorts:

- Cohort 1 - The general population cohort against which the a priori target threshold was measured, had a sample size of 242 women, of which 91 (37%) were pregnant; 11 of these pregnant women were also breastfeeding. The remainder of the sample was breastfeeding only. There were 61 LL subjects (25%) in this cohort.

- Cohort 2 - This was a low literacy augmented cohort, consisting of an additional 51 low literacy subjects.

The Applicant established a target threshold of 90% for the precaution “ask a healthcare professional before use”, which was compared to the lower bound of the two-sided exact 95% confidence interval for correct self-selection. For Differin OTC, the Applicant asserted that there was no clinical rationale for the proposed target threshold, as teratogenicity was not an issue; therefore, their 90% threshold determination was based solely on FDA’s stated concern during the development discussions.
Adult recruitment for the self-selection took place via mall intercepts at 25 sites across the United States. Women were recruited for the study if they appeared to fall into at least one of the following four groups: 1) between the ages of 18 and 50, 2) with noticeable acne, 3) visibly pregnant, 4) accompanied by a baby under 18 months. If the interviewing screener confirmed that they were 1) pregnant and/or breastfeeding, and 2) with acne (all self-reported), they were invited to take part in the study. Pregnant subjects were not asked about which trimester of pregnancy they were currently in.

Qualified subjects were directed to a research facility, where the REALM test (Rapid Estimate of Adult Literacy in Medicine, a validated literacy assessment tool) was administered. The subjects were asked to review the Principal Display Panel (PDP) and DFL of the proposed OTC Differin package, at their own pace. They were then asked “Is it ok for you to use this medication today or not?”, followed-up by “Why did you say that?” All subjects who self-reported pregnancy were administered a urine sample pregnancy test to confirm that they were pregnant. All subjects who self-selected incorrectly were then asked a clarification probe: “Earlier you said that this product was ok for you to personally use. However, the warning on the package states that you should ask a health professional because you are pregnant/breastfeeding. Please tell me why you thought it would be ok to use this product even though you are pregnant/breastfeeding.”

In contrast to the adult recruitment, adolescent recruitment for this study took place through “specialty sites” – pregnancy centers and support groups. Teens were administered an online questionnaire in a private room, in place of a face to face interview, to ensure maximal privacy and sensitivity. The online questionnaire ended at the self-selection question; the follow-up clarification probe was not asked. Although the study had a target recruitment of nine teens, the Applicant asserts that due to a delay in IRB approval for the adolescents, only two teens out of the 293 subjects were able to be enrolled in the study by the time it ended.

**Results of the Targeted Self-Selection Study**

In addition to only two adolescents in the entire study, there were also only 80 out of 242 subjects who were pregnant-only in the study, and an additional 11 subjects were both pregnant and breastfeeding. This is a significant issue with the study, because in development discussions regarding the labeled statement, FDA had focused its concerns on pregnant women. The relatively small sample size of pregnant women in the study leads to difficulty in drawing conclusions from age analyses of this subgroup in the general population.

In Cohort 1, 74.4% [2-sided exact 95% CI of (68.4%, 79.8%)] of the subjects correctly stated that they would ask a healthcare professional before using the product. The Applicant was not able to demonstrate that pregnant or breastfeeding women could adequately self-select to use the product. This conclusion is based on the following: the lower confidence bound (LCB) is 68.4%, over 20 percentage points below the target threshold of 90%; furthermore, the correct self-selection rate is statistically significantly lower than the 90% threshold since the confidence interval, around the observed rate, lies completely below the 90.0% target threshold equivalent to p<0.001. This suggests that a substantial proportion of pregnant or breastfeeding women would not consult a healthcare professional before using the product. **Table 9** shows the general population (Cohort 1) results by age, literacy, and pregnancy/breastfeeding status.
Because of potential concern about pregnant-only women using Differin® (as contrasted with the entire pregnant population together with the breastfeeding population), we conducted a subgroup analysis of the pregnant-only women in Cohort 1. As Table 9 shows, pregnant-only women correctly stated that they would ask a health professional before use 70.0% (56/80) of the time, with a 2-sided exact 95% CI of (58.7%, 79.7%). The Applicant was not able to demonstrate that pregnant women could adequately self-select to use the product based on the following: the LCB is over 30 percentage points below the target threshold of 90%; furthermore, the correct self-selection rate is statistically significantly lower than the 90% threshold since the confidence interval, around the observed rate, lies completely below the 90.0% target threshold equivalent to p<0.001. This suggests that a substantial proportion of pregnant women would not consult a healthcare professional before using the product.
<table>
<thead>
<tr>
<th>Age</th>
<th>Pregnant only</th>
<th>Breastfeeding only</th>
<th>Pregnant and Breastfeeding</th>
<th>Total</th>
<th>Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n/N)</td>
<td>% (n/N)</td>
<td>% (n/N)</td>
<td>% (n/N)</td>
<td>% (n/N)</td>
</tr>
<tr>
<td></td>
<td>NL (n)</td>
<td>LL (n)</td>
<td>Total (n)</td>
<td>NL (n)</td>
<td>LL (n)</td>
</tr>
<tr>
<td>13-17</td>
<td>100.0 (1/1)</td>
<td>--</td>
<td>100.0 (1/1)</td>
<td>--</td>
<td>0.0 (0/1)</td>
</tr>
<tr>
<td>18-24</td>
<td>69.6 (16/23)</td>
<td>46.7 (7/15)</td>
<td>60.5 (23/38)</td>
<td>84.6 (33/39)</td>
<td>56.3 (9/16)</td>
</tr>
<tr>
<td>25-34</td>
<td>80.0 (20/25)</td>
<td>83.3 (5/6)</td>
<td>80.7 (25/31)</td>
<td>78.0 (39/50)</td>
<td>75.0 (9/12)</td>
</tr>
<tr>
<td>35-44</td>
<td>62.5 (5/8)</td>
<td>100.0 (2/2)</td>
<td>70.0 (7/10)</td>
<td>76.9 (20/26)</td>
<td>75.0 (3/4)</td>
</tr>
<tr>
<td>45-54</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>100.0 (3/3)</td>
<td>0.0 (0/1)</td>
</tr>
<tr>
<td>Total</td>
<td>73.7 (42/57)</td>
<td>60.9 (14/23)</td>
<td>70.0 (56/80)</td>
<td>80.5 (95/118)</td>
<td>63.6 (21/22)</td>
</tr>
</tbody>
</table>

NL = Normal literacy
LL = Low literacy
Source: FDA Statistics
Because of the concern that younger pregnant-only women might be more likely to use the drug due to their cosmetic concerns, we looked at self-selection by age. Table 10 displays the variation in the observed correct self-selection rates across age groups for the women who were pregnant-only in Cohort 1. The rates did not differ significantly across the age groups (Fisher’s exact p-value=0.26). Of note however, due to the relatively small number of pregnant-only women in the study, there is relatively low statistical power to detect a difference in self-selection rates across age groups in this general population cohort.

Table 10: Pregnant-only Self-Selection by Age (General Population Cohort 1 – Normal and Low Literacy)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Correct self-selection rate % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-17</td>
<td>100.0 (1/1)</td>
</tr>
<tr>
<td>18-24</td>
<td>60.5 (23/38)</td>
</tr>
<tr>
<td>25-34</td>
<td>80.7 (25/31)</td>
</tr>
<tr>
<td>35-44</td>
<td>70.0 (7/10)</td>
</tr>
</tbody>
</table>

Table 11 shows the augmented low literacy (Cohort 2) results by age, literacy, and pregnancy/breastfeeding status. Table 11 only reflects the LL women who were recruited specifically for this augmented cohort. It does not include the LL women in Cohort 1.
Table 11: Correct self-selection rates in the augmented low literacy (Cohort 2)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Pregnant only % (n/N)</th>
<th>Breastfeeding only % (n/N)</th>
<th>Pregnant and Breastfeeding % (n/N)</th>
<th>Total % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-17</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>18-24</td>
<td>80.0 (4/5)</td>
<td>66.7 (6/9)</td>
<td>--</td>
<td>71.4 (10/14)</td>
</tr>
<tr>
<td>25-34</td>
<td>90.0 (9/10)</td>
<td>87.5 (14/16)</td>
<td>--</td>
<td>88.5 (23/26)</td>
</tr>
<tr>
<td>35-44</td>
<td>100.0 (1/1)</td>
<td>71.4 (5/7)</td>
<td>100 (2/2)</td>
<td>80.0 (8/10)</td>
</tr>
<tr>
<td>45-54</td>
<td>--</td>
<td>0.0 (0/1)</td>
<td>--</td>
<td>0.0 (0/1)</td>
</tr>
<tr>
<td>Total</td>
<td>87.5 (14/16)</td>
<td>75.8 (25/33)</td>
<td>100.0 (2/2)</td>
<td>80.4 (41/51)</td>
</tr>
</tbody>
</table>

NL = Normal literacy
LL = Low literacy
Source: FDA Statistics utilizing Sponsor data

Table 12 shows the variation in correct self-selection rates for the 39 low literacy women in the study who were pregnant only, excerpted from the two cohorts each displayed in Tables 10 and 11, respectively. For these low literacy women, there were significant differences in correct self-selection across age groups (Fisher’s exact p-value=0.06), with 18-24 year olds low literacy females having the lowest correct self-selection rates among women under age 45.

Table 12: Pregnant-only Low Literacy Self-Selection by Age

<table>
<thead>
<tr>
<th>Age group</th>
<th>Correct self-selection rate % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-24</td>
<td>55.0 (11/20)</td>
</tr>
<tr>
<td>25-34</td>
<td>87.5 (14/16)</td>
</tr>
<tr>
<td>35-44</td>
<td>100.0 (3/3)</td>
</tr>
</tbody>
</table>
Below are examples of the different reasons that study subjects gave for making an incorrect self-selection decision:

- “Looking at the ingredients, they don't seem harmful and I don't have sensitive skin and I don't see what it has to do with me being pregnant, it doesn't seem harmful.” (NL, Pregnant)

- “Literally everything has that warning on it and after repeatedly asking a doctor you learn it's usually okay as long as it doesn't say "Do Not Take If". (LL, Breastfeeding)

- “I always hear a specific acne medication can't be used by pregnant or breastfeeding women, but this is over the counter.” (LL, Breastfeeding)

- “Because I put it on my face, not on the baby and I put it on my skin; not in my blood so it wouldn't affect the baby.” (LL, Breastfeeding)

- “Because there are some things I feel I can use my instinct.” (LL, Pregnant)

- “What does my face have to do with my pregnancy.” (LL, Pregnant)

- “What does what I put on my face have to do with breastfeeding?” (LL, Breastfeeding)

- “The fact that it said once a day was reassuring, my doctors said I was safe using acne cream. I wasn't allergic.” (NL, Pregnant)

- “There are no harmful ingredients in this so I would use it and like I said the product doesn't have bad side effects.” (NL, Pregnant)

- “Because if you're only using it once a day it isn't going to hurt anything.” (NL, Breastfeeding)

- “Because it's for pimples. It wouldn't hurt the baby because it's for external use not internal.” (LL, Breastfeeding)

- “I figured I could pump my breast milk then feed my child that way and use the product.” (LL, Breastfeeding)

- “Because most doctors will probably say it is okay since it is just for acne.” (LL, Breastfeeding)

- “I don't see any information on how it's bad. Or what the side effects were. I'd lightly use it and then ask since I assume it's safe since it's over the counter. Even prenatal vitamins say to consult.” (NL, Breastfeeding)
• “It's a face treatment. It's washable and seems safe. The only problem would be is if it had an odor to it. Other than that, it should be fine.” (NL, Pregnant)

• “I don't think it's going to affect my child if it's on my face as long as I wash my hands.” (LL, Breastfeeding)

Additionally, 15 subjects who incorrectly self-selected stated as a response to the clarification probe that they had not seen the warning on the label. This subgroup may be indicative of a significant subpopulation that would not be aware of the labeled warning due to the Applicant’s failure to test this warning in the LCS.

Conclusions of the Targeted Self-Selection Study

Self-selection results were relatively poor, suggesting that a substantial proportion of pregnant or breastfeeding women would not consult a healthcare professional before using the product. Similar results were also seen for the subgroup of pregnant-only women – the focus of greatest concern. Looking at age and literacy levels within the pregnant only subgroup, only 55% of low literacy pregnant women 18-24 correctly self-selected, which was statistically worse correct self-selection than that of the higher childbearing age ranges. The study had two major methodological issues: 1) there was virtually no data collected on adolescents, which perhaps is the subpopulation most likely to use the drug and 2) pregnant women represented less than 40% the study population. The latter resulted in the overall relatively low statistical power of the study to detect differences between age groups of pregnant-only women in the general population cohort.

Verbatims reveal that incorrect selectors tended to not understand why an OTC topical product with a standard pregnancy labeled statement could theoretically pose a risk for a developing fetus or baby.

3.4.4 “Standard of Care” Survey of Doctors and Patients

What is a Standard of Care Study?
FDA does not ask applicants to conduct Standard of Care studies for Rx-to-OTC switches and has no specific definition of one; such studies have not historically been utilized in regulatory decision-making. The Applicant conducted this study in response to FDA’s request for data on current adapalene and topical retinoid prescribing practices, including data on how physicians counsel patients who are pregnant or who could become pregnant.
Objective of Physician Standard of Care Study

The objective of the Physician Standard of Care Study was to respond to FDA’s request for data by providing information on prescribing, counseling, and patient management by physicians who prescribe adapalene 0.1% gel.

Design and Conduct of Physician Standard of Care Study

To date, FDA has not been able to comprehensively assess the extent to which this sample may or may not be at all generalizable to the general prescribing population for adapalene, as the online physician panel utilized for the study is proprietary. Subsequent to submitting the NDA, the Applicant has explained that the study is not meant to be pivotal but rather qualitative in nature. FDA is not discussing most of the study results here, because 1) we have not been able to fully assess the sampling methodology and 2) we also have the following general observations about some of the study questions:

1) Physicians were not asked specifically about counseling that they provide regarding adapalene.

2) Physicians were not asked specifically about their perceptions of the adapalene 0.1% formulation.

3) Physicians were asked about the differences that they perceived between adapalene and the general category “of other topical retinoids”. Therefore, the study was able to capture some perceived advantages of adapalene over other products. However, physicians were not asked the converse - about the differences they perceived between other products and adapalene/other general topical retinoids. Therefore, the study was not able to capture some perceived advantages of other products over adapalene.

4) Physicians were asked whether they would encourage their patients to use topical retinoid products that became OTC, but it is unclear as to whether the physicians were to assume that the patients would be using the OTC topical retinoid under the physicians’ care and monitoring, or whether the patients would be using the OTC topical retinoid on their own and not within the context of ongoing physician treatment. Therefore, the findings from this question are unclear.

5) Physicians were asked a confusing question: whether they would “prescribe a topical retinoid to a female patient who is sexually active and states that she is either not using birth control or who is trying to get pregnant”. At least two interpretations of this question are possible: 1) the patient is sexually active, using birth control and not trying to get pregnant or 2) the patient is sexually active, not using birth control and trying to
get pregnant. Therefore, since the wording of the question was unclear, the findings from this question are also unclear.

6) Physicians were asked the question “Do you have any concerns about female patients of childbearing potential using prescription topical retinoids for their acne?” However, the physicians may have interpreted this question in various ways; if a physician was confident that s/he personally took every precaution with respect to their female patients of childbearing potential, they may have then stated that there were no concerns.

For readers who may wish to accept that the study is of sufficient rigor for purposes of providing insights, a subject-level analysis of the physician respondents reveals that almost 90% of the physicians voiced one concern or another about prescribing topical retinoids. Table 13 shows the Applicant reported results for each of the relevant questions. However, FDA’s subject level analysis pinpointed where there were overlaps and where there were differences about which specific physicians voiced concerns about which specific questions. When the data is examined on a subject level basis, it becomes apparent that only 12.6% of physicians surveyed had no concerns regarding any of the safety issues asked about. In other words, the overwhelming majority of physicians (almost 90%) had some type of concern about prescribing topical retinoids to their female patients of childbearing age.

Table 13: Pregnancy Related Counseling to Topical Retinoid Patients

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes % (n/N)</th>
<th>No % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you require a pregnancy test for women of childbearing potential before you prescribe a topical retinoid?</td>
<td>21.2 (32/151)</td>
<td>78.8 (119/151)</td>
</tr>
<tr>
<td>Do you give your patients of childbearing potential any special instructions when prescribing a topical retinoid?</td>
<td>60.3 (91/151)</td>
<td>39.7 (60/151)</td>
</tr>
<tr>
<td>Do you have any concerns about female patients of childbearing potential using prescription topical retinoids for their acne?</td>
<td>35.1 (53/151)</td>
<td>64.9 (98/151)</td>
</tr>
<tr>
<td>When female patients of childbearing potential using prescription topical retinoids come in for follow up visits, do you routinely perform pregnancy tests?</td>
<td>8.6 (13/151)</td>
<td>91.4 (138/151)</td>
</tr>
<tr>
<td>If you find out that one of your patients on prescription topical retinoids becomes pregnant while using the medication, do you advise them to stop taking it?</td>
<td>84.1 (127/151)</td>
<td>15.9 (24/151)</td>
</tr>
<tr>
<td>Answered “no” to all above questions</td>
<td></td>
<td>12.6 (19/151)</td>
</tr>
</tbody>
</table>

Source: Sponsor Report, FDA Statistics (subject level physician analysis)
Patient Standard of Care Study #1022234

Objective of Patient Standard of Care Study

The objective of the Patient Standard of Care Study was to assess how patients use topical retinoids in real world practice.

Design and Conduct of Patient of Care Study

To date, FDA has not been able to adequately assess the study design and conduct of this study. The medical marketing research firm that conducted the study contracted with three separate online panels that together conduct research in over 120 countries, with opt-in from Facebook and other social media sites. However, we have the following general observations about the study:

1) Female patients of childbearing age were not asked in the survey about whether they had been on long-term highly effective birth control when they first obtained their prescription for adapalene. If the patients’ physicians had already assessed that they were at a low risk of pregnancy, they may have not emphasized counseling as much in their patient interactions.

2) Patients were also not asked about what other retinoid medications they were either already on, or being simultaneously prescribed at the time that adapalene was initially prescribed to them. Concomitant medication specifics (for example, if they were on Accutane®) would have provided more clinical context regarding patient self-reports about simultaneous counseling that they may or may not have received regarding adapalene.

It is difficult to evaluate the extent of pregnancy counseling in females of childbearing age who were prescribed Differin® because there were only 31 of these patients. The survey question about pregnancy testing only referred to Differin® and not Epiduo® (although there were many more patients having been prescribed Epiduo®).

3) The study included 233 males and females from age 13-69. The total number of adapalene only female users of childbearing age was n=52. This is not a robust sample size for analysis.

4) Patients were asked about how often they used adapalene. Although a sizeable number reported that they used it 2-3 times per day, it is unclear whether patients meant that they always used adapalene 2-3 times per day or whether they meant that they used it 2-3 times per day only at times when their acne was particularly bothersome.
Results of Patient Standard of Care Study

At the current time, FDA does not have adequate documentation as to study design and conduct and therefore is not reporting a full discussion of results.

3.4.5 Actual Use Trial

What is an Actual Use Trial?
In an AUT, participants actually take the study drug home and may use it, so unlike an LCS or SSS, an AUT is a clinical trial, though usually it is uncontrolled. The purpose of an AUT is to simulate the OTC use of a product. Hopefully, the AUT can provide meaningful consumer data so we can attempt to predict if a drug will be used properly, safely, and effectively in a “naturalistic” OTC setting. Examples of elements an AUT can assess are:

- Adherence (taking the drug and performing any monitoring for efficacy and safety in accordance with the drug label)
- Safety (AEs that occur during the study)
- Effectiveness (whether the clinical benefit in the prescription setting is reproduced in the OTC setting). This is seldom done and was not done for Differin® Gel.

Actual use trials can assess the ability of the consumer to use the product for the indicated purpose (self-treat) and can also assess whether consumers are abusing or misusing the study drug. Some issues that might trigger the need for an AUT include:

- New OTC indication
- New method of use for an OTC drug
- New OTC warnings
- New OTC medical follow-up requirements or recommendations
- Specific concerns about self-selection or de-selection

Study Design:
The design of an AUT can vary. Usually AUTs have been single-arm, multi-center, uncontrolled, open-label studies (the Differin® Gel JUNO Trial is an example of this design). An AUT should be performed in a venue that simulates, as closely as possible, the true OTC environment. It is clear that a truly “naturalistic” environment cannot be perfectly achieved; data need to be collected. However, if no clinical sites are used, if the study participant can purchase study drug without restriction, and if there is no unsolicited healthcare provider involvement, a study can come close to simulating a real nonprescription purchase setting. Study elements that limit the naturalistic setting are the informed consent form, data collection tools like diaries which can serve as memory prompts to the study participant, and any other educational tools that may not be carried over into the true OTC setting. When study elements that limit the naturalistic setting are
used in the AUT, we cannot be certain that the same level of safety and efficacy will be achieved if the consumer uses the product without these additional elements. This issue is always considered when we provide comments to an applicant about their AUT design.

Ideally, all consumers who have an interest in the product should be the target of recruitment efforts. It is also reasonable to recruit targeted subgroups of interest (e.g., low health literacy, specific demographics, and medical conditions). These subgroups can provide more information about the potential safety or effectiveness concerns.

The acceptable success rate for pivotal issues related to actual use for an OTC product is a matter for discussion with applicants. Acceptable error depends upon the specific drug, specific indication, and safety concerns. Consideration needs to be given to how we should make decisions on approval of a drug when a small percentage of users could potentially be harmed by inappropriate use. However, on the other hand, a large percentage of users may benefit.

**Analysis:**
The number of study participants enrolled has varied with each drug and situation. Among the factors that could influence the number would be the incidence of the condition, the drug risks, and the cohorts. As with the LCS and SSS, data have been presented for AUT as a point estimate of correct response. The point estimate is compared to a pre-specified target threshold, whose acceptability should be supported by a sound clinical rationale.

**Pivotal Actual Use Study for Adapalene 0.1% Gel (Protocol 13049- JUNO trial)**

**Methods**

The JUNO trial was a 6-week, open label, multi-center (31 geographically dispersed pharmacy sites) trial in subjects self-reporting acne, a well-established OTC indication. All comers with acne were eligible to enroll. The trial was conducted from January 23, 2015 to May 2, 2015.

Initially, the Applicant proposed that 1,200 would enter and 800 would complete the trial. The low literacy target was 20-25%. Ultimately, 1,277 subjects entered the trial and 947 were included in the actual use population – those who gave informed consent/assent, purchased the drug and applied at least one dose. This group also constituted the safety population for analysis. The major inclusion/exclusion criteria were as follows:

- Self-reported acne
- Age 12 years to adult (assent required for children 12-17 years of age)
- In the judgment of the investigator or designee, the subject was likely to be harmed by participating in the study, or the subject was unlikely to follow the study procedures
Subject was pregnant – urine pregnancy test conducted in all female subjects of childbearing potential
Self-reported breastfeeding
Self-reported allergy to adapalene or any inactive ingredient

Potential subjects (Figure 4) were recruited by advertising and underwent minimal screening to exclude those who had participated in studies in the past 12 months or worked in a healthcare-related field. Upon arrival at a participating pharmacy site, subjects enrolled in the trial were offered the product package and asked to make a purchase decision. The DFL on packaging was nearly identical to that proposed for OTC marketing. The “Uses” section for the test label included a statement that the drug “helps prevent new acne pimples and acne blemishes from forming.” The Applicant has removed this statement from the proposed label.

The cost of one box containing one 45 gram tube was $7.00. Subjects were allowed to purchase a maximum of two boxes per visit and three boxes over the entire duration of the trial. Those who said “Yes” (selectors) to purchase gave informed consent/assent and female subjects of childbearing potential were required to self-administer a urine pregnancy test. All of the selectors underwent further medical screening to determine whether it was appropriate to use the drug. A healthcare professional participating as a screener would make the final decision on enrollment for each subject. These subjects then completed the REALM, or a teen version, to determine literacy.

Once the product was purchased, subjects were given basic instructions on completing the diary, contact information and when to schedule the next visit. Subjects were not provided information on how to use the product or for what conditions it should be used. Subjects who chose not to purchase (non-selectors) or who were found ineligible due to labeling contraindications or other exclusions (e.g., pregnancy) underwent a truncated screening to collect data on demographics, targeted medical history and clarification of the reason not to select or purchase the product for use.

On Visit 2 [Study close-out day; End-of-Trial visit (EOT)], subjects were expected to return diaries and unused product. All but one subject who attended Visit 2 returned a completed diary. Female subjects of childbearing potential underwent repeat urine pregnancy testing at EOT visit and all subjects completed body charts to document the body areas where drug was applied. They completed EOT medical histories and participated in interviews about their usage patterns or AE reporting over the course of the trial. All subjects were reimbursed for their time, travel and product purchases (reimbursement was not divulged to them prior to entering the trial).
Demographics

Based on discussions between the applicant and FDA, Galderma set a quota of ≥ 10% of the enrollees to be children 12-17 years of age. Subjects who were younger than 12 years old were allowed to make the screening visit (with a parent/guardian), but were not allowed to purchase the drug. Their reasons for interest were documented. See the demographics in Table 14.

Table 14: Subject Demographics (JUNO Trial – Use Population)

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Subjects (N=947)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>29.9 (12.72)</td>
</tr>
<tr>
<td>Median</td>
<td>28</td>
</tr>
<tr>
<td>Min, Max</td>
<td>12, 73</td>
</tr>
<tr>
<td><strong>Age subgroup, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>12-17 years</td>
<td>203 (21.4)</td>
</tr>
<tr>
<td>≥ 18 years</td>
<td>744 (78.6)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>304 (32.1)</td>
</tr>
<tr>
<td>Female</td>
<td>643 (67.9)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>492 (52)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>321 (33.9)</td>
</tr>
<tr>
<td>Other</td>
<td>88 (9.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>25 (2.6)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>12 (1.3)</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>6 (0.6)</td>
</tr>
<tr>
<td>Refused</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>REALM Score, n (≥ 18 years)</td>
<td>Normal Literacy (%)</td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>744</td>
<td>641 (86.2)</td>
</tr>
<tr>
<td>REALM-Teen Score, n (12-17 years)</td>
<td>Normal Literacy (%)</td>
</tr>
<tr>
<td>203</td>
<td>181 (89.2)</td>
</tr>
</tbody>
</table>

Source: Modified from the Applicant’s submission, Module 5.3.5.2, Synopsis – Table 4, p. 5-6, and Module 5.3.5.2, ‘Synopsis,’ Table 2, p. 3.

Table 14 shows a wide-ranging population enrolled in the trial by age, sex and race. The young mean and median ages are expected. The Applicant also captured an acceptable proportion of adolescent subjects (21.4%) and a majority female population (67.9%) to capture behaviors, as advised by FDA, potentially based on pregnancy status. The status of the actual use population (users) indicates that a lower proportion of the trial population was considered low literacy (adults and adolescents) than FDA advised (20-25%). This population is further defined in Table 15.

Also based on prior discussions with FDA, the applicant attempted to capture a proportion of subjects who self-reported acne and eczema and chose to purchase the drug. This was intended to further evaluate the potential for off-label use, extensive use and potential exposure on damaged skin that may increase potential for systemic absorption. According to the Applicant, 37 enrollees reported a history of eczema but chose not to purchase and use the drug. Of those, only three made the decision not to purchase because of their eczema. The applicant reports that 14 subjects reported both acne and eczema, selected to use the drug, and participated in the treatment phase. Only two subjects reported applying the product to eczema if “it might help,” and one of them determined that her eczema rash may have been an effect of the drug only after having continued application through the treatment period. No others (N=12) applied to sites where acne and eczema were commingled. There were nine selectors who were excluded from the use phase because they reported eczema without acne.

There was no enrichment for pregnant women in the AUT since there was a dedicated SSS conducted on that population (see Section 3.4.3 Targeted Self-Selection Study). Since the AUT was open to enroll all-comers, the women likely to be interested in using the product were also more likely to be of child-bearing potential since acne more commonly affects adolescents and younger adults. Ultimately, 43.9% of the enrolled population was women of childbearing potential (12-54 years of age) where such status was bracketed by menarche and menopause or defined by post-surgical status (e.g., post-hysterectomy, post-tubal ligation). Data were collected on the selection/purchase decisions of women who were determined to be pregnant or breastfeeding during screening, and assessment of these women was a secondary objective of the trial. FDA previously noted to the applicant that the 6-week trial duration was likely too short to capture an adequate number of interim
pregnancies to analyze the behaviors of those women, i.e., whether they would stop use or seek the advice of a healthcare professional.

**Table 15: Subject Disposition - JUNO Trial**

<table>
<thead>
<tr>
<th>Category</th>
<th>All Subjects</th>
<th>Normal Literacy&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Low Literacy&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1277</td>
<td>1047 (82%)</td>
<td>189 (14.8%)</td>
</tr>
<tr>
<td>Actual Use/Safety Population</td>
<td>947</td>
<td>822 (86.8%)</td>
<td>125 (13.2%)</td>
</tr>
<tr>
<td>Excluded from Use</td>
<td>330</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purchase Decision = ‘No’</td>
<td>169 (51%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>119</td>
<td>35</td>
</tr>
<tr>
<td>Actual Use Screen Failure&lt;sup&gt;c&lt;/sup&gt;</td>
<td>104 (31%)</td>
<td>71</td>
<td>18</td>
</tr>
<tr>
<td>Lost to Follow Up</td>
<td>41 (12.4%)</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>Other&lt;sup&gt;e&lt;/sup&gt;</td>
<td>14 (4.2%)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Subject Withdraw Consent</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Study Staff Decision</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Purchase Decision = ‘Yes’</td>
<td>919 (97%)</td>
<td>795</td>
<td>124</td>
</tr>
<tr>
<td>Ask a Health Professional First</td>
<td>28 (3%)</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Study Doctor, PA, Nurse</td>
<td>7</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>20</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Personal Healthcare Professional</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Completed Use Phase</td>
<td>938</td>
<td>813</td>
<td>125</td>
</tr>
<tr>
<td>Discontinued Use Phase Early</td>
<td>9</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>8</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Other (#30006)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>The literacy status of 41 subjects (3.2%) was undetermined. Those subjects are not included in these columns and were not entered into the trial.

<sup>b</sup>Enrolled subjects were those who answered the advertisements and passed the initial, minimal screening – identified as label evaluators.

<sup>c</sup>Screen failures would have been subjects meeting any exclusion criteria including the discretion of the healthcare professional during telephone screening.

<sup>d</sup>The percentage is of those excluded from use (N=330).

<sup>e</sup>Nearly all subjects excluded as “other” either did not sign Informed Consent or were unable to provide a urine sample with a positive/negative result for pregnancy testing. Some tests were “inconclusive.”

PA = Physician’s Assistant

Source: Modified from Applicant’s submission, Module 5.3.5.2, ‘Synopsis,’ Table 2.

**Table 15** shows the subject disposition of the JUNO Trial. The number of enrolled subjects was similar to the originally proposed study size to address the primary endpoints. The low
literacy cohort in the enrolled population (14.8%) is well below the proportion initially proposed for the trial (20-25%). The majority of subjects who were “excluded from use” (N=330) had decided not to purchase the drug after viewing the package (N=169). Of the 104 subjects who failed the screening (i.e., includes those who incorrectly selected to use the product), this reviewer found the following trends:

- Seven potential subjects were younger than 12 years of age:
  - Due to their age, two of these subjects reported that they would not purchase, or would ask a doctor first.
  - Five subjects were within 12 months of their 12th birthday. They wanted to purchase for use, and their selection decisions were mitigated.
  - The subjects who wished to use the product simply wanted to improve their acne and had been unsuccessful using other products.
- One subject reported an allergy to adapalene or other ingredients.
- Twenty subjects reported that they did not have acne:
  - Nine (0.7%, 9/1277) of these subjects selected to purchase and use the product, but were excluded from entering the use phase of the trial.
  - These subjects stated that they did not have acne, but wanted to, for example, “prevent acne,” “unclog pores,” or “remove the blemishes” and “even out the skin tone”.
  - On questioning, none commented that they wanted to use the product for non-acne conditions such as eczema, psoriasis, or age-related wrinkling or other skin changes.
- Several subjects (N=16; 1.3%, 16/1277) reported that they were pregnant (N=4) or breastfeeding (N=10), or were determined to be pregnant upon screening (N=2). Several (N=14) initially chose to use the product while pregnant or breastfeeding. On probing, subjects reported:
  - Not seeing the warning.
  - Not considering the seriousness of the warning, for example, stating “all medications say ask a doctor before use”.
  - Not considering use while breastfeeding to be a risk.
  - The topical formulation appeared to ease concern versus oral use
  - Believing there was minimal risk associated with use of the topical formulation, thus choosing to use the drug regardless of pregnancy status, either because of prior discussions with a doctor or pharmacist, or on their own volition.
- Twenty nine subjects were excluded based on the judgment of the investigator conducting the Visit 1 screening.

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Additional reasons for failing screening included subjects’ inabilities to meet other inclusion or exclusion criteria.
• Although it was not an objective of this trial, 35 subjects appear to have made a potentially clinically-relevant, incorrect selection decision, i.e., they selected to use the product when they had a contraindication, e.g., did not have acne, or should have spoken with a doctor first, e.g., the subject was pregnant.

The Applicant provided a more detailed account of the investigators’ judgments to exclude 29 subjects (last bullet above). Twenty five (25) wanted to purchase the product. Two subjects reported pregnancy, but one had a negative pregnancy test, and another reported missing two menstrual cycles and being concerned about possible pregnancy, though she also had a negative test. Three subjects had inconclusive pregnancy tests and were excluded. Another subject refused to provide a urine sample for the pregnancy test. Another subject had a positive pregnancy test but reported having had an elective termination prior to the screening visit.

Six subjects were excluded due solely to “interest in money” for participation in the trial. Two more subjects were considered to be under the influence of drugs or alcohol during the screening visit. Finally, nine subjects did not appear to comprehend the instructions for participation in the trial, understand interview questions, or raised concerns for staff over likely non-compliance with protocol.

The DFL states that subjects who are pregnant or breastfeeding or younger than 12 years of age should ask a doctor before using the product. Of the 28 subjects who stated they would do so (Table 15), eight fell into one of those categories. The other 20 subjects either had questions about adapalene itself, or wanted to check if there were any interactions with other drugs or products they were using concurrently.

Primary and Major Secondary Endpoints
The primary objectives of JUNO were to evaluate the frequency of use (labeled for once daily use) and to determine “off-label” use (i.e., non-acne use). Subjects who used the product even once were to be included in the final analysis. The Applicant determined the proportion of correct users as the number of subjects who had an overall correct behavior for the primary objectives out of the entire number of users. Correct behavior was defined as initial behavior (no more than once daily use at same location and use for acne only) including behaviors mitigated \textit{a priori} and behaviors mitigated \textit{post-hoc}.

Although the Applicant assessed subjects for “off-label” use, recruitment and advertising for the trial was, rightly, acne-specific. The investigators proposed to enrich the trial with subjects reporting both eczema and acne and they attempted to gather data on “off-label” use at the EOT interview.

Regarding mitigations, the Applicant set conditions whereupon initially incorrect responses would be revised as “correct.” For the primary endpoints, two \textit{a priori} conditions resulted in revisions: those subjects who 1) either reported that they mistakenly used the product >
once daily only one time with an explanation that they changed their use after the single mistake, or 2) they had been prescribed the product for a non-acne (“off-label”) indication by a healthcare provider.

Post-hoc mitigations were established based on subjects’ responses to EOT interview questions by trial staff and subjects’ diary data. From that data, the Applicant identified “core themes” that were used to assign categories of incorrect usage and determined whether mitigations were appropriate. Five mitigating circumstances were established for three endpoints:

- **Use product no more than once daily in same location (PRIMARY).**
  - Subjects who changed their application schedule or applied the product at night and the following morning, e.g., work or school schedule changes.
  - Subjects who, at any time, re-read the directions and changed behavior.

- **Use only for acne (PRIMARY).**
  - Acne is in the same area as another skin condition.

- **Apply to correct body area (SECONDARY; see below).**
  - Subjects used the product near a ‘warning’ area, i.e., eyes, mouth, or lips.
  - Subjects reported using the product on ‘damaged’ skin which was later determined to be a known effect of the medication, e.g., dryness.

The Applicant determined the point estimate and lower bounds of the two-sided exact 95% confidence limit. **The threshold for success is a lower bound > 85% for each primary endpoint.** The Applicant considered the thresholds consistent with those “commonly set for primary endpoints in consumer studies,” also stating that they had no clinically relevant concerns about overuse or off-label use based on the history of marketing of adapalene in the Rx setting. Subgroups were analyzed by age cutoffs at 12-17 years and ≥ 18 years, and by health literacy (low literacy = REALM < 60 or equivalent for children and adolescents).

The proportions of misusers did not differ much by literacy level or age. Of the 844 subjects considered by the Applicant to correctly use the product only once daily (Table 16), 61 subjects had use mitigated by an *a priori* criterion, and 16 subjects had use mitigated by post-hoc criteria as described above. Only 17 (22%; 17/77) of these mitigated subjects were in the 12-17 year old age bracket. There were no trends raising concern about the potential for misuse due to younger age. All subjects whose use was mitigated by an *a priori* criterion used the product more than once daily only a single time (N=61). These mitigated subjects reported several circumstances that may not infrequently occur more than once over a treatment period. Subjects reported reapplying adapalene after showering, having particularly bad “breakouts” on a particular day and hoping for a better effect, or forgetting that they had previously applied the product. For the subjects whose use was mitigated by the *post hoc* criteria, 12 subjects’ use was mitigated by a work/school/schedule change whereby the subjects used the product late at night followed by use the next day < 24 hours
later. The other four subjects’ use was mitigated because they re-read the directions and changed their use behavior.

Table 16: Primary Endpoint 1 - Analysis of Once Daily Use in Same Location

<table>
<thead>
<tr>
<th>Endpoints 1: Statistics</th>
<th>All Subjects (N=947)</th>
<th>Normal Literacy (N=822)</th>
<th>Low Literacy (N=125)</th>
<th>12-17 years (N=203)</th>
<th>≥ 18 years (N=744)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>844 (89.1)*</td>
<td>732 (89.1)</td>
<td>112 (89.6)</td>
<td>184 (90.6)</td>
<td>660 (88.7)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(87.0, 91.0)</td>
<td>(86.7, 91.1)</td>
<td>(82.9, 94.3)</td>
<td>(85.8, 94.3)</td>
<td>(86.2, 90.9)</td>
</tr>
</tbody>
</table>

CI = Confidence interval; *= endpoint met lower bound of two-sided exact 95% confidence limit for a priori threshold

* Final corrected use = number of subjects with overall correct behavior (uncorrected use + a priori mitigation + post-hoc mitigation) divided by actual use population.
Source: Modified from Applicant’s submission, Module 5.3.5.2, ‘Synopsis,’ Table 5, p. 7.

Subjects who used the product incorrectly without a mitigating factor (N=103) most frequently reported using it whenever they showered or washed their face, i.e., sometimes twice daily (34%; 35/103), sought to achieve greater, or faster, benefit (24.3%; 25/103), in an attempt to treat “severe” acne (18.4%; 19/103), or because they misread the directions or used it as per “my routine,” usually twice daily (8.7%; 9/103).

Regarding the second primary endpoint, determining the proportion of subjects who used the product only for acne, Table 17 demonstrates that the Applicant also met the a priori success threshold (98.5% - lower bound of 2-sided 95% CI > 85%). The proportions within subgroups stratified by health literacy (REALM scores) and age (12-17 years; ≥ 18) were similarly well above the threshold.

Table 17: Primary Endpoint 2 - Analysis of Acne-only Use

<table>
<thead>
<tr>
<th>Endpoints 2: Statistics</th>
<th>All Subjects (N=947)</th>
<th>Normal Literacy (N=822)</th>
<th>Low Literacy (N=125)</th>
<th>12-17 years (N=203)</th>
<th>≥ 18 years (N=744)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/M (%)</td>
<td>938/945 (99.3)*</td>
<td>814/820 (99.3)</td>
<td>124/125 (99.2)</td>
<td>202/203 (99.5)</td>
<td>736/742 (99.2)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(98.5, 99.7)</td>
<td>(98.4, 99.7)</td>
<td>(95.6, 100)</td>
<td>(97.3, 100)</td>
<td>(98.2, 99.7)</td>
</tr>
</tbody>
</table>

CI = Confidence interval; *= endpoint met lower bound of two-sided exact 95% confidence limit for a priori threshold

* Final corrected use = number of subjects with overall correct behavior (uncorrected use + a priori mitigation + post-hoc mitigation) divided by actual use population.
bM is the number of subjects who used the product and had no missing assessments (two subjects had missing assessments – both had normal health literacy as per REALM testing and were ≥ 18 years of age)
Source: Modified from Applicant’s submission, Module 5.3.5.2, ‘Synopsis,’ Table 6, p. 8.
Five subjects misuse was mitigated *post-hoc* (see above). They reported using the product on a non-acne condition because they also had acne on the same location. Only seven subjects misused on areas without acne. Those subjects reported using the product for psoriasis (1), anti-aging (1), “dark spots” (1), “eye puffiness” (1), “reduce pore size” (1), and “eczema” (two subjects # 18024 and 31043). All of them thought using the product would help their conditions. Also with regard to use of adapalene for non-acne conditions, although no subject reported using Rx-only adapalene gel at the time they entered the trial, based on interviews, 41 subjects reported having received a prescription for the gel at some time. All reported being prescribed and using the product for acne except for two (‘skin discoloration’ and ‘hormonal breakout’), and the duration of use ranged from approximately one month to more than five years, with most subjects using the product for less than one year (eight reported using adapalene for less than two months).

The major secondary objectives were to 1) evaluate the body areas where subjects applied the product, and 2) determine whether pregnant or breastfeeding women would ask a health professional before use as instructed on labeling. The endpoints were the proportion of subjects who used the product on the correct body areas (no damaged skin and avoiding contact with eyes/lips/mouth) and adherence to the pregnancy/breastfeeding warning. While a point estimate and confidence interval were calculated for the first secondary endpoint, no *a priori* threshold was set.

Similarly as for the primary endpoints, the Applicant set conditions for mitigating usage and selection decisions. They include the following:

- Subject unintentionally applied product to eyes, lips or mouth once or twice and with minimal exposure
- Subject unaware of pregnancy until after choosing to purchase product, i.e., subject had a positive pregnancy test after making a selection decision (Visit 1)
- Subject unaware of pregnancy during use phase of trial, i.e., subject had a positive pregnancy test at the EOT (Visit 2)
  - Because this type of trial is intended to simulate a naturalistic environment, contact between investigators and subjects is intentionally kept to a minimum. Although there were three subjects who became pregnant during the trial, there was no mechanism for contact to inform the investigator of these pregnancies at the time they became known to those subjects. The product labeling is intended to provide all necessary information for safe and proper use in an OTC setting (see subsection “Safety in JUNO Trial” below)
- Subject was pregnant or breastfeeding and had previously been prescribed the product, by their physician, under same conditions
- Subject reports having eczema and acne, but eczema is at a different location and subject applies product to acne sites only
Subject reports having eczema at the same sites as acne, but understands to use the product for acne only.

Table 18 demonstrates a high proportion of subjects applying the product to the correct body areas, areas that subjects self-reported the presence of acne. There were no great differences based on literacy level or age. Of the 921 who correctly used the product, nine had usage mitigated based on criteria established \textit{a priori}, and four were mitigated by \textit{post-hoc} criteria. Eight of the first nine subjects with mitigated behaviors unintentionally applied the product near their eyes, ears, or mouth, or did so because their acne was near those sites, but only once or twice. The ninth subject applied the product to damaged skin at the site of acne, but only once due to “stinging” skin. The final four mitigations were for application to acne sites near the lips (N=3) and on an area of dry skin (N=1), the latter an apparent effect of the drug product on the acne site. Therefore, 96\% (908/945) were initially correctly using the product. Of the incorrect users (N=24), 17 reported applying the product to damaged skin either because they had acne at the site, the subjects considered the damage mild, or the drug did not cause further irritation. The remaining seven subjects were “applying the product like lotion; all over the face” as categorized under the applicant’s “core themes.” There were no apparent differences, by subgroups, in the reasons why subjects misused. Selection decisions by women who were pregnant or breastfeeding are addressed in the review of the self-selection study and above in the subsection, Demographics.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{SE 1: Statistics} & \textbf{All Subjects} (N=947) & \textbf{Normal Literacy} (N=822) & \textbf{Low Literacy} (N=125) & \textbf{12-17 years} (N=203) & \textbf{\geq 18 years} (N=744) \\
\hline
\textbf{Subjects who used product on correct body areas}\textsuperscript{a} & N/M\textsuperscript{b} (%) & N/M\textsuperscript{b} (%) & N/M\textsuperscript{b} (%) & N/M\textsuperscript{b} (%) & N/M\textsuperscript{b} (%) \\
\hline
921/945 (97.5) & 799/820 (97.4) & 122/125 (97.6) & 194/203 (95.6) & 727/742 (98.0) \\
\hline
95\% CI & (96.2, 98.4) & (96.1, 98.4) & (93.1, 99.5) & (91.8, 98) & (96.7, 98.9) \\
\hline
\end{tabular}
\caption{Analysis of Use on Correct Body Area - Secondary Endpoint 1}
\end{table}

CI = 2-sided exact 95\% confidence interval
\textsuperscript{a} Final corrected use = number of subjects with overall correct behavior (uncorrected use + \textit{a priori} mitigation + \textit{post-hoc} mitigation) divided by actual use population.
\textsuperscript{b} M is the number of subjects who used the product and had no missing assessments (two subjects had missing assessments – both had normal health literacy as per REALM testing and were \geq 18 years of age).
Source: Modified from Applicant’s submission, Module 5.3.5.2, ‘Synopsis,’ Table 7, p. 8.
Safety in JUNO Trial

Pregnancy is not generally considered an AE, but any birth defects, congenital anomalies or other seemingly adverse outcome (e.g., spontaneous abortion) reported by women who were pregnant or who became pregnant during use of a test product during clinical trials would be considered an SAE. However, in the JUNO trial, the Applicant identified pregnancies as an AE since the labeling instructs to seek advice from a health professional before use, and female users of childbearing potential are expected to be aware of this warning to take
adequate precautions when determining whether the drug is appropriate for their use. During the trial, four women (subjects #05008, 10016, 15007 and 28002), all over 18 years of age, became pregnant.

Two of the women who became pregnant during the trial also reported coincident AEs, headaches and dry skin. Three spoke with a doctor during the trial, but none of those women discussed their use of adapalene with their doctors. Two did not stop using the product afterward (one had already applied her final dose and did not think disclosing its use was relevant). The third decided to terminate the pregnancy for unrelated, personal reasons. She was contacted by the investigators inquiring about her reasons. The fourth subject had not seen a doctor because she only discovered she was pregnant at the EOT visit. Following conclusion of the trial, the Applicant and primary investigator attempted on multiple occasions to contact (by email, telephone and letter) these women, to no avail. There is no information on the final outcomes of three pregnancies.

The Applicant indicates that skin-related AEs (e.g., erythema, scaling, dryness, pruritis, burning) may occur in up to 40% of product users as per the Rx labeling. The frequency of these AEs generally declines after the first month of daily use and the conditions typically improve spontaneously after drug discontinuation. In total, 471 (49.7%; 471/947) subjects in the user population reported at least one AE (N=1012 AEs). Over 88% were mild in severity and none were serious. There were no significant differences in the types of AEs reported when comparing subjects less than 18 years of age (N=114), to those greater than 18. Table 19 demonstrates the most frequently reported (>2%) AEs in the JUNO trial. In some instances, included AEs are closely related to the listed PT, e.g., nasal congestion and nasopharyngitis.
Table 19: Frequency of AEs (>2% total; N=1012) in JUNO Trial

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>All Subjects, N; (% AEs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>179 (17.7)</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>106 (10.5)</td>
</tr>
<tr>
<td>Erythema</td>
<td>46 (4.5)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>40 (3.9)</td>
</tr>
<tr>
<td>Nasal congestion/nasopharyngitis</td>
<td>39 (3.9)</td>
</tr>
<tr>
<td>Skin burning sensation</td>
<td>39 (3.9)</td>
</tr>
<tr>
<td>Skin exfoliation</td>
<td>39 (3.9)</td>
</tr>
<tr>
<td>Seasonal allergies</td>
<td>37 (3.7)</td>
</tr>
<tr>
<td>Acne</td>
<td>30 (3.0)</td>
</tr>
<tr>
<td>Sunburn</td>
<td>29 (2.9)</td>
</tr>
<tr>
<td>Back pain</td>
<td>23 (2.3)</td>
</tr>
<tr>
<td>Abdominal pain/discomfort</td>
<td>21 (2.1)</td>
</tr>
<tr>
<td>Rash/papular rash</td>
<td>21 (2.1)</td>
</tr>
</tbody>
</table>

Source: Modified from Applicant’s submission, AE datasets for JUNO Trial.

The proposed labeling warns users not to apply to damaged skin including where “cuts, abrasions, eczema, sunburned” skin is present. In total, 80 users reported having damaged skin during the use phase, either in the same area as their acne or at other body sites. Reports ranged from sunburn and other accidental burns to cuts/abrasions and dry, scaly or peeling skin. Twenty (25%; 20/80) reported using the product on damaged areas because their acne was located there as well. Most of these users indicated that their skin was only mildly irritated and not worsened by application, or reported understanding that some irritation was likely early in the use period. Some subjects who reported stinging or irritation stopped applying the product to those areas, but even these subjects reported only mild severity of those effects.

In the Rx setting, users with sunburn are advised not to use the product until “fully recovered.” The DFL instructs users not to use on sunburned skin, to avoid excess sun exposure and tanning beds, and to use sunscreen. In this trial, 29 users (3%; 29/947) reported “sunburn.” Fourteen (48.3%; 14/29) were < 18 years of age. All events except one (moderate) were considered mild, and 11 subjects were reported to either interrupt (N=6) using the product or reduce (N=5) their applied dose.

Ten subjects used adapalene on non-acne sites and four reported AEs. These subjects thought the product may help with their skin conditions, e.g., rosacea and psoriasis. All events but skin dryness, for one subject, were resolved or resolving by the EOT. Another notable circumstance is when subjects continue using other topical acne drugs, or drugs with potential for skin irritation, while also using adapalene. Concomitant topical acne drugs include various marketed products containing ingredients such as benzoyl peroxide, salicylic
acid, and dapsone. In such cases, irritation may worsen. These subjects reported a total of 63 AEs, mostly skin-related AEs or headache. Nearly all were mild.

Of subjects who applied the test product more than once daily (N=180), i.e., subjects initially considered as incorrect users by one of the primary endpoints, 88 (49%, 88/180) reported AEs (N=190). None of the AEs was serious, and they were nearly all reported as mild in severity. The most frequently reported events for these subjects were grouped under the System Organ Classes (SOC) Skin and Subcutaneous Tissue Disorders (N=64; 33.7%), Nervous System Disorders (N=31; 16.3%) and Injury, Poisoning and Procedural Complications (N=20; 10.5%). The most frequently reported AEs were skin conditions (e.g., dry skin, peeling skin, burning skin sensation, red/erythematous skin), headaches and seasonal or multiple allergies.

Subjects participated in the JUNO Trial’s use phase for a mean 41.4 days (median 42 days), of which over 93% (882/947) remained in the trial for at least five weeks. The Consumer Information Leaflet (Appendix 3) informed subjects that results would appear after two weeks of daily usage. Based on subject body chart reporting and tube weights recorded at the EOT visit, mean use of the product was 24.3 g with a maximum reported use of 129.5 g. Overall, 85.7% (812/947) used less than one tube of the drug product (< 40 g). Thus, one may estimate that less than one gram (~ ¼ teaspoon; 40 g over 41 days) was applied per day over duration of five weeks for most subjects. Further, there were no major differences in mean quantity used or range of quantities used when compared by age (12-17 years, 18-29 years, 30-39 years, 40-49 years, 50+ years) or health literacy level. In addition, a greater proportion of adolescent subjects used 40 g or more during the 6-week use period than adults (17.2% vs. 13.8%). Female subjects used slightly less (23.4 g) adapalene than male subjects (26.2 g) over the use phase.

Subjects were asked to describe their acne, but not necessarily its severity. The terms “blackheads,” “whiteheads,” “scarring,” “oily skin,” and “other” were allowed in response to those requests to describe acne. Therefore, it is difficult to determine whether subjects with, subjectively, more severe acne purchased/used more product than other subjects.

Thirteen subjects (1.37%; 13/947) used at least 80 g, nearly two tubes (90 g), or more of adapalene over the six week treatment phase. Nine were in the 12-29 year age bracket and five were women of childbearing potential. Of these subjects, the seven greatest users (> 91 g) reported no AEs that appeared related to use of the drug (skin-related). A few other high users did report skin-related AEs such as dry, red or pruritic skin, but all were mild and only one reported reducing the dose applied. None discontinued from the trial.

Nine subjects discontinued the JUNO trial due to AEs (Table 20). All AEs were mild in severity.
## Table 20: Findings for Discontinued Subjects - JUNO Trial

<table>
<thead>
<tr>
<th>Subject</th>
<th>Demographics</th>
<th>Medical History</th>
<th>Usage History</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>17047</td>
<td>18 years; M; normal literacy</td>
<td>NC</td>
<td>3/10/15 – 4/3/15; 32 g</td>
<td>Pruritis, redness at application site</td>
</tr>
<tr>
<td>20054</td>
<td>15 years; M; normal literacy</td>
<td>NC</td>
<td>3/22/15 – 3/25/15; 1 g</td>
<td>Redness, irritation at application site</td>
</tr>
<tr>
<td>24012</td>
<td>34 years; F; normal literacy</td>
<td>NC; Negative pregnancy test x 2</td>
<td>2/19/15 – 3/23/15; 7.4 g</td>
<td>Cold virus; peeling at application site</td>
</tr>
<tr>
<td>25008</td>
<td>14 years; F; normal literacy</td>
<td>NC; Negative pregnancy test x 1</td>
<td>Diary incomplete; ND</td>
<td>Rash, burning at application site</td>
</tr>
<tr>
<td>25012</td>
<td>14 years; F; normal literacy</td>
<td>NC; Negative pregnancy test x 2</td>
<td>3/10/15 – 4/16/15; 20.3 g</td>
<td>Sleepiness; increased acne</td>
</tr>
<tr>
<td>26043</td>
<td>27 years; F; normal literacy</td>
<td>NC; Negative pregnancy test x 2</td>
<td>3/15/15 – 4/8/15; 11.9 g</td>
<td>Worsening acne</td>
</tr>
<tr>
<td>26047</td>
<td>13 years; F; low literacy</td>
<td>NC; Negative pregnancy test x 2</td>
<td>3/15/15 – 4/15/15; 21 g</td>
<td>Virus; dry skin</td>
</tr>
<tr>
<td>27045</td>
<td>26 years; F; normal literacy</td>
<td>NC; post-hysterectomy</td>
<td>3/26/15 – 4/16/15; 19.7 g</td>
<td>Peeling skin* at application site</td>
</tr>
<tr>
<td>30020</td>
<td>51 years; F; normal literacy</td>
<td>NC; post-menopausal</td>
<td>3/9/15 – 3/22/15; 3 g</td>
<td>Increased blemishes</td>
</tr>
</tbody>
</table>

Source: Applicant’s amendment, Module 5.3.5.2, Case Report Forms (Discontinued Subjects).
M/F: Male/Female; NC: Non-contributory; ND: No data; *Subject 27045 was the only one to report AE not resolved.

### 3.5 Clinical Perspective

The following are intended to provide a brief clinical summary of the findings from Galderma’s application for OTC marketing of its Differin® Gel, 0.1%:

- The mean ± SD C\text{max} and AUC\text{0-24h}, following application of Differin Gel, 0.1%, appear to be within the systemic concentration range observed with the adapalene 0.1% strength products.
- When comparing the exposures of animals at the NOAEL for teratogenicity to human maximum use exposure, the margin of safety for adapalene is estimated to be approximately 70 times (204/2.9) for rats and 357 times (1036/2.9) for rabbits.

Findings from the JUNO Trial may predict how adapalene is likely to be used in the OTC setting. A summary of those findings is as follows:

- The JUNO Trial appeared to be well-designed with an adequate study size to claim that the major \textit{a priori} endpoints were met successfully.
  - The Applicant’s mitigation criteria for selection decisions and the major endpoints appeared reasonable overall.
  - The majority of subjects appeared to use the product as directed, both in dosing regimen and for the intended indication, treatment of acne.
Some subjects reported using the product more than once daily to seek greater benefit or to treat more severe “breakouts.”

- Subjects generally applied adapalene to only their target acne areas, avoiding more sensitive or damaged skin, or they understood that the product may be irritating and stopped use appropriately.
- The proportion of low literacy subjects was low, but there were no apparent differences in how subjects, differing by age, gender or literacy, selected to use or used the product over the duration of the trial.
- There were adequate numbers of adolescent subjects and female subjects enrolled in the trial.

- Few subjects were pregnant and wished to purchase and use the product without advice from a learned intermediary.

- While the Applicant provided details on the purchase decisions of breastfeeding women, the risks for infants in this circumstance may only be significant if mothers are applying the product to their chests and the drug transfers to the infant’s facial area. Risks associated with absorption and presence in breast milk are not known, but are likely minimal.

- Few subjects reported intending to use the product on non-acne conditions and few used the product on non-acne skin sites when they had acne and another non-acne skin condition.

- Reported AEs were mostly mild in severity and skin-related. There were no serious events and only eight subjects discontinued the trial due to AEs. Most subjects used less than one tube during the trial, but even those highest quantity users did not report AEs that raised any safety concerns.

- There were four pregnancies that occurred over the duration of the use period. Only one woman appeared to incorrectly continue to use the product when she ought to have sought the advice of a healthcare provider.

Although the single ingredient prescription adapalene drug products are all approved for use by pediatric patients 12 years of age and older. The OTC availability of this product may result in widespread off-label use by children younger than 12 years of age. Notably, Epiduo® was approved in 2013 for use by pediatric patients as young as 9 years of age. and FDA’s Division of Pediatric and Maternal Health currently recommends that firms developing new acne treatments study pubertal patients as young as 9 years, which is the lower end of the age range for onset of acne vulgaris.
4 Appendices

4.1 Appendix 1: Current Prescribing Information
DIFFERIN - adapalene gel
Galderma Laboratories, L.P.

---------
DIFFERIN®
(adapalene gel)
Gel, 0.1%
Rx Only

DESCRIPTION:

DIFFERIN® Gel, containing adapalene, is used for the topical treatment of acne vulgaris. Each gram of DIFFERIN Gel contains adapalene 0.1% (1 mg) in a vehicle consisting of carbomer 940, edetate disodium, methylparaben, poloxamer 182, propylene glycol, purified water and sodium hydroxide. May contain hydrochloric acid to adjust pH.

The chemical name of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. Adapalene is a white to off-white powder which is soluble in tetrahydrofuran, sparingly soluble in ethanol, and practically insoluble in water. The molecular formula is C_{28}H_{28}O_{3} and molecular weight is 412.52. Adapalene is represented by the following structural formula:

![Chemical Structure of Adapalene](image)

CLINICAL PHARMACOLOGY:

Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes all of which represent important features in the pathology of acne vulgaris.
Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene may normalize the differentiation of follicular epithelial cells resulting in decreased microcomedone formation.

**Pharmacokinetics:**

Absorption of adapalene through human skin is low. Only trace amounts (<0.25 ng/mL) of parent substance have been found in the plasma of acne patients following chronic topical application of adapalene in controlled clinical trials. Excretion appears to be primarily by the biliary route.

**INDICATIONS AND USAGE:**

DIFFERIN Gel is indicated for the topical treatment of acne vulgaris.

**CONTRAINDICATIONS:**

DIFFERIN Gel should not be administered to individuals who are hypersensitive to adapalene or any of the components in the vehicle gel.

**WARNINGS:**

Use of DIFFERIN Gel should be discontinued if hypersensitivity to any of the ingredients is noted. Patients with sunburn should be advised not to use the product until fully recovered.

**PRECAUTIONS:**

**General:**

If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during the use of adapalene. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with adapalene.
Avoid contact with the eyes, lips, angles of the nose, and mucous membranes. The product should not be applied to cuts, abrasions, eczematous skin, or sunburned skin.

Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning, or pruritus may be experienced during treatment. These are most likely to occur during the first two to four weeks and will usually lessen with continued use of the medication. Depending upon the severity of adverse events, patients should be instructed to reduce the frequency of application or discontinue use.

**Drug Interactions:**

As DIFFERIN Gel has the potential to produce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices, or lime) should be approached with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid in combination with DIFFERIN Gel. If these preparations have been used, it is advisable not to start therapy with DIFFERIN Gel until the effects of such preparations in the skin have subsided.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**

Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.3, 0.9, and 2.6 mg/kg/day and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day, approximately 4-75 times the maximal daily human topical dose. In the oral study, positive linear trends were observed in the incidence of follicular cell adenomas and carcinomas in the thyroid glands of female rats, and in the incidence of benign and malignant pheochromocytomas in the adrenal medullas of male rats.

No photocarcinogenicity studies were conducted. Animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or to sunlight. Although the significance of these studies to human use is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial UV irradiation sources.

In a series of in vivo and in vitro studies, adapalene did not exhibit mutagenic or genotoxic activities.

**Pregnancy:**

Teratogenic Effects. Pregnancy Category C. No teratogenic effects were seen in rats at oral doses of adapalene 0.15 to 5.0 mg/kg/day, up to 120 times the maximal daily human topical
dose. Cutaneous route teratology studies conducted in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day, up to 150 times the maximal daily human topical dose exhibited no fetotoxicity and only minimal increases in supernumerary ribs in rats. There are no adequate and well-controlled studies in pregnant women. Adapalene should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN Gel is administered to a nursing woman.

**Pediatric Use:**

Safety and effectiveness in pediatric patients below the age of 12 have not been established.

**ADVERSE REACTIONS:**

Some adverse effects such as erythema, scaling, dryness, pruritus, and burning will occur in 10-40% of patients. Pruritus or burning immediately after application also occurs in approximately 20% of patients. The following additional adverse experiences were reported in approximately 1% or less of patients: skin irritation, burning/stinging, erythema, sunburn, and acne flares. These are most commonly seen during the first month of therapy and decrease in frequency and severity thereafter. All adverse effects with use of DIFFERIN Gel during clinical trials were reversible upon discontinuation of therapy.

**OVERDOSAGE:**

DIFFERIN Gel is intended for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. The acute oral toxicity of DIFFERIN Gel in mice and rats is greater than 10 mL/kg. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

**DOSAGE AND ADMINISTRATION:**

DIFFERIN Gel should be applied once a day to affected areas after washing in the evening before retiring. A thin film of the gel should be applied, avoiding eyes, lips, and mucous membranes.
During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of the medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results should be noticed after eight to twelve weeks of treatment.

**HOW SUPPLIED:**

DIFFERIN (adapalene gel) Gel, 0.1% is supplied in the following size:

45 g laminate tube - **NDC 0299-5910-45**

**Storage:**

Store at controlled room temperature 68° - 77°F (20° - 25°C), excursions permitted between 59° and 86°F (15° - 30°C). Protect from freezing.

Marketed by:
GALDERMA LABORATORIES, L.P.
Fort Worth, Texas 76177 USA

Mfd. by:
G Production Inc.
Baie d’Urfe, QC, H9X 3S4 Canada
Made in Canada.

GALDERMA is a registered trademark.

P50045-1
Revised: April 2011
## 4.2 Appendix 2: Proposed Drug Facts Label

### Drug Facts

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adapalene 0.1%</td>
<td>Acne treatment</td>
</tr>
</tbody>
</table>

### Uses
- For the treatment of acne
- Clears up acne pimples and acne blemishes

### Warnings
- For external use only.

### Do not use
- on damaged skin (cuts, abrasions, eczema, sunburned)
- If pregnant or breast-feeding, ask a health professional before use.

### When using this product
- avoid unnecessary sun exposure, including tanning beds, and use sunscreen when going outdoors.
- irritation (redness, itching, dryness, burning) is more likely to occur:
  - in the first few weeks of use
  - if using more than one topical acne medication at a time.
- moisturizers may be used to relieve dry skin.
- avoid contact with eyes, lips and mouth. If contact occurs, immediately flush with water.
- during the early weeks of use, your acne may appear to worsen before it improves; this is not a reason to stop using the product.
- do not wax to remove hair in areas where product has been applied

### Stop use and ask a doctor if
- irritation becomes severe

### Keep out of reach of children
- If swallowed, get medical help or contact a Poison Control Center right away.

### Directions

#### Inactive Ingredients
- carbomer 940, edetate disodium, methylparaben, poloxamer 182, propylene glycol, purified water and sodium hydroxide. May contain hydrochloric acid to adjust pH.

### Questions?
- 1-866-735-4137
### 4.3 Appendix 3: Consumer Information Leaflet

**Patient Leaflet**

What is Differin and what is it used for?
- Differin is a once-a-day topical medication used for the treatment of acne in people age 12 and older.
- It works under the skin to unclog pores and clear up acne pimples and acne blemishes.

How long will it take for Differin to work?
- Results should start to appear after two weeks of daily usage.

What should I know before using the product?
- If pregnant or breast-feeding, ask a health professional before use.
- Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

How do I apply the product?
- Gently cleanse your entire face using a mild cleanser and pat dry.
- Differin should be applied as a thin layer to the entire face and any other affected areas of the skin once daily. Differin is not a spot treatment and should not be used to treat a single pimple or blemish.
- You should avoid contact with eyes, lips and mouth. If contact occurs, immediately flush with water.
- Do not apply product to damaged skin (cuts, abrasions, eczema, or sunburned skin).

How often do I apply the product?
- Apply this product once daily and you should try to apply the product at the same time each day if possible.

Can I use a moisturizer if my skin is dry?
- Yes.

What do I do if I need to be in the sun?
- When possible, avoid unnecessary sun exposure, including tanning beds.
- When going outdoors, use a sunscreen.
<table>
<thead>
<tr>
<th>When is my skin most likely to become irritated? And what do I do?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Irritation (redness, itching, dryness, burning) is more likely to occur:</td>
</tr>
<tr>
<td>o In the first few weeks of use</td>
</tr>
<tr>
<td>o If using more than one topical acne medication at a time.</td>
</tr>
<tr>
<td>• Moisturizers may be used.</td>
</tr>
<tr>
<td>o You may use a mild, non-comedogenic moisturizer (non-pore clogging)</td>
</tr>
<tr>
<td>• Irritation usually diminishes with use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What do I do if my skin becomes severely irritated?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• If irritation becomes severe, stop use and ask a doctor before using the product again.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Can I remove unwanted facial hair by waxing while using this product?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Do not use wax to remove hair in areas where product has been applied because skin is more sensitive after waxing.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What ingredients are used in Differin?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Differin contains:</td>
</tr>
<tr>
<td>The active ingredient is adapalene 0.1%. The other ingredients are: Carbomer 940, Edetate Disodium, Methylparaben, Poloxamer 182, Propylene Glycol, Purified Water, and Sodium Hydroxide. May contain Hydrochloric Acid to adjust the pH.</td>
</tr>
<tr>
<td>• <strong>Do not use</strong> Differin if you are allergic to any of these ingredients.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How should I store this product?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Differin should be stored at room temperature [68° – 77°F]. Keep from freezing.</td>
</tr>
<tr>
<td>• Do not use the product after the expiry date marked on the crimp of the tube.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Questions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Where can I get more information?</td>
</tr>
<tr>
<td><strong>Phone:</strong> 1-800-735-4137</td>
</tr>
</tbody>
</table>
4.4 Appendix 4: Carton Label
4.5 Appendix 5: Drug Utilization Database Descriptions

**IMS Health, IMS National Sales Perspectives™: Retail**
The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that adapalene products were distributed primarily to the outpatient retail pharmacy setting based on the IMS Health, IMS National Sales Perspectives™. We focused our analysis on only the outpatient retail pharmacy setting; therefore, these estimates may not apply to other settings of care in which these products are used (non-retail and mail-order/specialty pharmacy settings).

**IMS, National Prescription Audit**
The National Prescription Audit (NPATM) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPATM receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 86% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 40 - 70% (varies by class and geography) of mail service pharmacies and approximately 45-55% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

**IMS Health, Vector One®: Total Patient Tracker (TPT)**
Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software.
systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

**Encuity Research, LLC., TreatmentAnswers™**

Encuity Research, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.
4.6 Appendix 6: FDA Adverse Event Reporting System

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on AE and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid trade names or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every AE or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an AE or medication error in the U.S. population.

Data Mining of FAERS Using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. “Data mining” refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.