CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 7, 2016
From	Jane Filie, MD
Subject	Cross-Discipline Team Leader Review
NDA/ Supplement#	020380/ S-010
Applicant	Galderma Laboratories, L.P.
Date of Submission	September 10, 2015
PDUFA Goal Date	July 10, 2016
Proprietary Name / Non-Proprietary Name	Differin® Gel/ Adapalene
Dosage form(s) / Strength(s)	Topical gel 0.1%
Applicant Proposed Indication(s)/Population(s)	1. Treatment of acne 2. Clears up acne pimples and acne blemishes For consumers 12 years and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of acne for consumers 12 years and older

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Differin Gel (adapalene 0.1% gel) is a topical retinoid indicated for the treatment of acne. I recommend approval of Differin Gel for the treatment of acne in adults and children 12 years and older. If approved, it will be the first acne treatment approved since the OTC Drug Monograph for Topical Antimicrobial Products and it will be the first in its class (retinoid).

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 is a chronic, recurring disease,

not associated with mortality but it is associated with morbidity. Acne may have significant physical and psychological morbidity, such as permanent scarring, poor self-image, depression, and anxiety. Approximately 50 million people in the United States have acne vulgaris. Although it may affect any age group, acne occurs most frequently in teenagers, with up to 85% being affected, and may persist into adulthood. The prevalence of acne in adult women is about 12%.

Not many treatment options are available OTC and they are: 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. The existing over-the-counter (OTC) topical acne products are marketed under the final OTC Drug Monograph for Topical Antimicrobial Products. No new active ingredients have been added to the monograph since 1991. Professional guidelines recommend retinoids 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.

The efficacy for this product was established for its original approval in 1996, for prescription use. To demonstrate that this product could be safely and effectively used by consumers in the OTC setting, without a learned intermediary, the Applicant conducted consumer studies which included label comprehension and self-selection studies, as well as an actual use trial. Although the Applicant did not conduct the trials exactly as per our advice, the results did show that in general consumers used the product for the correct indication (treatment of acne) and that they used it correctly, once daily. There were no apparent differences in how subjects chose to use the product and how they used it based on age, gender or literacy. The consumer studies did show that women will use the product while pregnant or may become pregnant while using the product. The adverse events were consistent with what is labeled for this product and the usage data indicated that the expected use of the product is estimated to be 0.6 g, one-third of the average amount used in the MUsT (1.9g).

With respect to safety, teratogenic effects have been associated with drugs of this class (retinoids). This is a concern as women of childbearing potential comprise a large proportion of the population that will use this product. Adapalene is a third generation retinoid which has different receptor binding properties compared to the first generation retinoids such as isotretinoin, which is known to cause birth defects in humans. For that reason, it is plausible that these chemical differences confer to adapalene a less teratogenic profile. In order to better understand the potential systemic exposure with adapalene a bioavailability study under maximal use conditions (MUsT) with adapalene was conducted and this was compared to reproductive and developmental animal data. With these data the margin of exposure was calculated. Margin of exposure is a calculation that takes the highest animal no-observed-adverse-effect-level (NOAEL) and estimates a maximum safe level of exposure for human. When comparing the exposures of animals (rat) at NOAEL for teratogenicity to human maximum exposure, the margin of exposure for adapalene 0.1% is estimated to be 70-fold. One caveat is that the exact level of exposure required to cause teratogenicity in humans is unclear. This is a wide margin of exposure considering that this value was obtained using the highest human exposure as a conservative measure; if the calculation had been conducted with a mean value of systemic exposure the margin of exposure would be even higher. In addition, the actual use trial showed that subjects in general used in average one-third of what had been used for the MUsT, which is also reassuring.

In April 2016, an advisory committee meeting was convened to discuss the safety of adapalene for use in the over-the-counter setting. The committee, which included experts in the field of dermatology and reproductive toxicology, voted unanimously that the safety of adapalene gel 0.1% for OTC use had been adequately demonstrated and the totality of the data support the use of this product in the OTC use.

My recommendation for approval of Differin Gel (adapalene 0.1% gel) is based on the totality of the safety data. I acknowledge the limitations of post-marketing reporting however, other factors support my recommendation including the fact that there is no evidence in the literature to attribute a causal association of teratogenic effects with the use of adapalene during the approximately 20 years of marketing, the lack of new safety signals, the difference in chemical receptor binding properties, the wide margin of exposure obtained from the nonclinical and bioavailability study, and the fact that the use trial indicated that the expected use of the product is estimated to be an average of 0.6 g daily, one-third of the amount used in the MUsT, all support the notion that this product can be used safely in the OTC setting, contingent upon acceptance of labeling recommendations to optimize the adequate and safe use of this

product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• 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 (also known as cysts), particularly affecting pilosebaceous follicles of the face, chest, and upper back. • Approximately 50 million people in the United States have acne vulgaris.	• Acne is a chronic, recurring disease, not associated with mortality but it is associated with morbidity. Acne may have significant physical and psychological morbidity, such as permanent scarring, poor self-image, depression, and anxiety. • Although there is no standardized grading system for acne, it is generally divided into mild, moderate and severe. • It may affect any age group, but acne occurs most frequently in teenagers, with up to 85% being affected, and may persist into adulthood. • The prevalence of acne in adult women is about 12%. Children as young as 9 years old may have acne.
Current Treatment Options	• 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. • Not many treatment options are available in the OTC setting and they are: 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	• The existing over-the-counter (OTC) topical acne products are marketed under the final OTC Drug Monograph for Topical Antimicrobial Products. • No new active ingredients have been added to the monograph since 1991. • If approved, adapalene 0.1% will be the first acne treatment approved since the monograph and it will be the first in its class (retinoids). • Professional guidelines recommend retinoids 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. • Because acne is a chronic, recurring disease, maintaining suppression of microcomedone formation with a topical retinoid is deemed effective.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	resorcinol.	
Benefit	• The efficacy of Differin (adapalene 0.1% gel) was established for its original approval in 1996. • To demonstrate that consumers can use this product adequately and safely, consumer studies were conducted including label comprehension, self-selection studies and an actual use trial (AUT). • The 6-week AUT was to include anyone who wished to purchase the product, and it should demonstrate that consumers could adequately make a correct decision to use the product based on understanding of the label and use it according to the label. The primary objectives were to show that consumers would use the product to treat only acne and that they would use the product only once a day on the same site. • Populations of main interest were women of childbearing potential, particularly pregnant women, but also adolescents and individuals with low literacy.	• The consumer studies were not conducted exactly as the Agency requested: to focus specifically in women of childbearing potential, inclusion of sufficient number of adolescents, testing of the pregnancy warnings, testing of the comprehension of the sun avoidance, include approximately 25% of individuals with low literacy. There were also some design issues (see Section 7 Clinical Efficacy). • Despite some methodological issues, the results of the consumer studies were informative as to how this product will be used in the OTC setting: ○ Pregnant women will use the product. ○ Some chose to use the product in the study and we learned reasons why they would incorrectly make that decision. ○ In general, individuals did well in the use trial as most correctly used it for acne and not other conditions (although the advertisement for the study was directed to acne sufferers) and most used it correctly once daily. ○ The subjects in general did not overuse the product; the average amount of gel was approximately 0.6g a day, which is approximately one-third of what was used for the maximum use trials which increases safety of the product.
Risk	• Adapalene belongs to the class of retinoids which as a class are associated with congenital birth defects. • Animal studies showed that this drug can cause defects in animals when given in sufficiently high doses.	• Although adapalene belongs to the class of retinoids, it is a third generation retinoid. It is a modified compound which has different receptor binding properties compared to the first generation retinoids such as isotretinoin, which is known to cause birth defects in humans. For that reason it is plausible that these differences confer to adapalene a less teratogenic

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The Agency requested also a pharmacokinetic trial to assess bioavailability of the drug under maximum use conditions, to assess the extent of absorption through the skin (Maximum Use Trial or MUsT). The study did show that the drug produces systemic levels when used topically. • Data from the animal studies and from the MUsT were used to calculate the margin of exposure for teratogenic effects (congenital anomalies) between the human level of exposure and the animal No-Adverse-Effect-Level. The margin of exposure is at least 70-fold when comparing to rats and 357-fold when compared to rabbits. Although the absorption in humans is low and the ratios indicate a wide margin of safety, the amount of exposure in humans to cause a birth defect is unknown.	profile. • An assessment of the safety data from postmarketing databases from the Applicant, FDA Adverse Event Reporting System, as well as clinical trials and literature did not support a causal association between birth defects and the use of adapalene. • An advisory committee meeting was convened to discuss the safety of adapalene for OTC. The committee, which included experts in the field of dermatology and reproductive toxicology, voted unanimously that the safety of adapalene had been adequately demonstrated and that the totality of the data supports the OTC use of this product. • It is anticipated that this drug will be used by females of childbearing potential given the high prevalence in the general population and as demonstrated in the consumer studies.
Risk Management	• The Drug Facts will provide information to promote the safe use of the product. • The correct and safe use of this product can be enhanced with labeling. Recommendations to the label are being made informed by the consumer studies.	• Because this product will be used by females of childbearing potential, more information will be provided instructing consumers to speak with a doctor if pregnant (or planning to be pregnant) or breastfeeding. • Information to clarify how this retinoid differs from other retinoids is important. Even though the absorption through the skin is low, women need to know this information so they can themselves make a more informed treatment decision without a learned intermediary in the OTC setting. • Because there is evidence showing that increased package sizing of products leads to increased usage among consumers, I suggest that consideration be given to limiting package sizes.

2. Background

The Agency initially approved adapalene as a new molecular entity in 1996, for prescription (Rx) use, 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

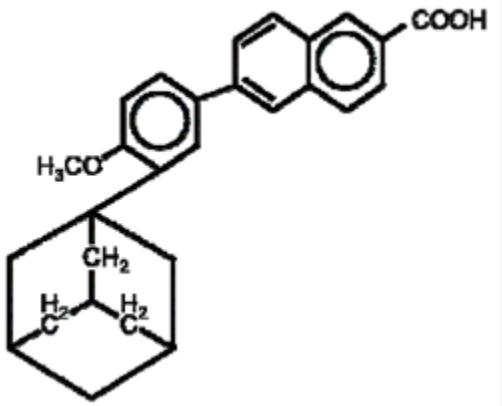
Adapalene 0.1% is also approved in combination with benzoyl peroxide 2.5 % as a topical gel (Epiduo®, NDA 22-320)). It was approved on 12/8/2008 for the topical treatment of acne vulgaris in patients 12 years of age and older and the indication was revised to include patients 9 years of age and older in February 2013, based on clinical studies conducted in this pediatric population. Differin Gel ® received a Pregnancy Category C when originally approved and it does not have a pregnancy contraindication. A higher strength of Epiduo containing adapalene 0.3%/benzoyl peroxide 2.5% was approved by the FDA in July 2015, under the trade name of Epiduo Forte®.

The Applicant seeks the indication "treatment of acne" in adults and children 12 years and older. The over-the-counter (OTC) label instructs the consumer to use once daily, and does not specify a limit on treatment duration. This product is not intended for spot treatment of acne, thus the consumer is instructed to apply a thin layer over the affected area, and if it is used on the face, to cover the entire face. The Applicant proposes to market the product as a 2 gram consumer sample tube, and in market-size tubes of 15 grams and 45 grams.

The 1% Differin gel is currently marketed as a prescription drug in the U.S., Canada, Japan, European Union and Australia, along with many other Latin American and Asian countries under several pharmaceutical forms (gel, cream, solution and lotion) for the cutaneous treatment of acne vulgaris. The 0.1% Differin® gel has also been marketed OTC in Russia since 2001.

Adapalene (6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid) is a naphthoic acid derivative with retinoid-like and anti-inflammatory properties. 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.

Adapalene has the molecular formula $C_{28}H_{28}O_3$ and the following structural formula:



Adapalene belongs to the drug class of retinoids. Retinoids are a family of compounds with structures that resemble those of vitamin A (retinol) and adapalene is a synthetic analog of retinoic acid. Retinoids are defined as natural and synthetic compounds that exhibit vitamin A–like biological activity or bind to nuclear receptors for retinoids. The formula differs from retinoic acid by replacement of double bonds with naphthoic acid aromatic rings, increasing stability.

Early use of systemic retinoids to treat acne and disorders of keratinization was limited by the toxic side effects of first-generation retinoids. This was largely solved through molecular modifications that yielded new generations of compounds with vastly improved margins of safety:

- First-generation retinoids include retinol (vitamin A), tretinoin (all-trans-retinoic acid; vitamin A acid), isotretinoin (13-cis-retinoic acid), and alitretinoin (9-cis-retinoic acid).
- Second-generation retinoids, also known as aromatic retinoids, were created by aromatization of the cyclic end group and include acitretin and methoxsalen (also known as etretinate; not marketed in the U.S.).
- Third-generation retinoids were created after the discovery of specific retinoid receptors and have diverse structures designed to optimize receptor-selective binding. Members of this generation include tazarotene, bexarotene, and adapalene.[1]

Retinoids exert their pharmacological activities by binding to specific retinoic acid nuclear receptors (RAR α, ß, γ) and cellular retinoid binding protein II (CRAB II). Compared to other retinoids, adapalene has much lower binding capacity to RABα and it does not bind to CRABII. The impact of these differences in binding are not entirely clear although could result in potentially different biological activities. The lack of activity of adapalene on RARα and CRAB II suggest that the drug may not be as potent a teratogen as other retinoids. Adapalene, though structurally distinct from retinoic acid, is considered a retinoid since it acts at retinoic acid

[1] Burkhart C, Morrell D, Goldsmith L. Dermatological Pharmacology. In: Brunton LL, Chabner BA, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e. New York, NY: McGraw-Hill; 2011. http://accessmedicine.mhmedical.com/content.aspx?bookid=1613&Sectionid=102164578. Accessed June 13, 2016.

receptors, but because of structural and difference in receptor binding some refer to adapalene as "retinoid-like".

Excerpted from the clinical review of Dr. Ryan Raffaelli (p. 16), he notes, "Retinoids are known skin irritants and teratogens. Use of these products may also make for heightened sun sensitivity because the products may decrease the number of protective layers of stratum corneum. Further, sun protection is important because retinoids are known to increase tumorigenic risk in animals following ultraviolet light exposure. While the significance of these findings in humans is unknown because photocarcinogenicity trials have not been conducted, animal studies may not be predictive, and human sensitivity to the drug is unknown, labeling recommends that sun and artificial ultraviolet light exposure be minimized or avoided."

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. Although it may affect any age group, acne occurs most frequently in teenagers, with up to 85% being affected, and may persist into adulthood. The prevalence of acne in adult women is about 12%.[2]

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[3]. 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.

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. These are the only products currently available OTC.

Below is Table 1 with the currently available treatments for acne, prescription and OTC, and Table 2 with the common side effects of topical acne therapies.

[2] Zaenglein AL, Pathy AL, Schlosser BJ, et al. American Academy of Dermatology Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2015.12.037.
[3] Zaenglein AL, Pathy AL, Schlosser BJ, et al. American Academy of Dermatology Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2015.12.037.

Table 1: Available Rx and OTC Drug Treatments for Acne Vulgaris

Treatment Class	Drug Product
Topical	
Benzoyl peroxide	Various products
Salicylic acid	Various products
Azelaic acid	20% cream; 15% gel
Antimicrobial/ keratolytic	Sulfur, Sulfur/resorcinol
Sulfa products	Sulfacetamide, Sulfacetamide/sulfur
Antibiotics	Clindamycin, Erythromycin
Retinoids	Adapalene, Tazarotene, Tretinoin
Systemic (oral)	
Antibiotics	Erythromycin, Doxycycline, Tetracycline, Minocycline
Retinoids	Isotretinoin
Oral contraceptives	Various products

Table 2: Common Side Effects of Some Topical Acne Therapies

Drug	Erythema	Sting/ Burn	Desquamation	Xerosis	Bacterial Resistance
Tretinoin 0.05%[1]	+++	++	++	++	-
Tretinoin 0.025%[1]	++	++	+	+	-
Adapalene	**+**	**+**	**+**	**+**	**-**
Azelaic acid	(+)	++	-	+	-
Benzoyl peroxide 2.5%[2]	+	+	+	++	-
Benzoyl Peroxide 5%[2]	++	++	+	++	-
Erythromycin[3]/ Clindamycin[3]	-	-	-	-	+++/ ++(+)

Source: Modified from Table 3, p. 5 (Gollnick, et al. (2014))
[1]Newer formulations are less irritating
[2]Newer formulations are less irritating
[3]Resistance occurs with monotherapy; ( ) uncommon
(Source: Clinical Review, Tables 1 and 2, p.15)

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.

Galderma (the Applicant) and FDA interacted on several occasions to discuss the development of adapalene for OTC marketing status. For a complete chronological list of FDA's interactions with the Applicant, the reader is referred to the clinical review by Dr. Ryan Raffaelli. Key issues that were discussed during the development program include:

- A pharmacokinetics assessment under maximal usage conditions was needed.

- FDA specifically requested that warnings against use in pregnancy and for sun avoidance be tested in label comprehension. FDA expressed concerns about teratogenicity and carcinogenicity potential as identified in animal studies and postmarketing experience for retinoid drug products.
- Assessment of 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.
- The Applicant was encouraged to enroll enough women of reproductive age, including adolescents, and pregnant women so that conclusions from the consumer behavior studies could be interpreted adequately.
- FDA 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.
- FDA 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. FDA recommended that the Applicant address concerns about overuse, by quantity used, body site, frequency of use and duration of use.

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. Product Quality

The review of Chemistry, Manufacturing and Controls (CMC) was performed by Dr. Donald Klein, PhD, and the secondary reviewer was Dr. Ramesh Raghavachari, PhD. The CMC reviewer recommended approval as there were no issues that would preclude approval.

There are no proposed changes to the drug substance, drug product or container closure compared to the product currently marketed under the NDA, and no Module 3 was submitted.

As there are no changes to the product, inspection of the manufacturing facilities was deemed unnecessary by Office of Product Quality and the Division of Nonprescription Drug Products concurred. With respect to environmental assessment a categorical exclusion was granted. Below is Table 3 showing the composition of Differin Gel.

Table 3: Quantitative and Qualitative Composition

	Formulation ID No: (b) (4)	
	% (w/w)	mg/g
Drug Substance		
Adapalene	0.1	1
Excipients		
Carbomer 940, NF	(b) (4)	
Propylene Glycol, USP		
Poloxamer 182		
Edetate Disodium, USP		
Methylparaben, NF		
Sodium Hydroxide, NF and/or Hydrochloric Acid, NF		
Purified Water, USP		

(Source: Nonclinical review, Table 1, p.5)

With respect to labeling, Dr. Klein recommended revisions to the Drug Facts to include a storage statement and the statement "Protect from freezing" which was resolved with the Applicant early in the review process.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by Dr. Cindy Li, PhD, and the secondary reviewer was Dr. Paul Brown, PhD. Because the Applicant has not made any changes to the formulation, the nonclinical reviewers find no impediment to approval from a nonclinical perspective, based on the Agency's previous review of the nonclinical information on the prescription adapalene products, the human use experience of adapalene, and the calculated margin of exposure for adapalene-associated teratogenicity. Dr. Li concluded (p.14) "Based on the calculated margin of exposures and adapalene's different pharmacological activity, there are less concerns for adapalene-induced retinoid related teratogenicity from a nonclinical perspective." She adds that "the level of exposure required to cause teratogenicity in humans is unclear and animal studies do not always predict human effects". In terms of labeling recommendations, because of the findings of adapalene-induced teratogenicity in animals and the presence of adapalene in breast milk in treated animals, Dr. Li recommends that the statement: "If pregnant or breast-feeding, ask a (b) (4) before use" remain on the OTC label. I concur with her recommendations.

Adapalene is a compound that exhibits biological activities similar to retinoids. Compared to typical retinoids, adapalene has much lower binding capacity to RARα and does not bind to CRAB II. Adapalene may differ from other retinoids in regard to its teratogenicity profile because of its different binding at RARα and CRAB II.

No new nonclinical studies conducted or submitted in support of the present OTC switch of adapalene. The Applicant is relying on the nonclinical data of the original approval. Differin® was approved as Pregnancy Category B and the prescription label does not have a pregnancy contraindication. Comprehensive nonclinical characterization of the pharmacological and toxicological effects of adapalene was conducted during the development of currently marketed adapalene products. Since the nonclinical profile of this product was fully addressed in the application for its original approval, my focus will be on the nonclinical data that explains the calculations of the margin of safety that was used for the benefit: risk assessment for this product and that support labeling recommendations by the nonclinical reviewers. For further details I refer the reader to Dr. Li's review.

The following are the key information on reproductive and developmental toxicity studies:

- Oral embryo-fetal development toxicity: 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.

- Dermal embryo-fetal development toxicity: 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 6 mg/kg/day (i.e. 36 or 72 mg/m2/day for rat or rabbit, respectively) was established in embryo-fetal development toxicity studies for both rats and rabbits.

- Reproductive function and fertility: There are no drug-related findings in the fertility and reproduction development studies in rats at up to 20 mg/kg/day.

- Prenatal and postnatal development studies: There are no drug-related findings in the prenatal and postnatal development studies in rats at up to 15 mg/kg/day.

- Placental/fetal exposure: In rats, the placenta acted as a partial barrier to drug and its metabolites during organogenesis and thereafter. Placental/fetal transfer was studied in pregnant female rats after single oral and repeated oral dose and after single intravenous administrations. A single oral dose of 0.1 or 1 mg/kg adapalene administered on gestation Day 13 gave exposures to the fetuses corresponding to 47% (0.1 mg/kg dose) and 28% (1 mg/kg dose) of the maternal plasma values in terms of AUC_{0-72}. After repeated oral administration at 0.1 or 1 mg/kg between gestation Days 6 and 13, fetal AUC values were less than 60% of the maternal plasma values. After a single intravenous dose of 0.5 mg/kg

^{14}C-adapalene on gestation Day 11 and 18, exposures of the fetuses corresponded to 12% and 30% of maternal plasma levels, respectively.

- Lactation: Adapalene is observed in the breast milk in treated lactating rats. When ^{14}C-adapalene was dosed either orally or intravenously to lactating rats, radioactivity was excreted in the milk and followed similar kinetics to the radioactivity in plasma, although with a lag time of approximately 3 hours.

For the estimation of the margin of safety, the NOAEL for teratogenicity of 6 mg/kg/day was established in dermal embryo-fetal development toxicity studies for both rats and rabbits. In a 10-day animal dermal pharmacokinetic (PK) study with 6 mg/kg/day adapalene gel, the mean $AUC_{0\text{-}24h}$ values of 204 and 1,036 ng·h/mL were achieved in rats and rabbits, respectively.

A margin of exposure is a calculation that takes the highest animal no observed adverse effect level (NOAEL) 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 mean and the highest human $AUC_{0\text{-}24h}$ values were 0.83 and 2.9 ng·h/mL, respectively:

- When comparing the exposures of animals at the NOAEL for teratogenicity to the highest human maximum exposure (2.9), the margin of exposure for adapalene is estimated to be approximately 70-fold (204/2.9) for rats and 357-fold (1,036/2.9) for rabbits.

- When using the mean human maximum exposure (0.83), the margins of exposure are 246-fold (204/0.83) for rats and 1,248-fold (1,036/0.83) for rabbits.

The following Table 4 is adapted from the submission showing the summary of the margin of exposure based on different clinical PK studies including the MUsT study and is presented in Dr. Li's review.

Table 4: Safety margins for teratogenicity based on the dermal rat teratogenicity study and human PK data obtained with 0.1% adapalene formulations

Formulation	Clinical PK Study No.	Number of subjects and age	Highest AUC_{0-24h} reported (ng.h/mL)	Safety margin**
Adapalene gel 0.1% (Differin 0.1%)	18115	25 (Adults)	3.47	59
	18254	6 (Adults)	1.46	140
	18254	18 (Adolescents 12 – 17 years)	2.90	70
Adapalene in Epiduo gel 0.1%*	18097	12 (Adults)	2.65	77
Epiduo Gel fixed combination		12 (Adults)	1.99	102
Adapalene lotion 0.1 %	18108	14 (Adults)	2.00	101
	18190	13 (Adolescents 12 – 17 years)	4.93	41

* Adapalene 0.1% monad in the Epiduo gel formulation, different for Differin gel.
** Safety margins calculated by dividing the $AUC_{(0-24h)}$ of 204 ng.h/mL corresponding to the dose of 6 mg/kg/day applied dermally to rats identified as the NOAEL for teratogenicity by the human exposure obtained in acne patients in the different studies performed with different 0.1% adapalene formulations.

(Source: Pharmacology/Toxocology review, p. 14)

Dr. Li also provided a comparison of teratogenicity findings in animals with adapalene and other prescription retinoids, namely tretinoin and tazarotene. The table shows that the lowest teratogenic dose for adapalene in oral embryo-fetal studies is higher with adapalene than that of other topical retinoids.

Table 5: Comparison of Lowest Teratogenic Dose Between Adapalene, Tretinoin, Tazarotene

		Adapalene	Tretinoin	Tazarotene
First Approved in		1996	1971	1997
Route		Dermal	Dermal	Dermal
Indication		ACNE Vulgaris	ACNE Vulgaris	ACNE Vulgaris
Formulation		0.1% Gel	0.01-0.025% Gel	0.05-0.1% Gel
Pregnancy Contraindication		No	No	Yes
		Lowest Teratogenic Dose in mg/kg		
Oral	Rat	25	0.4	0.25
	Rabbit	25	2	0.2
Dermal	Rat	> 6	> 1	0.25
	Rabbit	> 6	> 0.2	0.25

(Source: Pharmacology/Toxicology review, p. 13)

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). The nonclinical reviewer concluded, "Based on the calculated margin of exposures and adapalene's different

pharmacological activity, there are less concerns for adapalene-induced retinoid related teratogenicity from a nonclinical perspective." That the margin of exposure, using the highest systemic exposure from the human study as a conservative measure, shows a 70-fold safety margin." Based on this information I consider that a 70-fold margin provides assurance regarding exposure considering that the calculation is based on maximal use conditions.

5. Clinical Pharmacology

The clinical pharmacology review was conducted by Dr. Chinmay Shukla, PhD, and the secondary reviewer was Dr. Doahn Trahn, PhD. For this application the Applicant submitted a maximal use pharmacokinetic (PK) trial, RD.06.SRE.18254 also referred to as maximal use trial (MUsT). This trial which is currently recommended by the Agency for topical products was key for the assessment of safety for this product as its results were used for the calculation of the human margin of exposure relative to the systemic exposure known from the nonclinical studies.

The exact mechanism of action of adapalene in the treatment of acne vulgaris is unknown. Excretion appears to be primarily by the biliary route. Dermal absorption will be addressed with the MUsT.

Study RD.06.SRE.18254 was a multicenter, open label PK study in 24 subjects 12 years and older with moderate to severe acne vulgaris following once daily application of the to-be-marketed product for 29 days. The Applicant has made no changes to the formulation of the already marketed Differin Gel, 0.1%. Drug was applied on the entire area of the face, shoulders, upper chest and upper back. All 24 subjects completed the trial and this included 18 adolescent subjects (aged 12 to 17 years) and 6 adult subjects (aged 18 years and older). Pharmacokinetic assessment via serial blood sampling was done on Days 1, 15 and 29 and additional trough concentrations were assessed on Days 2, 10, 16 and 22 in adults and Days 2 and 16 in adolescent subjects.

By Day 29, systemic concentrations of adapalene were quantifiable in all 24 subjects and steady state was reached by Day 15. On Day 29 the mean ± SD $C_{max}$was 0.049 ± 0.030 ng/mL and AUC_{0-24} 0.83 ± 0.49 ng.h/mL, respectively. The mean AUC_{0-24} was 0.83±0.49, the median AUC_{0-24} was 0.68 and the range was 0.50-2.9. This maximum AUC_{0-24} value of 2.9 was used to calculate the margin of safety as noted in Section 4 Nonclinical Pharmacology/Toxicology. Below are Figure 1 and Table 6 showing the PK profile and PK parameters of adapalene on Day 1, Day 15 and Day 29.

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

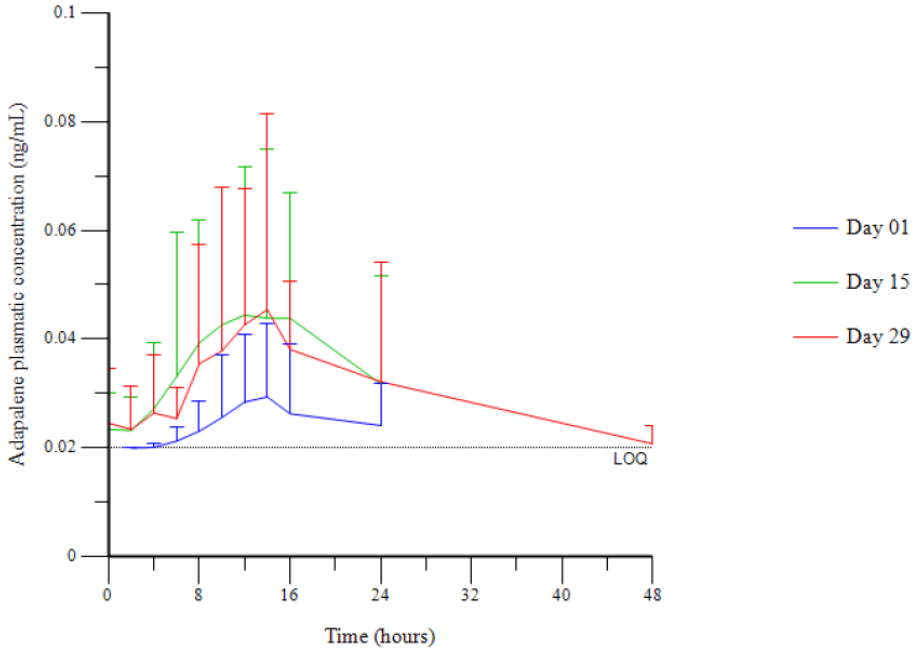


Table 6: Mean PK parameters on Day 1, Day 15 and Day 29

	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng.h/mL)	AUC_{0-t} (ng.h/mL)
Day 1 N=24, N quantifiable (%): 15 (63%)				
Mean±SD	0.033±0.015	14.3±5.4	0.57±0.14	0.41±0.27
CV%	45%	38%	25%	66%
Min, Max	<0.020, 0.066	8, 24	0.48, 0.96	0.15, 0.96
Median	0.031	14	0.52	0.35
Day 15 N=22, N quantifiable (%): 21 (95%)				
Mean±SD	0.054±0.032	12.8±5.3	0.87±0.43	0. 77±0.51
CV%	59%	42%	50%	67%
Min, Max	<0.020, 0.144	8, 24	0.48, 1.99	0.16, 2.00
Median	0.044	12	0.73	0.62
Day 29 N=24, N quantifiable (%): 24 (100%)				
Mean±SD	0.049±0.030	11.9±4.5	0.83±0.49	0.85±0.86
CV%	62%	38%	59%	101%
Min, Max	0.025, 0.171	0, 24	0.50, 2.90	0.17, 4.46
Median	0.042	12	0.68	0.65

SD=standard deviation; CV=coefficient of variation, defined as the ratio of SD to arithmetic mean
When all concentrations of a profile were BLQ, the following imputation rules were used:
LOQ value (0.02 ng/mL) for C_{max}
The lowest calculated value (i.e., 0.4752 ng.h/mL and 0.1547 ng.h/mL) for AUC_{0-24h} and AUC_{0-t}, respectively
No imputation for the mean calculation of T_{max}

(Source: Clinical Pharmacology review, Table 2, p. 5)

The most exposed subject (#8139-006) was a 16-year-old male subject. He received 1.89 gram of study medication on 1899 cm² BSA daily. He experienced adapalene levels above the limit of quantification starting with the first application. The highest systemic exposure was observed at Day 29 with a C_{max} reaching a value of 0.171 ng/mL and an AUC_{0-24h} of 2.897 ng.h/mL. It was this highest AUC in the study as noted in the table (range 0.50 -2.9) that was used in the determination of the safety margin assuming the largest absorption detected. This subject was not among those that used the highest amount of drug on the largest body surface area (BSA).

Dr. Shukla assessed other information with respect to the pharmacokinetics of adapalene 1%. In a comparison of the available data he compared the systemic concentrations of adapalene from this MUsT and noted that the systemic concentrations observed appear to be within the range of that of other topical adapalene containing products.

Age and gender did not influence the systemic absorption. The population included 24 subjects comprising eight adults (three males and three females) and 18 adolescents (10 males and 8 females). Even though the C_{max} and AUC in males appear to be numerically slightly higher than females (by about 10%), statistical analysis showed that ratios of AUC $_{0-24h}$, C_{max}, and C_{trough} between genders, and the same ratios between age groups, were not significantly different for any parameter. The results are shown as shown in Table 7 below.

Table 7: Inferential statistics: estimates of gender effect and age group effect on PK parameters

Parameter (Ratio between covariates	Ratio (90% CI)	p-value
Ratio between genders (male vs female) [a]		
AUC_{0-24h}	1.10 (0.90, 1.34)	0.439
C_{max}	1.10 (0.84, 1.44)	0.566
C_{trough}	0.95 (0.82, 1.10)	0.549
Ratio between age groups (12 to17 years vs. 18 and older) [b]		
AUC_{0-24h}	1.01 (0.80, 1.29)	0.919
C_{max}	1.04 (0.76, 1.43)	0.833
C_{trough}	1.05 (0.89, 1.25)	0.622

CI=confidence interval

For imputation, the following substitutions for missing results were made: the smallest calculated AUC value for the AUCs; otherwise LOQ was substituted for BLQ. For the calculations related to C_{max}, concentrations below the limit of quantification (BLQ) were replaced by the LOQ value (i.e., 0.02 ng/mL). In case of missing data (no sample collection, data excluded from analysis), no imputation was done and the data was excluded from analysis. Data were transformed into natural logarithms prior to analysis and the estimates and CI's were back-transformed into original scales by taking the antilog and presented in the summary table

a) Based the following model: parameter = subject + study visit + gender + random errors

b) Based the following model: parameter = subject + study visit + age group + random errors

(Source: Clinical Pharmacology review, Table 4, p. 10)

With respect to daily quantities used, mean daily medication use was 1.95 g/day (range 1.21 g to 2.92 g). The mean average daily medication use was slightly higher in males (1.97 g/day) than in females (1.92 g/day) and the mean average daily doses applied in adolescent subjects (1.85 g/day) were lower than those applied in adult subjects (2.24 g/day). The amounts applied per cm² of treated BSA ranged from 0.6 mg/cm² to 1.6 mg/cm² and the mean value was 1.1 mg/cm2.

The mean BSA treated was 1864.7 cm2 (range from 1387.4 to 2893.9 cm2). The mean BSA was higher in males (2092.3 cm2) than in females (1595.9 cm2). The mean total treated surface area was also higher in adult subjects (2022.5 cm2) than in adolescent subjects (1812.2 cm2). There were nine subjects that applied the study drug on >2000 cm2 surface area.

The mean percentage of treated surface area was 9.2% overall, and was higher in males (9.7%) than in females (8.7%). The mean percentage of treated surface area was lower in adolescent subjects (8.7%) than in adult subjects (9.4%). Below is Table 8 summarizing daily medication use, treated surface area and percentage of treated surface area.

Table 8: Summary of daily medication usage and treated surface area

	Males (N=13)	Females (N=11)	12-17 years (N=18)	18+ years (N=6)	Total (N=24)
Daily Medication Usage (g/day) determined at Baseline					
Mean	1.974	1.923	1.856	2.235	1.950
SD	0.5338	0.2488	0.3845	0.4224	0.4198
Median	1.890	1.910	1.895	2.145	1.905
Min - Max	1.21 – 2.92	1.38 – 2.26	1.21 – 2.81	1.83 – 2.92	1.21 – 2.92
Daily Average Medication Usage (g/day) [a]					
Mean	1.974	1.920	1.854	2.235	1.949
SD	0.5338	0.2558	0.3869	0.4224	0.4217
Median	1.890	1.910	1.895	2.145	1.905
Min - Max	1.21 – 2.92	1.35 – 2.26	1.21 – 2.81	1.83 – 2.92	1.21 – 2.92
Total Treated Surface Area (cm^2) [b]					
Mean	2092.262	1595.855	1812.172	2022.450	1864.742
SD	443.1489	243.5190	384.2249	584.6664	438.2693
Median	2109.400	1495.900	1778.800	1905.100	1778.800
Min - Max	1395.40 – 2893.90	1387.40 – 2196.70	1387.40 – 2787.30	1416.70 – 2893.90	1387.40 – 2893.90
Percentage of Treated Surface Area (%) [c]					
Mean	9.665	8.717	9.399	8.725	9.231
SD	1.5238	1.3865	1.6032	1.1576	1.5100
Median	9.510	8.590	9.490	8.600	9.420
Min - Max	6.92 – 13.05	6.80 – 11.27	6.92 – 13.05	6.80 – 10.21	6.80 – 13.05

SD=standard deviation

a) Daily average medication usage = total medication usage (g) throughout the study divided by actual study drug exposure (days)

b) The total treated surface area (cm^2) is calculated as the actual treated surface area of the upper back and upper chest, including shoulder, and the estimated facial surface area (2% of total body surface area)

c) The percentage of treated surface area is calculated as the total treated surface area divided by total body surface area × 100

(Source: Clinical Pharmacology review, Table 14, p.19)

Only three subjects had daily doses >2.5 g. Summary of systemic exposure of subjects at steady state in subjects applying the highest amount of study drug (> 2.5g) to the highest surface area (>2000 cm^2) is shown in Table 9 below.

Table 9: Systemic exposure to adapalene at steady state in subjects applying the highest amount of drug product (>2.5 g) to the highest surface areas (>2000 cm^2)

Subject No / Day		Age (years)	Daily dose weight (g)	Total treated surface area (cm^2)	Percentage pf body surface area (%)	C_{max}[a] (ng/mL)	AUC_{0-24h}[b] (ng.h/mL)
8076-009	Day 15 Day 29	15	2.81	2081.2	9.35	0.063 0.064	0.77 0.68
8076-013	Day 15 Day 29	18	2.51	2207.6	10.21	NR 0.049	NR 0.98
8076-017	Day 15 Day 29	43	2.92	2893.9	9.58	0.026 0.033	0.52 0.67

NR: Not reportable – the parameter could not be calculated

a) C_{max}: overall mean±SD, (median), min-max values obtained at Day 15 in this study: 0.054±0.032, (0.044), <0.02-0.144 ng/mL; at Day 29: 0.049±0.030, (0.042), 0.025-0.171 ng/mL

b) AUC_{0-24h}: overall mean±SD, (median), min-max values obtained at Day 15 in this study: 0.87±0.43, (0.73), 0.48-1.99 ng.h/mL; at Day 29: 0.83±0.49, (0.68), 0.50-2.90 ng.h/mL

(Source: Clinical Pharmacology review, Table 15, p. 20)

The adverse events noted in this trial with maximum use exposure were mild to moderate and commensurate with the known labeled effects on the prescription product. No discontinuations occurred due to adverse events.

The applicant has not conducted any new drug interaction studies or any new trials to assess the effect of renal and hepatic impairment on PK of adapalene following topical application of Differin Gel, 0.1%. The clinical pharmacology team has no labeling recommendations.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Sources of Clinical Data for the OTC Marketing Status

No new clinical efficacy trials with Differin Gel 0.1% were submitted with this NDA application. Below are the lists of studies conducted to support the approval of Differin Gel for OTC marketing. These included social science studies (Table 10) and clinical trials (Table 11) (excerpted from the clinical review, p. 24).

Table 10: List of Studies - Differin Gel, 0.1% for OTC Marketing Status

Type	Trial ID	1° Objective	Design	# Subjects	Diagnosis	Duration
LCS (U.S.)	100544	Comprehension – once daily; not on healthy skin	MC, label evaluation	586 (12-70 years); 130 low literacy; 282 12-18y	All comers	Single visit
SSS (U.S.)	103439	Self-selection in pregnant or BF women - advice seeking behavior	MC, label evaluation	293 (13 – 54 years); N= 2(< 18y)	Pregnant or BF; 91 pregnant (37%)	Single visit
SOCS* (U.S.)	1022234	Prescribing, counsel and care information by prescribers/ patients	Survey (qualita-tive)	233 (13 – 69 years)	Differin users and prescribers	N/A

Source: Applicant's submission, Module 5 and Module 1.14; ID – Identification; 1° - Primary; LCS – Label Comprehension Study; MC – Multicenter; SSS – Self-selection Study; BF – Breastfeeding; SOCS – Standard of Care Study; N/A – not applicable

*This study does not contribute to our assessment of the benefit-risk profile of Differin Gel used in the OTC setting. It had many limitations which are described in Ms. Cohen's review and in the background material in preparation for the April 15, 2016 Advisory Committee Meeting. It is included here only for completeness.

Table 11: List of Clinical Trials – Differin Gel, 0.1% for OTC Marketing Status

Type	Trial ID	Objective	Design	# Subjects	Diagnosis	Duration
PK (U.S.)	18254	Assess maximal usage PK	R,MC,OL	24 (18 were 12 – 17 years)	Acne vulgaris	29 days
Actual Use (U.S.)	100931	Use in OTC setting	MC,OL	947 (12 – 73 years); N=203 < 18	Report acne vulgaris	6 weeks

Source: Applicant's submission, Module 5.2 – Tabular listing of all clinical studies; ID – Identification; PK – Pharmacokinetics; R – Randomized; MC – Multicenter; OL – Open Label

The review strategy was as follows:

- Clinical Efficacy: Dr. Amy Woitach from the Division of Dermatology and Dental Products (DDDP) provided a general assessment and recommendation on the appropriateness of adapalene marketed in the OTC setting.
- Maximal Use Trial: Dr. Chinmay Shukla (see Section 5 Clinical Pharmacology)
- Label Comprehension, Self-Selection and Standard of Care Studies: Ms. Barbara Cohen and Scott Komo, DrPH
- Actual Use Trial: Dr. Ryan Raffaelli and Scott Komo, DrPH

Clinical Efficacy

No new clinical efficacy trials with Differin Gel were submitted with this NDA application. The clinical reviewer Dr. Amy Woitach, MD, from DDDP, the collaborative division, provided a general assessment and recommendation on the appropriateness of switching adapalene 0.1% from prescription to OTC marketing. Her secondary reviewer is Dr. David Kettl, MD. The clinical reviewers from DDDP do not recommend the approval for Differin Gel because in their opinion the concern of potential teratogenic effects, has not been adequately addressed and the Applicant has not provided an acceptable plan to mitigate the potential teratogenic risk without the presence of a learned intermediary. Nevertheless, the Office of the Division of Dermatological and Dental Products (Dr. Tatiana Oussova, Deputy Director for Safety), and the Office of Drug Evaluation III (Dr. Julie Beitz), recommend approval of Differin Gel. I do not fully concur with the clinical reviewers and I will discuss our difference in opinions following.

Dr. Woitach provided a synopsis of the efficacy data that supported the approval of the original application (excerpted from Dr. Woitach's review, p.5-6):

"A total of five controlled clinical studies were conducted with adapalene gel 0.1% in subjects with mild to moderate acne vulgaris, two of which were vehicle-controlled. Primary assessments were at 12 weeks. Table 1 below provides a summary of the results and a description of the study designs and outcome follows.

Table 1

Study Number		Week 12 % Reduction from baseline			
		Adapalene 0.1%	Retin-A 0.025%	Vehicle	p Value or 95% Conf Interval
C-89-61	Non-inflammatory lesions	**48%**	39%	35%	**.059**
	Inflammatory lesions	**46%**	44%	36%	.138
9105-CD271G-EV	Non-inflammatory lesions	26%		1%	**.001**
	Inflammatory lesions	34%		12%	**.01**
	Global Grade	1.21		1.34	**.058**
CR88091	Non-inflammatory lesions	73%	**81%**		-18,2
	Inflammatory lesions	65%	**71%**		-20,9
	Global Grade	**77%**	74%		-8,14
CR89064	Non-inflammatory lesions	63%	**64%**		-1,1
	Inflammatory lesions	55%	**60%**		-16,6
	Global Grade	54%	**57%**		-11,6
CR 89-32	Non-inflammatory lesions	**46%**	33%		**.2,26**
	Inflammatory lesions	**48%**	38%		-2,22

Vehicle controlled

1. Study C-89-61 a multicenter, randomized, double-blind, parallel study of 180 subjects randomized 2:2:1 to adapalene 0.1%, Retin-A and vehicle. In this study, adapalene failed to beat the vehicle and was not therapeutically equivalent to Retin-A.
2. Study 9105-CD 271G-EV a multicenter, randomized, double-blind, parallel study of 256 subjects randomized 1:1 to adapalene 0.1% gel and vehicle. The study provides statistical evidence to support that adapalene 0.1% gel is therapeutically better than vehicle ($p>0.05$) for the primary efficacy variables, inflammatory and non-inflammatory lesions.

Dose-ranging

3. Study CR 88051is a controlled, randomized, investigator masked, three arm, 2 center study 0.03% adapalene gel, adapalene 0.1% gel, 0.025% Retin-A gel. 89 subjects demonstrated that adapalene 0.1% was not therapeutically equivalent to Retin-A based on efficacy, but better tolerated than Retin-A based on local safety assessments.

Active-control

4. Study CR 89064 (European Study) is a multicenter, 268 subject, 2- arm active-control trial wherein the primary objectives are to demonstrate therapeutic equivalency of adapalene 0.1% gel, 0.025% Retin-A gel for both inflammatory and non-inflammatory lesions. Adapalene 0.1% was not therapeutically equivalency to Retin-A based on inflammatory lesions, was therapeutically equivalent based on non-inflammatory lesions, and better tolerated than Retin-A based on local safety assessments.

5. Study CR 89-32 is a multicenter, randomized, investigator masked parallel group study comparing adapalene 0.1% gel and 0.025% Retin-A gel in 290 subjects. The primary objectives are to demonstrate therapeutic equivalency of adapalene for both inflammatory and non-inflammatory lesions. Adapalene 0.1% was statistically better than Retin-A based on non-inflammatory lesions, was therapeutically equivalent based on inflammatory lesions, and better tolerated than Retin-A based on local safety assessments.

Approval was granted based on totality of the data showing a favorable risk/ benefit for adapalene gel 0.1%. Her main issue is not how effectively this product will be used in the OTC setting, but in her opinion this product has unresolved safety concerns that would preclude the approval of this product for OTC use."

Dr. Woitach expressed the following concerns in her review:

- Regarding use:
  - Subjects with low literacy appear to have a more difficult time than normal literacy subjects in comprehending instructions to use the product once daily.

  - A number of subjects used the product more than once daily and in some cases it appears to be based on subscribing to the idea that 'more is better'. Also concerned about application to larger body surface area, occlusion, simultaneous use of vitamin A or dietary supplements, and other retinoid-containing products such as cosmetics.

  - Subjects may use in damaged skin and under occlusion.

    CDTL Comment: In general consumers tested well in terms of once daily use. It is not uncommon a difference in the performance of low literacy subjects. This will be addressed through labeling to instruct consumers to use only once daily and provide language explaining that using more does not provide better improvement or sooner. Consumers also tested well with regard to not using on damaged skin. It is unlikely that the acne treated areas on the face would be occluded, and use of clothing is not considered occlusive as a diaper, or socks and shoes would be.

  - Due to study design, information on potential off-labeled use for conditions known to respond to retinoids (e.g. fine lines, wrinkles, melasma) and potential use on skin conditions that would increase systemic absorption could not be determined.

CDTL Comment: I acknowledge that the actual use study was not optimal to capture off-label use information because the advertising was directed towards acne sufferers. However, the actual use trial showed that of the nine subjects (9/1,277, 0.7%) that were excluded from the use phase of the trial because they did not have acne, said they wanted to "prevent acne", "unclog pores", "remove the blemishes" and "even out the skin tone". None of them wanted to use the product for non-acne conditions such as eczema, psoriasis, or age-related wrinkling or other skin conditions.

- Regarding use in pregnant women:

  - The data demonstrate 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. Additionally, pregnancy females would be unlikely to discuss adapalene use with their physician(s).

  - Four subjects in the actual use trial became pregnant within the 6-week study (median duration 42 days) and a number of other pregnant females would have used the product if not for investigator intervention. Based this trial along with the other consumer studies, if the product should become available OTC, adapalene will be used in pregnancy females. This use will likely occur in various stages of pregnancy. Also, given the reluctance of a number of practitioners to use retinoids in pregnancy, it is possible that a larger number of pregnancy females will be exposed to adapalene if the product moved into the OTC setting.

  - The teratogenic risk is unknown since the adapalene threshold for human teratogenicity is unknown.

  - Although the committee was unanimous in its support for OTC marketing, there appeared to be various levels of concern regarding the pregnancy labeling. The rationale that supports that product is safe to be used OTC, but should be contraindicated in pregnancy in labeling is inconsistent. This reviewer finds that the varied opinion on how to inform patients in the OTC setting about the use of adapalene in pregnancy supports the position of keeping the product available by prescription where these complicated concepts that the panel was trying to convey in labeling, can best be discussed with a learned intermediary.

    CDTL Comment: Although the applicant did not follow our recommendations regarding the recruitment in the self-selection study of the desired population, and the lack of testing of communications that we considered key, the study was still informative. We did learn that pregnant women will use the product and that they may become pregnant while using the product. We also learned some reasons why pregnant women would still take the product (not noticing the warning, misconception regarding the safety of an OTC drug, misconception that a dermal drug can be absorbed, among others). My recommendations will include elements in the label that will better inform so women can make a correct decision and if choosing to use it, to use the product properly. The totality of the safety data, acknowledging the limitations of post-marketing reporting, the

fact that there is no evidence in the literature to attribute a causal association of teratogenic effects with the use of adapalene, the margin of exposure obtained, the lack of new safety signals and the fact that the use trial indicated that the expected use of the product is estimated to be 0.6 g, one-third of the amount used in the MUsT give me assurance that this product can be used safely in the OTC setting with appropriate labeling.

- Regarding safety signals (pharmacovigilance, case reports):

  - Post marketing adverse event reporting would never be sufficient to further characterize the risk, and affected pregnancies would likely never be identified in the absence of "classic" retinoid embryopathy.

  - A literature report describes a 55-year-old female with Darier disease developed hepatitis with long-term used of adapalene 0.1% cream daily for 8 months. She applied 15 tubes of 30g adapalene over a period of 8 months, to a body surface area (BSA) of 15%.

  - In January 2016, Germany's Federal Institute for Drugs and Medical Devices recommended against releasing adapalene gel 0.1% (in 25 gram packages) from medical prescription (b) (4)

CDTL Comments: As noted above, the limitation of the post-marketing safety databases are known. Nevertheless this product has 20 years of marketing and the literature does not have reports or other information attributing teratogenic effects to adapalene. This reviewer acknowledges this literature report of hepatitis associated with the use of adapalene given the temporal association and positive dechallenge, however this represents a single case. I note that in the MUsT study none of the subjects had elevation of liver function tests. Hepatitis and elevation of hepatic enzymes are not labeled adverse events on either Rx labels for adapalene 0.1% or 3% gel.

Lastly, a search of the site of Germany's Federal Institute for Drugs and Medical Devices identified a core safety profile for adapalene gel and cream 0.1% (16/05/2011) and it states: "…Absorption of adapalene through human skin is low, and therefore interaction with systemic medications is unlikely…

…Pregnancy
Animal studies by the oral route have shown reproductive toxicity at high systemic exposure. Clinical experience with locally applied adapalene in pregnancy is limited but the few available data do not indicate harmful effects on pregnancy or on the health of the foetus exposed in early pregnancy. Due to the limited available data and because a very weak cutaneous passage of adapalene is possible, adapalene should not be used during pregnancy. In case of unexpected pregnancy, treatment should be discontinued." Accessible at: http://www.bfarm.de/SharedDocs/Downloads/EN/Drugs/vigilance/PSURs/csp/a-b/adapalene.pdf?__blob=publicationFile&v=3

I refer the reader to Section 8 Safety of this CDTL memo and to the review by the Office of Surveillance and Epidemiology for further information.

Consumer Studies

Label Comprehension Study

The Label Comprehension Study (LCS) was a single-visit study designed to address comprehension of the following primary objectives:

1. "Use once daily"
2. "Do not use on damaged skin"

Both objectives were assessed at the lower bound of the 95% confidence interval of the target threshold of 85%. 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. Also the Applicant declined to test the sun exposure warning as a primary objective; the tanning bed component of the sun exposure was tested as a secondary objective. The Applicant has proposed a Consumer Information Leaflet (CIL) but this has not been assessed in comprehension testing.

The study population was all comers. The LCS was conducted in 586 subjects 12 years of age and older at eight sites. The study population was all comers. Five hundred fifteen (515) subjects were enrolled as follows:

- Cohort 1, which was the general population cohort, and 71 subjects were enrolled in the augmented low literacy cohort, which was recruited to increase the number of low literacy (LL) subjects in the study.
- Cohort 2, (low literacy population), which constituted 22% of the 586 enrolled subjects, included the low literacy subjects from both Cohort 1 and the augmented low literacy cohort.

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 important 18 to 24-year-old age group. Only 33 respondents in the entire study were between the ages of 18 and 24 years old. Hispanics were significantly under-represented in the study population, particularly in the adolescent population.

For "Use once daily," comparing the normal literacy (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 pvalue< 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. See Table 12.

Table 12: Label Comprehension Study Results – Primary Objectives

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

LCB = 2-sided exact 95% lower confidence bounds
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)
(Source: Statistical review, Table 5, p.10)

Comprehension rates by gender and literacy level for the primary objectives are presented in Table 13:

- 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 pvalue=0.32).

Table 13: Comprehension for the Primary Objectives by Gender and Literacy – All Ages

Primary Objective	Normal Literacy % (n/N) (LCB)		Low Literacy % (n/N) (LCB)	
	Female	Male	Female	Male
Directions: Use once daily	96.0 (267/278) (93.0)	97.2 (173/178) (93.6)	85.3 (52/61) (73.8)	88.4 (61/69) (78.4)
Do Not Use: On damaged skin (cuts, abrasions, eczema, sunburned)	97.5 (271/278) (94.9)	97.2 (173/178) (93.6)	100.0 (61/61) (94.1)	98.6 (68/69) (92.2)

LCB = 2-sided exact 95% lower confidence bounds
(Source: Statistical review, Table 6, p. 12)

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).

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. Table 14 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 NL adolescents (95.7%) and LL adolescents (84.9%). The difference overall in comprehension rates between males and females was not statistically significant (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 pvalue= 1.00).

Table 14: Comprehension of Primary Objective "Use Once Daily": NL vs LL Adolescents (Age 12-17)

Normal Literacy % (n/N) (LCB)			Low Literacy % (n/N) (LCB)		
Total NL	Female NL	Male NL	Total LL	Female LL	Male LL
95.7 (200/209) (92.0)	96.0 (119/124) (98.8)	95.3 (81/85) (88.4)	84.9 (62/73) (74.6)	83.9 (26/31) (66.3)	85.7 (36/42) (71.5)

*LCB = 2-sided exact 95% lower confidence bound
(Source: Statistical review, Table 7, p. 12)

Awareness of the need to avoid tanning beds and the need to consult a physician for potential users under age 12 tested well.

In summary, the two primary objectives of this study - "Use once daily" and "Do not use on damaged skin" tested well among NL participants. Ms. Cohen notes the following issues:

- 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.

- The comprehension of "do not use on damaged skin" may have been artificially inflated due to the wording of the question, which potentially cued the response. As this was designated as a primary study objective, clinical team would need to weigh in on whether this potentially inflated comprehension is of concern when consumers use the product.

- Due to the lack of adequate representation of participants 18 to 24 years old in the sample, definitive conclusions cannot be drawn about either the overall comprehension of this key subgroup or the differences between its NL and LL participants.

- Although low literates and 12 to 14 year olds tested significantly lower than other NL and older participants, respectively, for these labeled statements, their actual comprehension scores are not lower than some of the comprehension scores associated with other product approvals. Potential study biases could have artificially inflated all of the scores.

- Hispanics were underrepresented particularly in the adolescent population.

- Children 12 to 14 years olds are most likely to use acne products, yet they are least likely to understand, respectively, "use once daily" and "under 12 years of age, ask a physician", in the event that they decide on their own to share with younger siblings.

- 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.

Self-Selection Study

The primary objective of the targeted self-selection study (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.

The self-selection study was conducted from November 2013 to January 2014 among 293 unique pregnant/breastfeeding females ages 13 to 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 LL 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.

There were 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. Also there were only two adolescents in the entire study. 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.

The Applicant was not able to demonstrate that pregnant or breastfeeding women could adequately self-select to use the product. In Cohort 1, 74.4% of the subjects [2-sided exact 95% CI of (68.4%, 79.8%)] correctly stated that they would ask a healthcare professional before using 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%. This suggests that a

substantial proportion of pregnant or breastfeeding women would not consult a healthcare professional before using the product.

Table 15 shows the general population (Cohort 1) results by age, literacy, and pregnancy/ breastfeeding status.

Table 15: Self Selection Results -General Population Correct Self-Selection

Age	Pregnant only % (n/N)			Breastfeeding only % (n/N)			Pregnant and Breastfeeding % (n/N)			Total % (n/N)		Grand Total % (n/N)
	NL	LL	Total	NL	LL	Total	NL	LL	Total	NL	LL	
13-17	100.0 (1/1)	--	100.0 (1/1)	--	--	--	--	0.0 (0/1)	0.0 (0/1)	100.0 (1/1)	0.0 (0/1)	50.0 (1/2)
18-24	69.6 (16/23)	46.7 (7/15)	60.5 (23/38)	84.6 (33/39)	56.3 (9/16)	76.4 42/55)	100 (1/1)	66.7 (2/3)	75.0 (3/4)	79.4 (50/63)	52.9 (18/34)	70.1 (68/97)
25-34	80.0 (20/25)	83.3 (5/6)	80.7 (25/31)	78.0 (39/50)	75.0 (9/12)	77.4 (48/62)	75.0 (3/4)	100.0 (1/1)	80.0 (4/5)	78.5 (62/79)	79.0 (15/19)	78.6 (77/98)
35-44	62.5 (5/8)	100.0 (2/2)	70.0 (7/10)	76.9 (20/26)	75.0 (3/4)	76.7 (23/30)	100.0 (1/1)	--	100.0 (1/1)	74.3 (26/35)	83.3 (5/6)	75.6 (31/41)
45-54	--	--	--	100.0 (3/3)	0.0 (0/1)	75.0 (3/4)	--	--	--	100.0 (3/3)	0.0 (0/1)	75.0 (3/4)
Total	73.7 (42/57)	60.9 (14/23)	70.0 (56/80)	80.5 (95/118)	63.6 (21/22)	76.8 (116/151)	83.3 (5/6)	60.0 (3/5)	72.7 (8/11)	78.5 (141/181)	62.3 (38/61)	74.4 (180/242)

(Source: Social science review, Table 12, p. 20)

The Applicant was not able to demonstrate that pregnant women could adequately self-select to use the product. Because of potential concern about pregnant-only women using Differin® (as contrasted with the entire pregnant population together with the breastfeeding population), a subgroup analysis of the pregnant-only women in Cohort 1 was conducted. As Table 15 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%). based on the following: the LCB is over 30 percentage points below the target threshold of 90%. This suggests that a substantial proportion of pregnant women would not consult a healthcare professional before using the product.

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 16 shows 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 16: Table 13: Self-Selection Results - Pregnant-only General Population Correct Self-Selection by Age

Age group	Correct self-selection rate % (n/N)
13-17	100.0 (1/1)
18-24	60.5 (23/38)
25-34	80.7 (25/31)
35-44	70.0 (7/10)

(Source: Social science review, Table 13, p.13)

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 and likewise, the subgroup of pregnant-only women – the focus of greatest concern. Regarding age and literacy levels within the pregnant only subgroup, only 55% of low literacy pregnant women 18 to 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.

Ms. Cohen concluded that overall the LC and SSS taken together show that a significant number of adult women of childbearing age will use Differin® OTC even if they know they are pregnant when starting the product. She also notes that while it is true that correct comprehension is not the same as correct behavior, it is also the case that according to the clinical reviewer, correct usage of once a day was seemingly validated in the actual use study.

Regarding labeling, Ms. Cohen recommends that a pregnancy and breastfeeding statement remain in the DFL, and that the pregnancy warning be somehow strengthened. She contends that if for no other reason many consumers are aware of this statement on the Drug Facts Label and to delete it altogether would imply to consumers that this product is inherently safer than many products on which it currently appears. Also, because it appears from the self-selection study that breastfeeding women will use this product, she recommends that a statement about hand washing after application be incorporated into the CIL.

She also recommends that the label contain additional language (either in the DFL or CIL) to implicitly nudge consumers toward use as directed only once a day and/or explicitly discourage overuse. Explanations as to why overuse will not lead to quicker results may be

helpful. I concur with her recommendations and I will further address the labeling changes in Section 12 Labeling.

Actual Use Trial

This trial was reviewed by Dr. Ryan Raffaelli, MD, and the statistical analysis by Scott Komo, DrPH. The actual use trial – JUNO, was a 6-week, open label, multi-center trial conducted in 1277 subjects, ages 12 years and older, who self-reported having acne. Of the total, 947 subjects chose to purchase the study drug. Females that were pregnant, were excluded from the use phase of the trial, as well as women who self-reported breastfeeding.

The primary objectives were:

- To evaluate the correct frequency of use (i.e., no more than once daily in the same location).
- To determine whether the product was used for acne only (i.e., not off-label use).

The secondary objectives were:

- To evaluate if the product was used on correct body areas (i.e., was not used on damaged skin and contact with eyes, lips, and mouth were avoided)
- To determine if pregnant or breastfeeding women stated they would ask a health professional before use as instructed on the warnings section of the Drug Fact Labels
- To assess self-reported adverse event (AE) data in an unsupervised OTC environment

Twelve hundred seventy-seven (1277) subjects entered the AUT. Nine hundred forty-seven [947 (74.2%)] of the 1277 screened subjects chose to purchase the study drug, used it at least once, and were included in the actual use and safety populations. This included 822 subjects (86.8%) of normal literacy (NL) and 125 subjects (13.2%) of low literacy (LL). FDA expects that in consumer behavior studies 22-28% of the subjects have low health literacy. In the study, the majority of the subjects were females (68%), a substantial proportion of the subjects were adolescents (21%) and the majority (52%) subjects were white. The Applicant set a quota of ≥ 10% of the enrollees to be children 12-17 years of age.

The threshold for success rate was the lower bound > 85% for each primary endpoint. Overall, both primary objectives performed well with 89.1% (2-sided 95% exact LCB: 87.0%) of the subjects correctly using the product once daily in the same location and 99.3% (2-sided 95% exact LCB: 98.5%) of the subjects used the product exclusively for acne.

In the AUT, the correct use rates for both of the primary objectives were high - "Use the product once daily in the same location" and "Use the product exclusively for acne". However, in the small number of women (6) who were pregnant at Visit 1, only a small proportion of the women correctly (16.7%; 1/6) stated they would ask a health professional before using the product. This result is consistent with the self-selection results from the SSS. The proportions of subjects in the NL and LL groups who used the product correctly were similar (89.1% and 89.6%, respectively). When considered by age, 90.6% of the subjects who were 12 to 17 years of age and 88.7% of the subjects who were ≥ 18 years of age used the product correctly. See Table 17 below.

Table 17: Correct actual use by literacy and age

Endpoint	Final Correct Actual Use Rate n/N (%) (95% CI)				
	All Subjects	Normal Literacy	Low Literacy	12-17 Years	≥ 18 Years
Once Daily Use in the Same Location	844/947 (89.1) (87.0, 91.0)	732/822 (89.1) (86.7, 91.1)	112/125 (89.6) (82.9, 94.3)	184/203 (90.6) (85.8, 94.3)	660/744 (88.7) (86.2, 90.9)
Exclusive Use in Acne	938/945 (99.3) (98.5, 99.7)	814/820 (99.3) (98.4, 99.7)	124/125 (99.2) (95.6, 100)	202/203 (99.5) (97.3, 100)	736/742 (99.2) (98.2, 99.7)

95% CI: 2-sided 95% exact lower confidence bound
(Source: Statistical review, Table 20, p. 27)

The most frequent reasons for using the product incorrectly were:

- using it whenever they showered or washed their face, i.e., sometimes twice daily (34%; 35/103)
- seeking to achieve greater, or faster, benefit (24.3%; 25/103)
- to treat "severe" acne (18.4%; 19/103)
- because they misread the directions or used it as per "my routine," usually twice daily (8.7%; 9/103)

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.

Regarding off-label use, it should be noted however, that the advertising used to recruit subjects was targeted at consumers who self-reported acne sufferers which made it difficult to estimate the rate of off-label use in the general public. 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. It should be noted however, that the advertising used to recruit subjects was targeted at consumers who self-reported acne sufferers which made it difficult to estimate the rate of off-label use in the general public. According to Dr. Raffaelli, there was a discrepancy in the number of subjects with eczema identified. Dr. Raffaelli identified 48 subjects with eczema or were currently experiencing an exacerbation, of those 23 made a purchase decision, 14 participated in the treatment phase and nine were excluded because they did not have acne. purchased and used the product. 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.

It should be noted that the advertising used to recruit subjects was targeted at consumers who self-reported acne sufferers which made it difficult to estimate the rate of off-label use in the

general public. Among the 104 subjects who incorrectly selected to purchase the product, 20 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.

Regarding pregnancy, the results indicate that pregnant women will use the product. 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. Nearly half (43.9%) of the enrolled population was women of childbearing potential (12-54 years of age). 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. Two of the women did not know they were pregnant until the pregnancy test was administered and the remaining 3 women did not specifically state (unprompted) that they would ask a health professional before using the study product. 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.

At Visit 1, six women were pregnant and only one (16.7%) correctly stated she would ask a health professional before using the product. This result is consistent with the self-selection results from the SSS. During the trial, four women, all over 18 years of age, became pregnant. 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. The fourth subject had not seen a doctor because she only discovered she was pregnant at the end-of-trial (EOT) visit. There is no information on the final outcomes of three pregnancies.

Regarding pediatric consumers, seven potential subjects were younger than 12 years of age:

- Two of these subjects reported that they would not purchase due to their age, or would ask a doctor first.
- Five subjects were within 12 months of their 12th birthday and they wanted to purchase for use, because they simply wanted to improve their acne and had been unsuccessful using other products.

Although the single ingredient prescription adapalene drug products are all approved for use by pediatric patients12 years of age and older. If available it is possible that children younger may use the product as acne may occur in children as young as 9 years old.

Regarding quantities used, 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. 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. Dr. Raffaelli estimated that the subjects used an average of 0.6 g applied per day (which is approximately 1/3 of the average daily amount of 1.95 g used in the MUsT trial) as noted in his review (p. 43).

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 12 to 29 years old 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.

Regarding adverse events, here were no important differences in the event reporting by age or gender. Most events (88%) were mild, although 49.7% of subjects reported at least one, with the most common being headache, dry skin and erythema. Skin-related events accounted for four of the top seven Preferred Terms reported. Notably, none of the seven highest quantity users (> 91 g) reported any skin-related events. Only 2% of users reported applying the product to damaged skin or non-acne sites and 3% reported sunburn. Nearly all reported events by these subjects were mild and many noted that continuing application of the product did not worsen skin irritations.

Dr. Raffaelli concluded that the trial was well designed and adequately powered to achieve most of its objectives and I concur. The trial showed that in general consumers will be able to use the product correctly. The proportion of LL 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. 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.

Standard of Care Studies

The Applicant conducted a Standard of Care (SOC) study. It contained a physician SOC sub study that enrolled 151 physicians and a patient SOC sub study that enrolled 233 patients. The Applicant conducted a Standard of Care (SOC) study to examine current physician practices and consumer experiences with prescription adapalene products (Differin® and EpiDuo®) as well as other retinoid and retinoid-like acne products. The study was conducted as two sub-studies, a physician SOC and a patient SOC, where participants answered questionnaires. Methodological issues involving both the physician and patient standard of care sub studies were identified and thus the Division decided not to use these studies in its regulatory decision-making. For further information I refer the reader to the Social Science review by M. Cohen

CDTL Conclusions on the Evidence of Effectiveness

Overall, the Applicant provided the evidence that this product can be used in the OTC setting, contingent upon agreement with labeling changes that are ongoing at the time this review is being finalized. Despite several drawbacks in the consumer studies such as lack of testing of the pregnancy warning and sun exposure avoidance, not recruiting enough pregnant women and adolescents, the consumer studies provided valuable information to inform labeling. Overall consumers tested well with the primary objectives established "once daily use on the same location" and "exclusive use on acne". Despite the fact that the proportion of subjects with LL did not meet the expected 22-28% of the population, the results showed that selection and use of the product did not differ significantly by age, gender or literacy.

8. Safety

Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In all phase 2/3 trials worldwide in which the applicant has so far evaluated the safety of adapalene gel, 2,121 subjects have applied the drug at least once, with 661 treated in trials (up to 12 months' duration) to support original approval of the NDA. In the MUsT, 24 subjects were enrolled. Eighteen were < 18 years of age, with six over age 18. Thirteen were male and 11, female. All 24 received the study drug. On average, subjects applied 1.95 g/day ranging 1.2 to 2.9 g. Three subjects applied daily doses > 2.5 g. Mean dose applied by adolescents was less than that applied by adults > 17 years of age (1.85 g/day vs. 2.24 g/day). The total treated body surface area (BSA) averaged 1,864.7 cm2 (range 1,387.4 – 2,893.9 cm2). BSA was greater in adults vs. adolescents (2,022.5 cm2 vs. 1,812.2 cm2). All exposures were over 1,300 cm2.

Table 18 below shows the maximum concentrations and areas under the curve following trial exposures of up to 2 g 0.1% adapalene applied daily for 30 days with different formulations. The Applicant indicates that normal daily use may provide maximum exposure of 0.5 g per day, such that a 15 g tube is equivalent to a 30- day supply.

Table 18: Maximum Systemic Exposure in Trials with Adapalene 0.1% Formulations

Formulation	Clinical Study#	Subjects	N	N quantifiable (at steady state)[a]	Most exposed subject	
					AUC_{0-24h} (ng.h/mL)	C_{max} (ng/mL)
Epiduo gel, 0.1%	SRE.18097	Adults	12	1	1.99	0.13-0.21
Monad adapalene, 0.1 %	SRE.18097	Adults	12	1 to 2	2.65	0.16
Adapalene Lotion, 0.1%	SRE.18108	Adults	14	1	2.00	0.13
	SRE.18190	Adolescents	13	5	4.93	0.24
Adapalene 0.1 % Gel	SRE.18115	Adults	25	4 to 7	3.47	0.20-0.31
	SRE.18254	Adults Adolescents	24 (6 adults +18 adolescents)	21 to 24[b]	2.90	0.17

a Steady state: PK sampling dates varied across studies from Day 10/15 to Day 28/30
b LOQ=0.02 ng/mL for study SRE.18254 only; LOQ=0.1 ng/mL for other studies

Source: Clinical review, Table 11, p. 46-47)

The Applicant assessed exposure in the naturalistic setting of the Juno trial. The mean duration of treatment was 41.4 days (median 42 days), with 93.1% of subjects (882/947) remaining in the trial for at least five weeks. This length of daily use should have provided the average subject the opportunity to see some improvement. A 45 gram tube was available for purchase and subjects could purchase a maximum of three tubes (135 g). The directions on the label were to apply a "thin layer" over the entire affected area. There was no maximum dose. Based on subject body chart reporting and tube weights at the EOT visit, mean use of the product was 24.3 g (standard deviation 16.87) 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):

- Regarding literacy level, LL subjects had a slightly higher mean usage (26 g), median usage (26.3 g vs. 22.2 g) and similar range of quantities used (1.4- 116 g).
- Regarding age, subjects ≥ 18 years had a slightly lower mean usage (24.1 g vs. 25.1 g), but higher median usage (22.8 g vs. 20.6 g) than subjects 12 to 17 years of age. There were no trends in total quantity used when subjects were stratified by alternative age brackets (12 to -17 years, 18 to -29, 30 to -39, 40 to -49 and 50+).
- Regarding gender, women used slightly less (23.4 g) than men (26.2 g) over the duration of the trial.

In the total user population, 13 subjects (1.37%; 13/947) used more than 80 g, or close to two tubes of adapalene over the 6-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.

Sources of Safety Data

The following were the sources of safety data:

- Clinical trials

- Post-Marketing Data:
    - Applicant's post-marketing pharmacovigilance
    - FDA Office of Surveillance and Epidemiology review

Clinical trials

The following are the clinical trials used by Dr. Raffaelli to evaluate safety:

- MUsT – A Pharmacokinetic Study to Determine the Systemic Exposure in Differin® 0.1% Topical Gel During Dermal Application Under Maximal Use Conditions for 4 Weeks in Adolescent and Adult Subjects with Acne Vulgaris
- Actual Use Trial – JUNO- Pivotal Actual Use Study for Adapalene 0.1% Gel Safety in Clinical Trials Safety in Postmarketing data

In the MUsT, hematology, biochemistry and urine pregnancy and drug screen laboratory panels were tested at screening for all subjects. End-of-trial labs were tested where indicated. In addition, tolerability was assessed with scales for erythema, scaling, dryness and stinging/burning. There were no significant trends, compared to baseline, in lab values over the duration of the trial. While subjects reported some skin changes in the tolerability assessments, none were severe and none resulted in discontinuation. There were no serious adverse event reported. In the MUsT, 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." Of note, no subjects presented increases of liver enzymes and this information is relevant because of a case report presented by OSE of a patient who presented hepatitis while using adapalene which is described in the section Post-Marketing Safety Evaluation by the Office of Surveillance and Epidemiology following.

In the JUNO trial there were nine discontinuations due to adverse events. They were mostly skin related known adverse effects were mild and these did not raise any safety concerns. 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 treatment phase. Reports ranged from sunburn and other accidental burns to cuts/abrasions and dry, scaly or peeling skin. Twenty (25%) reported using the product on those areas, mostly because their acne was in the area 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 treatment period. Some subjects who reported stinging or irritation stopped applying the product to those areas, but even these subjects reported only mild effects.

The Applicant indicated that skin-related adverse events (AEs) such as erythema, scaling, dryness, pruritis, burning, may occur in up to 40% of product users as per the prescription 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, to those greater than 18 years of age. Table 19 demonstrates the most frequently reported (>2%) AEs in the Juno trial.

Table 19: Frequency of AEs (>2% total; N=1012) in Juno trial

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

(Source: Clinical review, Table 13, p. 51)

Dr. Raffaelli identified those subjects (N=88) who reported AEs and who applied the test product more than once daily. Of all subjects who used the product more than once daily (N=180), 49% (88/180) reported an AE (N=190). None of the AEs were serious, and rarely even moderately severe. The majority of AEs reported were skin-related disorders which is expected and included in labeling for adapalene.

Dr. Raffaelli also noted concomitant use of 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. As stated elsewhere, users of adapalene who continue to use other topical acne products are likely to stop their regimen and seek medical advice if skin irritation becomes severe or persists.

Postmarketing Data

Applicant's Post-Marketing Safety Database

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 cases where 276 pregnancy cases were identified 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 20).

Table 20: Pregnancy Outcomes from Galderma's Pharmacovigilance Database

Outcome	Postmarketing surveillance
Ongoing at time of report	27
Lost to follow-up	126
Healthy baby	83
Elective termination	7
Miscarriage	16
Other	17
Total	**276**

(Source: Clinical review, Table 14, p. 57)

Eight cases 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.

Post-Marketing Safety Evaluation by the Office of Surveillance and Epidemiology

The Office of Surveillance and Epidemiology (OSE) was consulted to assess the available postmarketing data available including drug utilization data, a review of abnormal pregnancy outcomes associated with adapalene with a focus on congenital anomalies and other topical retinoids in the FAERS database, and the medical literature. In addition DNDP requested a review of all serious adverse events (SAEs) associated with adapalene with focus on off-label use on large body surface areas (BSA). The reviewers were Patty Greene, PharmD (drug utilization analyst), Lopa Thambi, PharmD and Hongliu Ding, MD, PhD. The secondary reviewers were Lynda McCulley, PharmD, Allen Brinker, MD, Lockwood Taylor, PhD, and Rajdeep Gill, PharmD.

Drug utilization

With regard to drug utilization, OSE noted a decrease from approximately 1.2 million prescriptions dispensed or 673,000 unique patients in the 12-month period ending in November 2011 to 974,000 prescriptions dispensed or 563,000 unique patients in the 12-month period ending in November 2015. The largest proportion of use was among women aged 12-45 years. the most common diagnosis associated with the use of adapalene was acne. For single-ingredient

adapalene and combination adapalene/benzoyl peroxide products, patients aged 12-45 years accounted for more than 90% of total patients across the entire review period. Of the 12-45 year old patients, females accounted for approximately 64%-74% of patients using single-ingredient adapalene products and for approximately 59%-60% of patients using combination adapalene/benzoyl peroxide products.

Pharmacovigilance
The Division of Pharmacovigilance (DPV) identified 18 serious cases of adapalene associated abnormal pregnancy outcomes in FAERS. 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]. There was one case of a congenital anomaly in the literature which described adapalene-associated anophthalmia and agenesis of the optic chiasma. This literature case was described in a previous DPV review. Of the five congenital anomaly cases, three fetuses were aborted. The five cases of congenital anomaly associated with adapalene in FAERS appear to be isolated malformations. Based on DPV's previous review of six cases and the current review of five additional cases, we do not find reasonable evidence to support a causal association between adapalene and these events.

Additionally, DPV identified 68 serious cases of abnormal pregnancy outcomes associated with single ingredient topical retinoids (alitretinoin, bexarotene, tazarotene, and tretinoin). The most frequently reported event was miscarriage (24) followed by a congenital heart defect (11), brain defects (10), and cleft palate (8). Forty-three exposures were reported in association with tretinoin, the most common strength was 0.05%. Twenty-eight exposures occurred with tazarotene, the most common strength was 0.05%.

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 in FAERS. It describes the case of a 55-year-old female with Darier disease who had been treated with acitretin (oral retinoid) long-term who developed hepatitis but recovered after discontinuing the medication (positive dechallenge). Ten months later she was treated again for a relapse of her disease with topical adapalene 0.1%. She applied 15 tubes of 30g of adapalene on approximately 15% of her body surface over 8 months. She developed hepatitis but again recovered upon discontinuation of the medication. The OSE reviewer concluded that this case supports an association between adapalene and hepatitis given the temporal association, the clinical presentation, laboratory values, positive dechallenge and absence of other causes of hepatitis.

Below is a table summarizing the most frequent serious adverse events associated with adapalene identified in FAERS (excerpted from OSE review, p. 18)

Table 20. Most frequently reported MedDRA PTs with N≥ 4 for adapalene, 1/1/1969-11/17/2015 by decreasing number of FAERS reports per PT. Total number of reports*=237

Row	MedDRA PT	Number of FAERS Reports	Labeled^ (Yes/No), Location or Other Category
1	Dermatitis	59	Yes, AR
2	Dry Skin	22	Yes, P, AR
3	Abortion Spontaneous**	15	No
4	Condition Aggravated	14	DR
5	Maternal Exposure During Pregnancy**	14	No
6	Erythema	11	Yes, P, AR
7	Pruritus	11	Yes, P, AR
8	Drug Ineffective	10	U
9	Alopecia	9	No
10	Maternal Drugs Affecting Foetus**	9	No
11	Abortion Induced**	8	No
12	Acne	8	IR
13	Pregnancy**	8	No
14	Eyelid Oedema	7	Yes, AR
15	Skin Exfoliation	7	P
16	Exposure During Pregnancy**	6	No
17	Headache	6	No
18	Face Oedema	5	Yes, W/P, AR
19	Rash	5	Yes, AR
20	Scar	5	DR
21	Skin Irritation	5	Yes, P, AR, PI
22	Application Site Reaction	4	P
23	Depression	4	No
24	Intracranial Pressure Increased	4	No
25	Product Use Issue	4	U
26	Vision Blurred	4	No

*A report may contain more than one preferred term
**DEC (drug-event combination) reviewed in the Adapalene and Abnormal Pregnancy Outcomes section
^ Definitions: BW = Box Warning, C = Contraindications, W/P = Warnings/Precautions, P=Precautions, AR = Adverse Reactions, DI = Drug Interactions, OD = Overdosage, SP= Use in Specific Populations, PCI = Patient Counseling Information, MG = Medication Guide or Other Categories: CM= Confounded by Concomitant Medications, DR = Disease-related, IR = Indication-related, PR= Procedure-related, U = Uninformative

Pharmacovigilance literature review
As part of the postmarketing pharmacovigilance, their literature search, "DPV identified one case of fetal growth retardation, anophthalmia, and agenesis of optic chiasma necessitating a medical abortion which was discussed in a previous review (OSE, Brinker, 2004). These events appear to be isolated anomalies and we do not find reasonable evidence to support a causal association between adapalene and these events at this time." (excerpted from OSE review, p. 27)

Pharmacoepidemiology literature review
Dr. Ding conducted a epidemiology review, which did not suggest an increased risk of birth defects and he explains in the review: "Findings from epidemiologic studies of topical retinoids in general 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. Furthermore, these pregnancy studies had small sample sizes and other methodological limitations that prevent conclusions regarding the safety of adapalene and other topical retinoids. Findings of a potential increased risk of ulcerative colitis and all-cause mortality are difficult to interpret. Based on a lack of a clear pattern of congenital anomalies consistent with retinoid embryopathy, and a lack of compelling medical literature in FAERS cases and epidemiological data, there does not appear to be a signal for adapalene-associated congenital anomalies at this time." (excerpted from OSE review, p. 26)

The overall conclusion from the review by OSE states: "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 embropathy. Additionally, DPV did not identify any new safety signals associated with adapalene at this time and will continue routine surveillance. Findings from epidemiologic 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 also had small sample sizes and other methodological limitations that prevent conclusions regarding the safety of adapalene and other topical retinoids."

CDTL Conclusions on the Evidence of Safety

Adapalene 0.1% has a long marketing history along with other higher concentration of 0.3%. The data from the clinical trials did not show any new safety signals particularly with the maximum expected use of the product in the MUsT. The AUT also did not identify any new AEs, but it showed that in general consumers will adequately use the product and not over use it. The AE of most concern is the teratogenic effect associated with retinoids as a class. Collectively, the safety data which includes the Applicant's assessment of the case reports identified of its own database, coupled with the extensive review by OSE does not support a causal association of adapalene and teratogenic effects. The different chemical properties of adapalene and the wide safety margin also provide assurance regarding safety of this product with respect to teratogenic potential. Lastly, the use of this product in the OTC setting was also discussed in an advisory committee meeting where the members, including reproductive toxicology experts, voted unanimously that the safety of adapalene gel 1% had been adequately demonstrated. This

product can be used safely in the OTC setting contingent upon acceptance of labeling recommendations to optimize the adequate and safe use of this product.

I note that the clinical reviewers from DDDP stated that in January 2016, Germany's Federal Institute for Drugs and Medical Devices recommended against releasing adapalene gel 0.1% (in 25 gram packages) from medical prescription (b) (4) *When I searched the site of Germany's Federal Institute for Drugs and Medical Devices I identified a core safety profile for adapalene gel and cream 0.1% dated 16/05/2011 and it states:*

"...Absorption of adapalene through human skin is low, and therefore interaction with systemic medications is unlikely...

...Pregnancy
Animal studies by the oral route have shown reproductive toxicity at high systemic exposure. Clinical experience with locally applied adapalene in pregnancy is limited but the few available data do not indicate harmful effects on pregnancy or on the health of the foetus exposed in early pregnancy. Due to the limited available data and because a very weak cutaneous passage of adapalene is possible, adapalene should not be used during pregnancy.
In case of unexpected pregnancy, treatment should be discontinued." Accessible at: http://www.bfarm.de/SharedDocs/Downloads/EN/Drugs/vigilance/PSURs/csp/a-b/adapalene.pdf?__blob=publicationFile&v=3

Given the totality of safety data, acknowledging the limitations of post-marketing reporting, the fact that there is no evidence in the literature to attribute a causal association of teratogenic effects with the use of adapalene, the margin of exposure obtained, the lack of new safety signals and the fact that the use trial indicated that the expected use of the product is estimated to be 0.6g, one-third of the amount used in the MUsT provide me assurance that.

9. Advisory Committee Meeting

On April 15, 2016, a Nonprescription Drug Advisory Committee (NDAC) meeting was convened to discuss the approval of NDA 20380 Differin Gel 0.1% as this represents the first in the class of retinoid drugs to switch from Rx to OTC marketing. The concern is the availability of this product in the OTC setting without a learned intermediary when there is a known association of teratogenic effects with drugs of this class. The committee included members of (NDAC), as well as dermatology (Dr. Kenneth Katz, MD), and reproductive toxicology (Dr. Anthony Scialli, MD, and Stephen Harris, PhD) specialists. After being presented with data from the Applicant and FDA's review of nonclinical, maximum use trial, and post-marketing safety data, as well as results from consumer studies which included label comprehension, self-selection, and actual use studies, the committee voted **unanimously (16 votes YES vs 0 NO)** that the safety of adapalene gel 0.1% for OTC use for the treatment of acne had been adequately demonstrated and the totality of the data support the use of this product OTC, for the treatment of acne for adults and children 12 years and older. The basis for the committee's favorable vote was:

- Very low absorption showed in the MUsT.

- Consumers demonstrated that they could adequately diagnose the condition and use the product properly without overusing the product.

- Lack of reported safety signals in the post-marketing databases and literature and there has been no evidence of retinoid embryopathy with its topical use.

- According to Dr. Stephen Harris, PhD, toxicology expert. the nonclinical studies were sufficient and adequately conducted and the multiples of exposure were reassuring ("I don't believe there's any teratogenic risk in human exposure, pregnant women especially. These studies satisfy my concern regarding reproductive risk.")

- Other toxicology expert, Dr. Antony Scialli, MD, also supported the use of adapalene 0.1% in pregnant women ("…So I'm not concerned. And actually, if a woman asked my advice on use of this product during pregnancy, I'd tell her to go right ahead,…")(Transcript for the April 15, 2016 Meeting of the Nonprescription Drugs Advisory Committee, p. 233, 235-239, accessible at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/UCM506325.pdf)

- Despite the fact that the Applicant did not conduct the self-selection study as requested by FDA to evaluate more pregnant women, and that the sensitivity of humans to this drug is unknown, the wide margin of safety based on the nonclinical data and the MUsT, was convincing to the committee that this product was safe for OTC use.

Much of the discussion evolved around what would be appropriate labeling for this product. The committee was divided with respect to the inclusion of warnings regarding use in pregnant and lactating women in the label. Some members opined that since teratogenicity in their opinion is not a concern with this product given the wide safety margin, the label should not carry any such language, because it may cause women undue anxiety. Other members had a different opinion because not having information about why this drug is different from other retinoids in the class may cause more anxiety to consumers and physicians as the teratogenic effects if this drug class are known and being silent may also cause distress and confusion. Similar discussion occurred regarding a warning regarding breastfeeding and likewise the opinions diverged for the same reasons.

10. Pediatrics

Pediatric and Research Equity Act

The Applicant does not seek approval of this product in children less than 12 years of age. This application does not trigger the Pediatric Research Equity Act because there is no change to the approved formulation, indication, dosing regimen or route of administration.

Consult to Maternal Health

The Division of Pediatric and Maternal Health (DPMH) was consulted to provide their assessment of the available data to address the concern of teratogenicity and their opinion with respect to the use of adapalene 0.1% by OTC consumers without a learned intermediary. The review by Dr. Tamara Johnson, MD and Dr. Melissa Tassinari, PhD, concluded that there is no robust safety signal to establish an association between adapalene and an increase in incidence for major congenital malformations. The reviewers noted that there is a large safety margin between the human systemic exposure and the animal exposure associated with adverse development outcomes.

The reviewers conducted their own review of the published literature, and found only one case of anophthalmia as the first report of a malformation following maternal use of adapalene in the first trimester. One source searched (LactMed) stated that there is a low risk to the breastfed infant due to the low systemic exposure. They also reviewed data from the applicant's clinical development program and noted that 40% of the pregnancies in the pharmacovigilance database were lost to follow-up nevertheless, the estimated rate of miscarriage (13.6%) was not increased over the 15-20% rate of miscarriage in the U.S. Also after reviewing the Applicant's 169 reported pregnancy outcomes following exposure to adapalene, the reviewers noted six cases (3.5%. 6/169) that had first trimester exposure and a type of malformation that might be expected for a retinoid, but none presented a full retinoid embryopathy. This rate was not higher than the estimated background rate of major congenital malformations which is 2-4% in the U.S. general population. No pattern of malformations was observed in this small sample.

Consult to Pediatrics

Another review by DPMH was conducted by Dr. Mona Khurana, MD and the secondary reviewer was Dr. Hari Sachs, MD. In this review DPMH gave their assessment whether the studies submitted in the NDA supported the safe use of this product by adolescents in the OTC setting. The reviewer evaluated the results of the MUsT, post-marketing safety data from a pediatric-focused safety review by the Office of Surveillance and Epidemiology presented at a May 7, 2012 Pediatric Advisory Committee meeting, and the consumer studies. Dr. Khurana noted that there were no safety concern in adolescents that are distinct from that in older patients of reproductive potential. She also suggested consideration be given to expand pediatric use down to 9 years of age based on the fact that some children younger than 12 years of age expressed they would like to use the product and there is another prescription adapalene-containing product approved for children 9-12 years of age. At this time extension of the indication to children 9 to 12 years of age will not be granted, as the sponsor has not requested the inclusion of this population, and children in this age group had not been included in the consumer studies. Dr. Khurana also made labeling recommendations to strengthen warnings on skin irritation. New language addressing skin irritation will be proposed by the Agency.

11. Other Relevant Regulatory Issues

505(b)(1) application

This application is a 505(b)(1) application.

Exclusivity

The Applicant conducted an Actual Use Trial which supported the OTC switch of Differin gel and will be considered for purposes of exclusivity.

Debarment Certification and Financial Disclosures

FDA Form 3454 was submitted. The application contains a signed debarment certification and the appropriate certifications regarding financial interests for all the clinical investigators who contributed to the studies submitted in the application. The quality of the submission was adequate and no reason was identified to question the integrity of the data.

Good Clinical Practices

The Applicant asserts that all trial procedures complied with Good Clinical Practice Guidelines and principles under the Declaration of Helsinki, as well as all applicable laws and regulations.

Office of Scientific Investigation Audit

The Office of Scientific Investigations conducted an audit of the pivotal consumer study, the Juno trial which was the actual use trial. No action was indicated, based on the review by, Sharon Gershon, PharmD, as no significant violations or major deficiencies were identified that would have impacted the conduct of the trial or the integrity of the data submitted. She concluded that the study appeared to have been conducted adequately, and the data submitted by the Sponsor may be used in support of the respective indication.

Environmental Assessment

A categorical exclusion was granted. See CMC review by Dr. Donald Kline.

12. Labeling

The proprietary name was reviewed by Dr. Grace Jones, PharmD, Division of Medication Error and Prevention Analysis. The secondary reviewer was Dr. Alice Tu, PharmD. She concluded that the proposed name Differin Gel (Adapalene) Gel, 0.1% was acceptable on November 9, 2015. The review by the labeling team has not been finalized at the time this review is being written and labeling negotiations are ongoing. The primary reviewer is Yoon Kong, PharmD and the secondary reviewer is Steven Adah, PhD.

Several labeling recommendations have been made by the clinical teams from DNDP and DDDP, social science, and labeling teams. Consideration has been given also to the suggestions made by the NDAC at the latest meeting. The committee had diverging opinions regarding the maintenance or not of the pregnancy and breastfeeding warnings.

I recommend that the pregnancy and breastfeeding warnings remain on the label. The warnings do not imply a contraindication per se as the Rx label for adapalene 0.1% does not have a contraindication for this product and the safety data available indicates that the product is safe for OTC use. The labeling is meant to provide more information so women of childbearing age can make the best individual choice without a learned intermediary and to encourage discussions with their doctors. Some recommendations are meant to improve the correct and safe use of this product based on findings from the consumer studies. For further details on proposed labeling I refer the reader to the Clinical review and the Labeling review.

My current recommendations are listed below:

- Information to clarify how this retinoid differs from other retinoids is important. Even though the absorption through the skin is low, women and healthcare providers need to know this information.
- Because there is evidence showing that increased package sizing of products leads to increased usage among consumers, I suggest that consideration be given to limiting package sizes.
- The word "retinoid" will be placed next to the name of the active ingredient. And consumers will be instructed to read the Consumer Information Leaflet (CIL) .
- Labeling "If pregnant or breast-feeding, ask a doctor before use" will remain in a more prominent position in the Warnings section.
- Labeling to "Stop use and ask a doctor…if you become pregnant or are planning to become pregnant" will be included to encourage women to think about other options and make an informed decision whether to use this product or not.
- Because some consumers used the product more than once as shown in the consumer studies, the word "only" will be highlighted, "Use **only** one time a day" and information regarding the expected time to achieve effect will help consumers understand the mode of use more clearly
- Language informing when to expect an effect also to mitigate overuse of the product ("may take up to 3 months").
- Because consumers and healthcare providers associate retinoids in general with birth defects, the CIL will provide language to clarify that although other retinoids have shown to cause birth defects, there is no evidence that this product (Differin Gel) causes birth defects if used as directed.

13. Postmarketing Recommendations

I recommend that consideration be given to limitation of quantity of drug be made available to consumers. I recommend that tube sizes be limited to no more than 45 grams and multipackaging not be allowed unless the Applicant can provide data to demonstrate that consumers will not misuse or overuse because of the availability of the product.

14. Recommended Comments to the Applicant

None.

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANE FILIE
06/17/2016