CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020380Orig1s010

OTHER REVIEW(S)

Addendum Labeling Review for Differin
Draft Labeling

SUBMISSION DATES:	June 13 (via email), 22 (via email), 29 (DARRTs) and July 6 (DARRTs), 2016
NDA/SUBMISSION TYPE:	20-380/S-010/ Efficacy Supplement
ACTIVE INGREDIENTS:	Adapalene 0.1%
DOSAGE FORMS:	gel (2-g, 15-g and 45-g tubes)
SPONSOR:	Galderma Laboratories, L.P. 14501 North Freeway Fort Worth, Texas 76177 Contact: Sean Griffin Director, Regulatory Affairs Telephone:(817)961-5334 Fax: (817)720-1040
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I. BACKGROUND

NDA 20380 proposes an Rx to OTC switch for adapalene gel 0.1%. An initial review of the proposed switch was completed and filed on June 24, 2016. Deficiencies in that review were provided to the sponsor in an information request (IR) on June 10 and June 17, 2016 (via emails).

Following review of the June 10 (sponsor response dated June 13) and June 17 (sponsor response dated June 22) deficiencies, additional IR's were sent to the sponsor on June 30 (via email, but entered into DARRTs on July 1), July 5, (DARRTs) and July 6, 2016 (via email, but entered into DARRTs on July 7). Responses were received on July 6, 2016 (DARRTs).

This review covers the six information requests (June 10 (via email), June 17 (via email), June 30 (via email, but entered into DARRTs on July 1, 2016), July 5 (DARRTs) and July 6 (via email, but entered into DARRTs on July 7, 2016) and the sponsor's responses to these.

Submitted Labeling	Date(s) Submitted
2 gram immediate container (physician sample)	July 6, 2016 (final revised labeling)
15 gram immediate container	July 6, 2016 (final revised labeling)
45 gram immediate container	July 6, 2016 (final revised labeling)
2 gram outer carton (physician sample-not for sale)	July 6, 2016 (final revised labeling)
15 gram outer carton	July 6, 2016 (final revised labeling)
45 gram outer carton	July 6, 2016 (final revised labeling)
Consumer information leaflet	July 6, 2016 (final revised labeling)

II. REVIEWER'S COMMENTS

A. Information request sent to sponsor on June 10, 2016 (Response received June 13, 2016)

1. Drug Facts Label – All SKUs

FDA Request -

a. The ***Active*** ingredient should read as follows: Adapalene 0.1% (retinoid)* with the statement "*read consumer information leaflet" underneath of it.

b. ***Warnings***

(1) **Do not use**

Under this subheading:

- On damaged skin (cuts, abrasions, eczema, sunburned)

The "-ed" after the term "sunburn" should be deleted.

The sponsor should add the following bulleted statement:

- If you are allergic to adapalene or any of the ingredients in this product

(2) **If pregnant or breast-feeding**. Revise the statement ask a (b) (4) before use to:

If pregnant or breast-feeding, ask a doctor before use**.**

(3) **When using this product**

Add the following bulleted statement:

- it may take up to 3 months of once daily use to notice results

Revise the statement (b) (4) to:

- limit sun exposure, including light from tanning beds, and use sunscreen when going outdoors.

Add a third sub-bullet under the "irritation" bullet to read as follows:

- but, usually lessens with continued use of this product

Remove the statement:

- (b) (4)

The following bulleted statement: (b) (4) should be revised to:

- avoid product contact with eyes, lips and mouth. If contact occurs, immediately flush affected area with water

For bulleted statement (b) (4) should be revised to:

- during the early weeks of use, your acne may appear to worsen before it improves (this is normal); continue using as directed, unless you get irritation that becomes severe

For bulleted statement (b) (4) should be revised to:

- do not (b) (4) wax to remove hair in areas where the product has been applied

Add the following bulleted statement:

- Wash hands after use.

(4) **Stop use and ask a doctor if**

Add the following bulleted statements:

- you become pregnant, or are planning to become pregnant, while using the product
- you see no improvement after 3 months of once daily use

The following allergy sensitivity should be added to this subsection:

- you have symptoms of an allergic reaction (such as itching, rash, hives, swelling of the lips, eyelids and face, shortness of breath)

c. **Directions**

The Directions begin with the following statements:

(1) (b) (4)

a) The statement "Use once daily" should be revised to:

- Use **once** daily at night

The statement [redacted] (b) (4) should be revised to:

- Clean the skin gently and pat dry before applying the product

b) The following statement [redacted] (b) (4) should be revised to:

- Cover the entire affected area with a thin layer. If your acne is on the face, apply the product to the entire face.

c) The following bulleted statement should be added:

- Do not use more than one time per day. Applying more than directed will not result in faster or better results, but may worsen skin irritation.

(2) [redacted] (b) (4)

1. It is recommended that the sponsor revise to:

- Ask a doctor

Reviewer's Comments to June 13, 2016 Sponsor Response: the sponsor accepted all of the FDA suggestions with the exception of:

When using this product

It is recommended that the sponsor add the following bulleted statement:

- it may take up to 3 months of once daily use to notice results

The sponsor proposed the following language in response to our recommendation:

- [redacted] (b) (4)

The sponsor commented that [redacted] (b) (4)

Directions

The Directions begin with the following statements:

[redacted] (b) (4)

Use once daily

The FDA recommended the statement to be revised to

- Use **once** daily at night

The sponsor in response proposed the following statement as they believe there is no evidence that use at night is best:

- Use **once** daily

Reviewer Comments to Sponsor's June 13 DFL Response:

The statement [redacted] is not supported by substantial evidence [redacted] Therefore, the sponsor's proposed alternative to the 3 month statement was not considered acceptable given the available clinical data and will be refused. The sponsor will be directed to make the change to:

- it may take up to 3 months of once daily use to notice results

The removal of the "at night" modifier from "Use once daily" is acceptable. The explanation provided by the sponsor is sufficient to support not adding the "at night" modifier.

2. Consumer Information Leaflet (CIL)

a. How long will it take for Differin to work?

Delete the statement; [redacted] Revise to the following statement:

- It may take up to 3 months of daily use for results to appear.

b. What should I know before using this product?

Revise the following statement from "If **pregnant or breast-feeding,** ask a [redacted] before use" to:

- **If pregnant or breast-feeding,** ask a doctor before use. Some other retinoid drugs have been shown to cause birth defects. There is no evidence that Differin causes birth defects when used topically as directed.
- **Do not use** Differin if you are allergic to adapalene and or any of the ingredients in this product

c. How do I apply the product?

1. Revise the following statement from [redacted] to:
   - Gently clean the affected areas using a mild cleanser and pat dry.
2. Clarify what is meant by a "mild cleanser" (what makes a cleanser mild?).
3. Revise the following statement from [redacted] to:
   - Apply Differin as a thin layer to the affected areas of the skin [redacted] If you get acne on the face, clean, dry and apply the product to the entire face. Differin is **not** a spot treatment and should not be used to treat a single pimple.

3. Revise the following statement from [redacted] to:

- Avoid contact with the eyes, lips and mouth. **If contact occurs, immediately flush with water.**

4. Add the following statement:
   - Wash hands after use.
5. Delete the "-ed skin" after the term "sunburn" so the statement reads as follows:
   - Do not apply the product to damaged skin (cuts, abrasions, eczema, or sunburn)

d. How often do I apply the product?

1. Revise to the following:
   - Apply this product (b) (4) and try to apply the product at the same time each day, but best at night.
2. Clarify "mild cleanser" in terms of what makes a cleanser mild.

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

Revise to the following:

- Yes. Avoid products containing alpha hydroxy or glycolic acids which may worsen irritation.

f. What do I do if I need to be in the sun?

1. Revise the first bulleted statement from (b) (4) to:
   - When possible, limit sun exposure, including light from tanning beds.
2. Revise the second bulleted statement from (b) (4) to:
   - When going outdoors, use a sunscreen as labeled. Your skin may be more sensitive while using Differin. If you must use this product during the day, allow it to dry before applying sunscreen.

g. When is my skin most likely to be become irritated? And what to do?

1. Under the first bulleted statement "Irritation (redness, itching, dryness burning) is more likely to occur", revise the second sub-bullet from (b) (4) to
   - If using abrasive skin cleansers, products with drying effects or more than one topical acne medication at a time. You may want to delay starting Differin until any irritation from using other product(s) has gone away.
2. Under the second bulleted statement, delete the following sub-bullet:
   - (b) (4)
3. Revise the third bulleted statement from (b) (4) to:
   - Irritation usually lessens after 4 weeks of continued use.

h. What do I do if my skin becomes severely irritated?

Clarify the term "severe" in the following:

- If irritation becomes severe, stop use and ask a doctor before using the product again.

i. Can I remove unwanted facial hair by waxing while using this product?
Revise the bulleted statement to:

- Do not use wax to remove hair in areas where the product has been applied because it may worsen skin irritation.

j. What ingredients are used in Differin?
Remove the second bulleted statement which reads:

- (b) (4)

Reviewer's Comments to June 13 Sponsor's CIL response:

The sponsor agreed with all of the proposed changes with the following exceptions:

1. As with the DFL, the sponsor wants to substitute DNDP's proposed 3 months of use statement (b) (4) As noted above this is not acceptable and the sponsor will be directed to accept DNDP's original statement.
2. The sponsor has proposed a revised statement to that proposed by DNDP for the heading **If pregnant or breastfeeding**. The sponsor's proposed statement is not acceptable (b) (4) . The sponsor will be directed to accept DNDP's original statement.
3. The sponsor was asked to provide a definition for a "mild cleanser". The sponsor modified their statement to read "mild (non-irritating) cleanser". This modification is acceptable.
4. As noted for the DFL, the sponsor has proposed removing modifiers referring to application at night given there is no evidence that time of day impacts efficacy of the product. DNDP has agreed and therefore this revision is acceptable.
5. The sponsor has proposed a revision to the language under Moisturizer use. The added language clarifies why use of a moisturizer may be beneficial when using Differin. The changes are acceptable.

The following deficiencies were sent to the sponsor on June 17, 2016. The comments were a mixture of stated deficiencies along with a tracked-changes version of the DFL and CIL (See email dated June 17, 2016 @ 5:46 pm). The sponsor provided responses to the outer carton and immediate container labels on June 22 and responses to the CIL deficiencies on June 29, 2016.

B. Information request sent to sponsor on June 17, 2016 (Response received on June 29, 2016)

1. **Principal Display Panel (PDP) for 2-g, 15-, and 45-carton count SKUs**
   a. **Statement of Identity**
      (1) FDA Request- For the pharmacological category, identify the product as an "acne treatment" for consistency as you have used under the Purpose section of the Drug Facts label. Use this term consistently throughout your labeling to prevent confusion.

Sponsor's response - The sponsor has revised accordingly on all labels.
Reviewer's comment – This revision is acceptable.

(2) FDA Request- Revise SOI to the following: adapalene gel 0.1% Acne Treatment.

Sponsor's response - The sponsor has revised accordingly.
Reviewer's comment – This revision is acceptable.

(3) FDA Request-Submit revised labeling so that the SOI is at least 25% to 50% of the most prominent printed matter on the PDP.

Sponsor's response - The sponsor has revised so that SOI is 25% of the most prominent printed matter on the PDP.
Reviewer's comment – This revision is acceptable.

(4) FDA Request- Reformat the orientation of the proprietary name Differin Gel and SOI, "adapalene gel 0.1%, to comply with 21 CFR 201.61 (c). Your current proposed PDP labels has these terms relatively perpendicular (vertical) to the package's base, instead of relatively parallel to the base as required.

Sponsor's response - The sponsor has revised accordingly on all labels. Also, the sponsor has added the term "Gel" after "Differin" wherever the term "Differin" appears on other parts of the labeling for this product.
Reviewer's comment – These revision are acceptable.

b. (b) (4)
FDA Request- Remove the " (b) (4) as it is not appropriate. If you would like to keep this statement on the PDP, it is suggested (b) (4) FDA approved".

Sponsor's response - The sponsor has revised so that the statement "FDA APPROVED" is located in horizontal fashion on the PDP with a yellow bullet in front of it.
Reviewer's comment – This revision is acceptable.

c. (b) (4) **claim** –
FDA Request- Remove the statement (b) (4) as this may be confusing to consumers (b) (4)

Sponsor's response - The sponsor has revised so that the statement reads as follows: "PREVIOUSLY AVAILABLE ONLY BY PRESCRIPTION". This statement is located in horizontal fashion on the PDP with a yellow bullet in front of it.

Reviewer's comment – This revision is acceptable. This statement is truthful and informs consumers that this was previously available as a prescription in a matter of fact of manner. The appropriateness of this claim was discussed between the clinical reviewer and the Deputy Director of ODEIV, and was found acceptable.

d. (b) (4)

FDA Request-Provide data to support this statement (b) (4) for this proposed OTC Differin Gel 0.1% product or remove it.

Sponsor's response - The sponsor has revised so that the statement reads as follows: "Dermatologist Developed". It is located in horizontal fashion on the PDP with a yellow bullet in front of it.

Reviewer's comment – This revision is acceptable as it is technically a truthful statement regarding the product. The sponsor justified this revised statement as they indicated that they have employed a number of full-time dermatologists during the development of this product from formulation development to clinical development in the design and review of actual use and pharmacokinetic studies conducted to support this efficacy supplement for Rx to OTC switch of adapalene 0.1% gel. The appropriateness of this claim was discussed between the clinical reviewer and the Deputy Director of ODEIV, and was found acceptable.

e. (b) (4) **claim** –

FDA Request- It is recommended that the sponsor revise to "**One Time A Day Acne Treatment**" for clarity and consistency with the Drug Facts label and consumer information leaflet.

Sponsor's response – The sponsor did not accept our recommendation. The sponsor proposed the following statement: "**Once Daily Topical Retinoid***"; there is a sentence corresponding to the asterisk immediately below this statement which reads "Read consumer information leaflet before use". The sponsor expressed concern with the change in language from "once daily" to "one time a day" since the specific language "once daily" was tested in as the primary endpoint in label comprehension (LCS) and actual use studies (AUS) conducted.

Reviewer's comment – Upon internal discussion, the division and the ODEIV agreed to consider and accept the sponsor's original proposed language "once daily" as it was the specific language tested in LCS and AUS. The sponsor will maintain in the labeling wherever it appears for consistency. The sponsor revision from (b) (4) to "topical retinoid"is found acceptable since it directs consumers to read the CIL prior to use; CIL contains more detailed information regarding safe and effective use of the product.*

h. In addition, the sponsor has added the following asterisked statement to the front of the PDP (beneath the bulleted statements):

*Read consumer information leaflet before use

Reviewer's comment – This revision is acceptable. This directs consumers to the CIL to read prior to use of the product for information regarding the efficacy and safety of the product.

f. **Day Supply** –

FDA Request- Remove the (b) (4) statements for 15-g and 45-g products respectively, (b) (4) .

Sponsor's response - The sponsor has removed.
Reviewer's comment – This revision is acceptable.

g. (b) (4) graphic design -

FDA Request- Remove the (b) (4) graphic design from the PDP and anywhere else proposed in the labeling (b) (4)

Sponsor's response - The sponsor has removed the (b) (4) graphic design and replaced with the following design:

(b) (4)

Reviewer's comment – This revision is acceptable. (b) (4)

2. **Outer Panels except the Principal Display Panel, 15- and 45-g outer cartons**

a. (b) (4) claim-

FDA Request-Revise statement from [redacted] to:
"First FDA approved over-the-counter topical retinoid* for acne treatment".
Also, include the following statement:

> * **Read carton and enclosed consumer information leaflet before using this product. Keep this carton and consumer information leaflet. They contain important information.**

This may be placed in a flag prominently on the outer carton in close proximity to the "**First FDA approved over-the-counter topical retinoid* for acne treatment**" where it would be the most visible to the consumer at point of purchase.

Sponsor's response - The sponsor has revised accordingly. The sponsor has added the asterisked statement immediately below the "**First FDA approved over-the-counter topical retinoid* for acne treatment**" statement.

Reviewer's comment – This revision is acceptable.

b. These comments refer to the claims and statements present within the outline of the actual size tube figure.
(1) FDA Request- Refer to the comments made for the statement of identity for the PDP and revise all labels accordingly.

Sponsor's response - The sponsor has revised accordingly.
Reviewer's comment – This revision is acceptable.

(2) FDA Request- Remove the following claims [redacted]

Sponsor's response - The sponsor has removed these claims.
Reviewer's comment – This revision is acceptable.

(3) FDA Request- Remove the statement [redacted]

Sponsor's response - The sponsor has removed this statement.
Reviewer's comment – This revision is acceptable.

(4) FDA Request- Justify or remove the statement "Dermatologist developed [redacted] (b) (4) " as data are required for review and approval of such a statement for Differin Gel 0.1% marketed OTC.

Sponsor's response - The sponsor has revised so that the statement reads as follows: "Dermatologist developed [redacted] (b) (4) ".
Reviewer's comment – This revision is acceptable (see discussion under II. Reviewer's Comments (B)(1)(d)- June 13, 2016 submission).

(5) FDA Request- Remove [redacted] (b) (4) graphic design here and wherever it appears in the labeling.

Sponsor's response - The sponsor has revised accordingly.
Reviewer's comment –This revision is acceptable (see discussion under II. Reviewer's Comments (B)(1)(g)- June 13, 2016 submission).

In addition to the above changes the sponsor made two additional changes that were not requested by FDA.

(1) The proprietary name and established name has been removed from within the outline picture of the actual size of the tube product.

Reviewer's comment – This is acceptable.

(2) The distribution and trademark information has been moved from beneath the DFL to within the picture of the actual size tube on the outer panels except the PDP for outer cartons; also, the country of . Also, the Galderma logo has been added to the bottom of this information.

Reviewer's comment – This is acceptable as all the required information is present and available on the label (distributor information 21 CFR 201.1 and country of origin 19 CFR Part 134).

3. Drug Facts Label – All SKUs

a. ***Warnings-When using this product***

(1) FDA Request- Revise sponsor's proposed language from:

- [redacted] (b) (4)

to

- it may take up to 3 months of once daily use to notice results (see Reviewer's Comments section II (A)(1)(c)- June 13, 2016 submission).

Sponsor's response - The sponsor has revised accordingly.
Reviewer's comment –This revision is acceptable.

(2) FDA Request -Revise to the preferred order of the bullets as listed and use the same shape and color for all bullets (e.g., main and sub-bullets should be the same, per 21 CFR 201.66(d)(4) appearing before these statements:

- limit sun exposure, including light from tanning beds, and use sunscreen when going outdoors
- do not wax to remove hair in areas where the product has been applied
- during the early weeks of use, your acne may appear to worsen before it improves (this is normal); continue using as directed, unless you get irritation that becomes severe
- irritation (redness, itching, dryness, burning) is more likely to occur:
  - in the first few weeks of use
  - if using more than one topical acne medication at a time
  - but irritation usually lessens with continued use of this product
- it may take up to 3 months of once daily use to see results
- avoid product contact with eyes, lips, and mouth. If contact occurs, immediately flush the area with water
- wash hands after use

Sponsor's response - The sponsor has revised in the recommended order and revised so that all the bullets (sub-bullets are the same as that of the main bullets).

Reviewer's comment –These revisions are acceptable.

b. **Directions**

(1) FDA Request-The sponsor was asked to change the age ranges to:

adults and children 12 years of age and older

and

children under 12 years of age

Sponsor's response - The sponsor has revised accordingly.

Reviewer's comment –These revisions are acceptable.

(2) FDA Request- Revise from "Ask a doctor" to "ask a doctor".

Sponsor's response - The sponsor has revised accordingly.

Reviewer's comment –This revision is acceptable.

(3) FDA Request- Revise from the following statement

- Use **once** daily at night

to

- Use only one time a day

Sponsor's response – The sponsor still concerned with recommended proposed language of "one time a day" language (see Reviewer's Comments section II (B)(1)(e)- June 13, 2016 submission).

Reviewer's comment –Upon internal discussions, the sponsor's original proposed language of "once daily" was found acceptable as it was the specific language tested in the LCS and AUS.

c. **Other Information**

FDA Request- Revise from "Store at room temperature 68°-77°F." to "store at room temperature 68°-77°F."

Sponsor's response - The sponsor has revised accordingly.
Reviewer's comment –This revision is acceptable.

d. **Annotated Specifications for Drug Facts Labels**

(1) FDA Request-Revise the font specifications so that they meet the font specifications required under 21 CFR 201.66(d) (2). For example, the font type or size of the headings should be 8-point and the subheadings should not be smaller than 6-point type.

Sponsor's response - The sponsor has made revisions to meet the font specifications.
Reviewer's comment –This revision is acceptable.

(2) FDA Request- Provide the specifications for characters per inch and leading per 21 CFR 201.66(d) (3) (e.g., annotate the specifications directly to the DFL or annotate the specifications in tabular format alongside the label).

Sponsor's response - The sponsor has made the necessary revisions to meet the specifications.
Reviewer's comment –This revision is acceptable.

(3) FDA Request- Revise bullets so that they all are a solid circle or solid square bullet of 5-point type size (21 CFR 201.66 (d) (4)). Also, ensure that bullets follow format specifications per 21 CFR 201.66 throughout your proposed label.

Sponsor's response - The sponsor has made revisions to meet the specifications.
Reviewer's comment –This revision is acceptable.

(4) FDA Request- The bulleted statements are difficult to read and follow from line to line. Revise so that the first bulleted statement on each horizontal line of text so that it is either left justified or separated from an appropriate heading or subheading by at least two square "ems" (21 CFR 201.66(d)(4)).

Sponsor's response - The sponsor has made revisions to satisfy the requirements for the 15 g and 45-g outer cartons. However, the sponsor needs to revise the 2-g DFL to comply with the format specifications in 21 CFR 201.66 (d) so that the first bulleted statement of each horizontal line of text shall be left-justified.

Reviewer's comment –The sponsor should revised the 2-g outer carton labeling so that the format requirements are met per 21 CFR 201.66(d) so

that the first bulleted statement of each horizontal line of text shall be left-justified.

(5) FDA Request-Revise such that additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading are vertically aligned with the bulleted statements appearing on the previous line.

Sponsor's response - The sponsor has made revisions to satisfy the requirements for the 15 g and 45-g outer cartons. However, the sponsor needs to revise the 2-g DFL to comply with the format specifications in 21 CFR 201.66 (d) so that if more than one bulleted statement is placed on the same horizontal line, the end of one bulleted statement, the completed additional bulleted statement(s) shall not continue to the next line of text. Also, additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements appearing on the previous line.

Reviewer's comment –The sponsor should revised the 2-g outer carton labeling so that the format requirements are met per 21 CFR 201.66(d) so that if more than one bulleted statement is placed on the same horizontal line, the end of one bulleted statement, the completed additional bulleted statement(s) shall not continue to the next line of text. Also, additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading shall be vertically aligned with the bulleted statements appearing on the previous line .

(6) FDA Request- Submit revised annotated font specifications following the recommendations in this review for DFL and PDP in same tabular format that was submitted in your May 2, 2016, submission.

Sponsor's response - The sponsor has submitted the requested information.
Reviewer's comment –They are acceptable.

e. **Immediate Container Labels for 2-g, 15-, and 45(tubes) count SKUs**

(1) FDA Request-Revise label so that the proprietary name and SOI are as follows and appears in this order: Differin Gel, adapalene gel 0.1%.

Sponsor's response - The sponsor has revised accordingly.
Reviewer's comment –This revision is acceptable.

(2) FDA Request- Delete the underline and bold the word "once".

Sponsor's response - The sponsor has revised accordingly.
Reviewer's comment –This revision is acceptable.

(3) FDA Request- Identify the location of the expiration and lot numbers on the immediate container labels (21 CFR 201.10(i) and 21 CFR 201.17).

Sponsor's response - The sponsor has identified the crimp of the tubes as the location of this information. .
Reviewer's comment –This is acceptable.

(4) FDA Request- For the 2-g package size, add the following statement: "**Warnings: For external use only**. Do not use on damaged skin (cuts, abrasions, eczema, sunburn)" for consistency with all labels and this is important safety information be conveyed to the consumer.

Sponsor's response - The sponsor has revised accordingly.
Reviewer's comment –This revision is acceptable.

(5) FDA Request-For the 15-g and 45-g package sizes, add the following statement: "Purpose: Acne Treatment" as you have done so for the 2-g physician sample immediate container. Delete the "-ed" after word "sunburn".

Sponsor's response - The sponsor has revised accordingly.
Reviewer's comment –This revision is acceptable.

(6) FDA Request- Remove the (b) (4) graphic design wherever it appears in the label and labeling.

Sponsor's response - The sponsor has revised accordingly so that the (b) (4) graphic design has been replaced with the following design:

Reviewer's comment –This revision is acceptable.

Upon review of the revised labels submitted, the following should be revised by the sponsor to be consistent with the DFL:

a) **Directions-** Revise from (b) (4) to "adults and children 12 years of age and older".
   1. Under the Directions for this age group, revise from (b) (4) to "clean the skin gently and pat dry before applying the product".

b) **Directions-** Revise from (b) (4) to "children under 12 years of age" (this was unintentionally left out of the original

communication but was provided in a subsequent communication to the sponsor).

1. Under the **Directions** for this age group, revise from [redacted] (b) (4) to "ask a doctor**".**

c) If pregnant or breast-feeding- Revise from "ask a [redacted] (b) (4) before use" to "ask a doctor before use".

C. **June 29, 2016 submission (DARRTs)**

It is noted that this submission contains revised CIL- in response to June 17, 2016 labeling IR.

1. Consumer Information Leaflet (CIL)

Frequently Asked Questions

(1) FDA Request- Reorder the questions and answers to the following:

What is Differin Gel and what is it used for?
What should I know before using the product?
How often do I apply the product?
How do I apply the product?
How long will it take for Differin to work?
What do I do if I need to be in the sun?
Can I use a moisturizer if my skin is dry?
When is my skin most likely to become irritated? And what do I do?
What do I do if my skin becomes severely irritated?
Can I remove unwanted facial hair by waxing while using this product?
What ingredients are used in Differin?
How should I store this product?
Other Questions?

Sponsor's responses - The sponsor has revised accordingly.
Reviewer's comment –This is acceptable.

What is Differin Gel and what is it used for?

(2) FDA Request- The sponsor should revise to:

- Differin is a topical retinoid medication used for the treatment of acne in people age 12 years and older.

(3) FDA Request-The sponsor should add the following second bulleted statement as follows:

- Use only one time a day.

Sponsor's responses - The sponsor has addressed deficiencies 2 and 3 adequately.
Reviewer's comments–These revisions are acceptable.

How long will it take for Differin Gel to work?

(4) FDA Request-The sponsor should revise to:

- It may take up to 3 months of daily use for results to appear.

(5) FDA Request-The sponsor should revise to:

- Do not use more than once time a day. Applying more than directed will not provide faster or better results, but may worsen skin irritation.

Sponsor's responses – The sponsor has addressed deficiencies 4 and 5 adequately.

Reviewer's comment –These revisions are acceptable.

What should I know before using the product?

(6) FDA Request-It is recommended that the sponsor revise statement from "**If pregnant or breast-feeding,** ask a (b) (4) before use to change to:

- **If pregnant or breast-feeding,** ask a doctor before use.

(7) FDA Request- The sponsor should add the following bullet:

- Some other retinoid drugs have been shown to cause birth defects. There is specific no evidence that Differin gel 0.1% causes birth defects in humans when used topically as directed.

Sponsor's response - The sponsor has addressed deficiencies 6 and 7 adequately.

Reviewer's comment – These revisions are acceptable.

(8) FDA Request-The sponsor should add the following bullet:

- **Do not use** Differin if you are allergic to adapalene and or any of the ingredients in this product

Sponsor's response – The sponsor revised accordingly.

Reviewer's comment – This revision is acceptable.

How do I apply the product?

(9) FDA Request- The sponsor should revise (b) (4) *to* "**only one time a day**".

Sponsor's response - The sponsor revised to "**only <u>one time a day</u>**" with the statement "**<u>one time a day</u>**" underlined.

Reviewer's comment – The sponsor should remove the underline, since emphasis is made with bold font (see discussion under II. Reviewer's Comments (A)(1)(c)- June 13, 2016 submission).

Can I use a moisturizer if my skin is dry?

(10) FDA Request-The sponsor should revise to the following statement to replace (b) (4) with "decrease" so that it should read:

- Yes, use of a moisturizer may help decrease dryness and other signs of irritation. Avoid products containing alpha hydroxy or glycolic acids which may worsen irritation.

Sponsor's response – The sponsor revised accordingly.
Reviewer's comment: The revisions are acceptable.

D. **July 6, 2016 submission (DARRTs)**

It is noted that this submission contains sponsor's responses to the June 30 (via email- same as the one in DARRTs dated July 1, 2016), July 5th and July 6th (via email- same as the one in DARRTs dated July 7, 2016) labeling IRs.

1. Immediate Container Labels for 2-g, 15-, and 45(tubes) count SKUs

1) FDA Request-
Directions- Revise from (b) (4) to "adults and children 12 years of age and older" to be consistent with the DFL.
2) FDA Request-
Under the **Directions** for this age group, revise from (b) (4) to "clean the skin gently and pat dry before applying the product" to be consistent with the DFL.
3) FDA Request-
Directions- Revise age ranges from (b) (4) to "children under 12 years of age" to be consistent with the DFL.
4) FDA Request-
Directions for "children under 12 years of age" revised from (b) (4) to "ask a doctor".
5) FDA Request-
Under the **"If pregnant or breast-feeding, ask a** (b) (4) **"** statement should be revise to the following: **"If pregnant or breast-feeding,** ask a doctor before use".

Sponsor's response- The sponsor has addressed deficiencies 1, 2, 3, 4 and 5 adequately.
Reviewer's comment – These revisions are acceptable.

2. Consumer Information Leaflet (CIL)

Frequently Asked Questions

How do I apply the product?

(1) FDA Request- The sponsor should revise from "**only <u>one time a day</u>** to "**only one time a day**".

Sponsor's response - The sponsor revised to "**only one time a day**" with the statement "**<u>one time a day</u>**" underlined removed.
Reviewer's comment – The sponsor revised accordingly and it is acceptable.

3. Annotated Specifications for Drug Facts Labels

(1) FDA Request-

Per the labeling IR sent on June 17th, 2016 (via email), it was requested that you ensure that bullets follow format specifications per 21 CFR 201.66 throughout your proposed label. Also, it was requested that the bullets be revised such that additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading are vertically aligned with the bulleted statements appearing on the previous line in accordance with 21 CFR 201.66 (d). However, the labeling submitted on June 29, 2016, via email for the 2-g outer carton (card) is not in compliance.

Revise the labeling of the 2-g outer carton (card) to be in compliance so that the additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading are vertically aligned with the bulleted statements appearing on the previous line in accordance.

Sponsor's response – In an email dated July 1, 2016, the sponsor replied that due to space constraints for the 2-g outer carton (card), they followed the modified format as outlined in the Guidance to Industry Labeling OTC Human Drug Product in the **Bulleted statements** section (21 CFR 201.66(d)(10)). The sponsor asked if this was acceptable per their interpretation of this Guidance.

Reviewer's comment – The sponsor has chosen to use a modified Drug Facts format based on 201.66(d)(10). As presented, the draft Drug Facts takes up ~50% of the outer carton label space. It is evident that if Drug Facts was in a normal format it would take up more than 60% of the outer carton labeling space. Therefore, the modified format is acceptable.

4. Additional comments identified on July 1 and July 5, 2016.

(1) The bullets used in Drug Facts for all three SKUs, are rectangular in shape and do not appear to align horizontally or vertically with the text font. The bullets should be revised to square bullets and the sponsor should ensure that the text is fully left justified. This comment has been made to the sponsor previously.

Sponsor's response- The sponsor raised a question regarding whether they should indent or not indent the sub-bullets under the bulleted statement that begins with "irritation (redness, itching, dryness, burning) is more likely to occur" in the "**When using this product**" subsection of the **Warnings** section of the DFL in an email dated July 5, 2016. Upon internal discussion, it was found acceptable to indent these sub-bullets under the "irritation…" bullet for clarity; the indentation of the sub-bullets under the "irritation…" bulleted statement, allows the consumers to easily read and identify that the "irritation" is the subject being referred to in the three sub-bullets underneath of it.
Reviewer's comment – The bullets were revised as requested and the text left justified with the noted exceptions above. These changes are acceptable.

(2) For all outer cartons (e.g., 2-, 15- and 45-g),

a. the following should be in lower case:
ingredient (in "Active ingredient")
treatment (in "Acne treatment")
information (in "Other information"
store (in "store at room temperature…")
protect (in "protect from freezing")
ingredients (in "Inactive ingredients")
all the inactive ingredients listed in the "Inactive ingredients" section should all be in lower case
Under "May contain statement", "hydrochloric acid" should be in lower case

b. Also, remove the "-s" under the section entitled "Uses" so that it should read as "Use".

c. Under "**When using this product**", place a period after the 6th bulleted statement so that it reads as follows:
▪avoid product contact with eyes, lips, and mouth. If contact occurs, immediately flush the area with water.

d. Under the "**Stop use and ask a doctor if**", a comma should be added after the word, eyelids.

(3) For the CIL, periods should be added after these statements:

a. **How often do I apply the product?**
• Apply this product only one time a day and try to apply the product at the same time each day

b. **How do I apply the product?**
• Wash hands after use

c. **When is my skin most likely to become irritated? And what do I do?**
• In the first few weeks of use
You may want to delay starting Differin Gel until any irritation from using the other product(s) has gone away

Sponsor's response- The sponsor has addressed deficiencies 2 and 3 adequately.
Reviewer's comment – These revisions are acceptable.

(4) Also, the sponsor on their own accord revised the following section of the CIL, **What ingredients are used in Differin Gel?** , so that all the other ingredients are all in lower case to be consistent with the DFL. Also, the terms "hydrochloric acid" has been revised to all lower case, as well.

Reviewer's comment – These revisions are acceptable.

III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Differin Gel 0.1% topical acne treatment (topical retinoid) outer cartons and immediate containers (tubes) and

consumer information leaflet. Request that the sponsor submit final printed labeling (FPL) identical to the following label submitted on July 6, 2016 (via email), when available:

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

Submitted Labeling	Date(s) Submitted
2 gram immediate container (physician sample)	July 6, 2016
15 gram immediate container	July 6, 2016
45 gram immediate container	July 6, 2016
2 gram outer carton (physician sample-not for sale)	July 6, 2016
15 gram outer carton	July 6, 2016
45 gram outer carton	July 6, 2016
Consumer information leaflet	July 6, 2016

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

YOON KONG
07/07/2016

STEVEN A ADAH
07/07/2016

Labeling Review for Differin *Draft Labeling*

SUBMISSION DATES:	September 10, 2015; January 21, May 2 and 4, 2016
NDA/SUBMISSION TYPE:	20-380/S-010/ Efficacy Supplement
ACTIVE INGREDIENTS:	Adapalene 0.1%
DOSAGE FORMS:	gel (2-g, 15-g and 45-g tubes)
SPONSOR:	GlaxoSmithKline Consumer Healthcare Galderma Laboratories, L.P. 14501 North Freeway Fort Worth, Texas 76177 Contact: Sean Griffin Director, Regulatory Affairs Telephone:(817)961-5334 Fax: (817)720-1040
REVIEWER:	Yoon Kong, Pharm.D., OND/ODEIV/DNDP
TEAM LEADER:	Steve Adah, Ph.D., OND/ODEIV/DNDP
PROJECT MANAGER:	Lara (Monsurat) Akinsanya, OND/ODEIV/DNDP

I. BACKGROUND

The original prescription product, Differin 0.1% gel was approved on May 31, 1996, with the indication for the topical treatment of acne vulgaris in adults and children ages 12 years and older by the Division of Dermatology and Dental Products (DDDP). Since that time, there have been a number of prescription products approved for Differin in different strengths and dosage forms.

The sponsor submitted an efficacy supplement which proposes for a full prescription to over-the-counter (OTC) marketing status switch for Differin (adapalene) 0.1%, Gel. The indications expressed within the proposed OTC labeling as:

- For the treatment of acne
- Clears up acne pimple and acne blemishes

This efficacy supplement would be the first in class prescription to OTC switch for a topical retinoid product.

On November 24, 2015, the Division of Medication Error Prevention and Analysis (DMEPA) found the sponsor's proposed proprietary name, Differin Gel, conditionally acceptable. Subsequently, sponsor provided labels with this proprietary name with the January 21, 2016, submission.

Information requests (IRs) were issued on January 11, April 26 (via email), April 27 (via email), 2016 with sponsor's responses provided on January 21, May 2 and May 4, 2016 (see below):

January 21, 2016, labeling information requests:
FDA Question 1: Provide annotated font and format Drug Facts label specifications for all proposed draft labeling per 21 CFR 201.66. Also, provide font specifications for all the statements on the PDP.
Sponsor Response: Submitted in submission.
FDA Question 2: Submit a complete, unannotated patient leaflet
Sponsor Response: Submitted in submission.

April 26, 2016, labeling information request:
FDA Question 1: Provide samples for all your proposed package sizes (including outer carton and immediate containers).
****Sponsor Response: Representative samples of the proposed package sizes are being sent via UPS to the attention of Lara Akinsanya. Please note that the samples provided will not be labeled with the proposed artwork, however, the components provided are identical to those intended for commercial use.***
.Sponsor submitted 15-g and 45-g immediate container (tubes) of the prescription strength Differin gel product. Sponsor submitted outer cartons for the 15-g and 45-g strength products without any labeling information on them (i.e., plain white outer cartons).

April 27, 2016, labeling information requests:
FDA Question 1: Provide annotated font specifications for DFL and PDP in a clear tabular format (see attached as an example to guide them) to help facilitate review for all package sizes (e.g., 2g, 15 g and 45 g).
Sponsor Response: Provided font specifications for the DFL and PDP.
FDA Question 2: Provide revised DFL to be compliant with 21 CFR 201.66(d) (2) for annotated font/format specifications. For example, the font type or size of the headings shall be the larger of either the 8-point or greater type and the subheadings should not be smaller than 6-point type.
Sponsor Response: Sponsor indicated in email dated April 27, 2016, that they "would prefer to not revise all component artwork until text has been finalized if at all possible."

FDA Question 3: Provide revised DFL to be compliant with 21 CFR 201.66(d)(4) so that the first bulleted statement on each horizontal line of text shall be either left justified or separated from an appropriate heading or subheading by at least two square "ems". Additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading should be vertically aligned with the bulleted statements appearing on the previous line.
Sponsor Response: Sponsor indicated in email dated April 27, 2016, that they "would prefer to not revise all component artwork until text has been finalized if at all possible."
FDA Question 4: Provide the specifications for characters per inch and leading need to be provided as per § 201.66(d) (3).
Sponsor Response: Sponsor indicated in email dated April 27, 2016, that they "would prefer to not revise all component artwork until text has been finalized if at all possible."

On April 26, 2016 CMC requested that the sponsor revise the DFL and the label to include both a storage statement and the statement "Protect from freezing". In response, the sponsor submitted revised labeling on May 2, 2016.

May 4, labeling information request:
FDA Question 1: Submit revised immediate container labels (tubes) as well for package sizes.
Sponsor Response: Submitted on May 4, 2016.

Submitted Labeling	Date(s) Submitted
2 gram immediate container (physician sample)	September 10, 2015; January 21, May 4, 2016
15 gram immediate container	September 10, 2015; January 21, May 4, 2016
45 gram immediate container	September 10, 2015; January 21, May 4, 2016
2 gram outer carton (physician sample-not for sale)	September 10, 2015; January 21, May 2, 2016
15 gram outer carton	September 10, 2015; January 21, May 2, 2016
45 gram outer carton	September 10, 2015; January 21, May 2, 2016
Consumer information leaflet	September 10, 2015; January 21, May 2, 2016

II. REVIEWER'S COMMENTS

A. Principal Display Panel (PDP) for 2-g, 15-, and 45-carton count SKUs

In general, this discussion of the PDP provides preliminary comments for the sponsor. There may be changes or additions to the recommendations below based on discipline reviews or team discussion.

The changes described will be uniform for all SKUs. If there are differences among any of the SKUs, it will be explained in this section.

1. **Proprietary Name**
   "Differin Gel" was submitted on September 22, 2015, as the proprietary name and was conditionally accepted by Division of Medication Error Prevention and Analysis (DMEPA) on November 24, 2015. As part of submission dated January 21, 2016, the sponsor submitted revised labels to reflect "Differing Gel". This is acceptable.
2. **Statement of identity**
   a. According to 21 CFR 201.61, the last part of the statement of identity (SOI) is the pharmacological category or principal intended action of the drug. The submitted labels do not contain this information. The product as part of the pharmacological category should be identified as an "acne medication" or "acne treatment". The sponsor has used the statement "acne treatment" in the Purpose section of the Drug facts label. It should be conveyed to the sponsor the term "acne treatment" should be consistently used throughout labeling.
   b. The SOI shall be presented in bold face type on the PDP, shall be in a size reasonably related to the most prominent printed matter on the PDP., The sponsor will be asked to revise SOI to the following: adapalene gel 0.1% Acne Treatment.
   c. According to our current division policy, the statement of identity should be at least 25% to 50% of the most prominent printed matter on the PDP. Currently, the sponsor's statement of identity is only 20% of the most printed matter on the PDP (e.g., proprietary name- Differin Gel). Sponsor will be asked to increase the SOI to 25-50% of the most prominent matter on the PDP.
   d. The terms "Differin Gel" and "adapalene gel 0.1%" should be in a horizontally placed on the PDP per 21 CFR 201.61(c). The sponsor's current proposed PDP labels has these terms relatively perpendicular (vertical) to the package's base, instead of relatively parallel to the base as required. The sponsor will be asked to reformat the proprietary name, Differin Gel, and SOI (adapalene gel 0.1% Acne Treatments to be in compliance with 21 CFR 201.61(c).
3. (b) (4) This is misleading (b) (4)
4. (b) (4) **claim** – (b) (4)
5. (b) (4) **claim** –Internal division policy has been such that claims require substantial data/evidence to support such a claim. The sponsor has not submitted such studies to clearly demonstrate (b) (4) The sponsor will be asked to provide data to justify the claim or it should be removed.

Of note, there is discrepancy among reviewers within the review team regarding the technical pharmacological category of adapalene (chemical structure is retinoid-like, but its pharmacological activity is that of a retinoid); the prescription label indicates it as a "retinoid-like". During internal meetings the review team agreed that this product can be referred to as a retinoid (see clinical review).

6. (b) (4) **claim** – It is recommended that the sponsor revise to "**One Time A Day Acne Treatment**" to reflect the proposed language on the CIL and this was the term proposed on the PDP for the actual use study ("JUNO" trial) (see clinical review).
7. **Net quantity of contents** – The net quantity of contents conforms to 21 CFR 201.62.
8. (b) (4) – The PDP also states (b) (4) The sponsor will be asked to remove statements (b) (4)
9. There is a picture of a (b) (4) graphic design (b) (4) The sponsor will be asked to remove (b) (4) from all labeling.

B. Principal Display Panel (PDP) for 2-g outer carton count SKU

*The sponsor calls the outer carton container for the 2-g physician sample product a "card" consisting of a front card containing PDP and back card containing Drug facts label). For the purposes of clarity and consistence, this will be referred to as the 2-g outer carton container (front with PDP and back with DFL).

1. In addition to the items discussed above in II.A, this SKU is a physician sample ("SAMPLE. NOT FOR SALE"). The "Sample. Not for Sale" statements are located at the bottom of the PDP. This is acceptable.
2. It does not have the picture of the tube along with the all the statements contained within the picture. As a picture of the tube is not required it is acceptable that this actual size picture of the tube is not present on the 2-g PDP.
3. In addition to the elements of the PDP found on the 15-and 45-g cartons, the 2-g PDP has the distribution information and "Made in Canada" statement on it at lower right corner. In accordance with 21 CFR 201.1, this is acceptable.
4. There is a picture of a (b) (4) graphic design (b) (4) As discussed above (see II.A.9) it was agreed that it should be removed.

C. Outer Panels except the Principal Display Panel, 15- and 45-g outer cartons

1. (b) (4) claim- This is (b) (4) not an accurate statement . The sponsor should consider revising to: "**First FDA approved over-the-counter topical retinoid* for acne** (b) (4)"

The clinical team was concerned that consumers who are familiar with the risks associated with retinoids may find the above statement confusing. Also, no data was submitted regarding the consumer's understanding of the term "retinoids". They recommended that the sponsor should add an asterisk after the term "retinoid" with the following statement flagged or highlighted in some fashion for prominence on the outer carton where it would be the most visible to the consumer at point of sale:

> * **Read carton and enclosed consumer information leaflet before using this product. Keep this carton and consumer information leaflet. They contain important information.**

2. There is an outline of the picture of the actual size of the tube product with the statement "ACTUAL SIZE" at the base of the tube (cap area). This picture and statement is acceptable as it provides information to the consumer that may be useful at point of purchase. Moreover, this is in alignment with the DMEPA's Guidances for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Error (April 2013).
3. Within the picture of the outline picture of the tube, there are claims and statements present within it.
   a. The statement of identity should be revised to be in compliance with 21 CFR 201.61 (see discussion under II. Reviewers' Comments (A) (2) (a-c)).
   b. The proprietary name, Differin Gel and established name, adapalene with strength, 0.1%, are placed in perpendicular (vertically aligned) in orientation to the rest of the claims and statements within the picture outline of the tube. The sponsor will be asked to reformat the proprietary name, Differin Gel, and SOI (adapalene gel 0.1% Acne Treatments to be in compliance with 21 CFR 201.61(c).
   c. There are claims preceded by check marks at the top of the picture:

(b) (4)

"Oil-free"
"Fragrance-free"

(b) (4)

The following claims should be removed from the label:

(b) (4)

(b) (4) claim is not meaningful to the consumer and is misleading

(b) (4)

(b) (4) Moreover, the sponsor did not provide clinical information to substantiate this claim.

The claim (b) (4) is misleading (b) (4)

The claim (b) (4) requires substantiated studies to demonstrate that this is the case; sponsor did not provide such studies. In addition, (b) (4) (b) (4) is not a term that the average consumer may understand (b) (4)

The statement (b) (4) is inaccurate and is misleading to the consumer (b) (4) This statement should be removed.

The "Oil-free" and "Fragrance-free" claims were found to be acceptable (see CMC review).

d. The statement (b) (4) is included on the draft labeling of the outer panel of the carton. This statement should be removed since it is not clear to the average consumer the meaning of the term (b) (4) (see discussion under II. Reviewers' Comments (C) (3) (c)).
e. According to our draft labeling SOPs, such claims as (b) (4) and similar claims such as this one should be supported by sufficient data. The sponsor should either provide justification for this statement or should remove it.
f. (b) (4) The sponsor should remove it (see discussion under II. Reviewers' Comments (B) (2)).

The proposed labeling layout submitted was a bit unusual for the 15-g and 45-g outer cartons. It was difficult to determine of the outer package configuration. On April 22 and 26, 2016, a labeling IR specifically requested samples of proposed package sizes (including outer carton and immediate containers), however, the sponsor in response, only provided submitted immediate containers of the prescription strength labels for the 15- and 45-g tubes and plain outer cartons for these strengths without any text. Even though, the samples of the outer carton for the 15-g and 45-g did not contain any printed labeling, it did allow for the team to see how the package would sit on a shelf at point of sale.

Upon inspection of the plain outer cartons that were received from the sponsor the form is such that the bottom of the package conforms to a rectangular package and the rest of the pack conforms to a more cylindrical form (midway to top of the package). With such a unique carton form, "other shape of container" (neither a rectangular nor cylindrical shape container), the information required on the PDP per 21 CFR 201.60 appears within that 40 percent of the total surface of the container. The unique shape of the outer carton is acceptable.

D. Drug Facts Label – All SKUs

1. The ***Active*** ingredient should read as follows: Adapalene 0.1% (retinoid)* with the statement "*read consumer information leaflet" underneath of it.
2. The ***Purpose*** is listed as "Acne Treatment". This is acceptable as it complies with 21 CFR 201.66(c) (3) and accurately reflects adapalene's drug product category.
3. ***Uses***
   The first bulleted statement:"For the treatment of acne" is acceptable as this is the indication approved for the prescription product and will be the same use for OTC switch.
4. ***Warnings***
   a. The first statements under ***Warnings*** "**For external use only**." is appropriate as this product is for topical use and thus, complies with 21 CFR 201.66 (c) (5).
   b. **Do not use**
   Under this subheading is the following bullet:
   - On damaged skin (cuts, abrasions, eczema, sunburned)

   The "-ed" after the term "sunburn" should be deleted. Otherwise, the warning under the subheading "**Do not use"** appear reasonable based on the sponsor's justifications, would be clearly understood by the consumer, and is acceptable.

   The sponsor should add the following bulleted statement:
   - If you are allergic to adapalene or any of the ingredients in this product

   This statement is consistent with the "Contraindications" of the prescription label of adapalene and should be included to convey safety information regarding the product.
   c. **If pregnant or breast-feeding,** ask a (b) (4) before use statement. Typically, the pregnancy/breast feeding statement (21 CFR 201.63(b) and 21 CFR 201.66(c) (5) (ix)) is located before the "Keep out of reach of children" statement, but in this case the sponsor has moved this statement closer to the top of statements under ***Warnings*** section. The movement of this statement closer to the top lends prominence to this section as pregnancy is a concern expressed by the clinical team regarding this class of drug products with potential safety risks associated with this product and pregnancy (teratogenicity effects). (see clinical review). Having the statement closer to the top of this section will serve to alert consumers, especially women of child-bearing age to talk to their physician prior to purchase. Due to the potential teratogenicity concerns the sponsor should revise the statement to:

   If pregnant or breast-feeding, ask a doctor before use**.**
   d. **When using this product**
   The following bullets are proposed under this subheading:
   - (b) (4)
   - irritation (redness, dryness, burning) is more likely to occur:
   - in the first few weeks of use
   - if using more than one topical acne medication at a time
   - (b) (4)

(b) (4)

It is recommended that the sponsor add the following bulleted statement:

- it may take up to 3 months of once daily use to notice results

This information is important to let the consumers know when they can expect therapeutic results to help consumers self-treat acne condition effectively and to avoid unnecessary adverse events. Moreover, this information is provided in the prescription label for adapalene 0.1% gel product under the Dosage and Administration (therapeutic results should be noticed after 8-12 weeks of treatment).

For the proposed bulleted statement (b) (4) it is recommended that it be revised to the following:

- limit sun exposure, including light from tanning beds, and use sunscreen when going outdoors.

The bulleted statement on irritation is a condition that has been associated with adapalene gel 0.1% in the prescription label and is acceptable in the section of the warnings. The sponsor should add a third sub-bullet under the "irritation" bullet to read as follows:

- but, usually lessens with continued use of this product

The following bulleted statement should be removed:

- (b) (4)

The sponsor should revise the following bulleted statement from (b) (4) to:

- avoid product contact with eyes, lips and mouth. If contact occurs, immediately flush affected area with water

This statement is part of the adapalene 0.1% gel Dosage and Administration section of the prescription label, but has been revised slightly so these instructions would be clearer to the average consumer. This is acceptable.

For bulleted statement (b) (4) it is recommended that it be revised to the following:

- during the early weeks of use, your acne may appear to worsen before it improves (this is normal); continue using as directed, unless you get irritation that becomes severe

The revised statement helps to make it clear to the consumer about therapeutic expectations of product and when to stop using product due to severe adverse reaction (e.g., severe irritation)..

For bulleted statement (b) (4) should be revised to the following:

- do not (b) (4) wax to remove hair in areas where the product has been applied

This bulleted statement is part of the adapalene 0.1% gel Dosage and Administration section of the prescription label and is acceptable.
To limit exposure to just the user of the product, the sponsor should add the following bulleted statement:

- Wash hands after use.

e. **Stop use and ask a doctor if**
The following bullet is under this subheading:

- irritation becomes severe

The sponsor should add the following bulleted statements:

- you become pregnant, or are planning to become pregnant, while using the product
- you see no improvement after 3 months of once daily use

The additional pregnancy statement under this sub-section will alert and direct potential consumers who are of child-bearing age to discuss the use of this product with their physician potential (see discussion under II. Reviewers' Comments (C) (4) (c)). The addition of the bulleted statement regarding lack of results after 3 months was discussed previous (see discussion under II. Reviewers' Comments (D) (4) (d)).

The following allergy sensitivity should be added to this subsection:

- you have symptoms of an allergic reaction (such as itching, rash, hives, swelling of the lips, eyelids and face, shortness of breath)

The inclusion of this bulleted statement is important information for consumers to know so that they can appropriately self-treat and self-diagnose allergic symptoms associated with adapalene use. Also, the addition of this statement is consistent with the prescription label and with the proposed CIL and is acceptable.

f. **Keep out of reach of children** statement follows 21 CFR 21 CFR 330.1(g) and is acceptable.

5. **Directions**
The Directions begin with the following statements:
(b) (4)

a. Use <u>once</u> daily
The directions are limited to adults and children 12 years and older. This is acceptable as this is the age population for the prescription product. It should be conveyed to the sponsor that they should remove the underline from the term "once" wherever it appears in the labeling as it does not comply with 21 CFR 201.66(d)(1-3)). Sponsor may bold the term "once" for emphasis instead.

It is also recommended that the sponsor remove the underline under "once" and bold instead. Also, the sponsor should add the following "at night" so that the first bulleted statement under this section reads as follows:

- Use **once** daily at night

The adapalene product for the prescription label indicates that it should be applied once a day to affected areas after washing in the evening before retiring. The following bulleted statements appear under the "Use once daily…" bulleted statements are "Clean skin thoroughly before applying the product" and "Cover the entire affected area with a thin layer".

For the proposed first bulleted statement, it should be revised to the following:

- Clean the skin gently and pat dry before applying the product

This information is consistent with the CIL.

The sponsor should revise the following statement from (b) (4) to:

- Cover the entire affected area with a thin layer. If your acne is on the face, apply the product to the entire face.

(b) (4) The consumer needs to apply a thin layer to the entire face if the consumer has acne on any part of the face due to the nature of acne development.

b. The sponsor should add the following bulleted statement:
   - Do not use more than one time per day. Applying more than directed will not result in faster or better results, but may worsen skin irritation.

(b) (4)

c. It is recommended that the sponsor revise to:
   - Ask a doctor

Simpler language is appropriate for OTC products for better comprehension by the average consumer. The use of term doctor keeps consistency throughout the label where the term "doctor" is also used in the warnings section.

6. ***Other information***
   In response to a CMC IR (April 27, 2016), the sponsor responded on May 2, 2016, with updated information regarding the storage and freezing information on the labeling. Sponsor included this information in this section. CMC found this acceptable (see CMC review).
7. ***Inactive ingredients***
   The inactive ingredient section follows 21 CFR 201.66(c) (8) and is acceptable. CMC found this acceptable (see CMC review).
8. ***Questions and comments?***
   The information in this section follows 21 CFR 201.66(c) (9) and is acceptable.

E. Annotated Specifications for Drug Facts Labels

1. The font specifications provided for the labels (January 21, 2016 submission) were difficult to read. On May 2, 2016, the sponsor provided a Drug Facts Information Box with the font specifications in response to April 27, 2016, labeling information request (IR).

   Also, as part of the April 27, 2016, labeling IR, the sponsor was asked to provide the following:
   a. Revised font specifications so that they meet the annotated font specifications in 21 CFR 201.66(d) (2). For example, the font type or size of the headings should be 8-point and the subheadings should not be smaller than 6-point type.
   b. Specifications for characters per inch and leading need to be provided as per 21 CFR 201.66(d) (3).
   c. Bullets used in the label should be either be uniformly throughout the label be a solid circle or solid square bullet of 5-point type size per 21 CFR 201.66 (d) (4). Also, bullets should follow format specifications per 21 CFR 201.66 throughout your proposed label.

   However, the sponsor responded that they would prefer not to revise until text has been finalized. This was deemed acceptable back in May; however, as we are near the PDUFA goal date of this application, the sponsor should provide this information.
2. The bulleted statements are difficult to read and follow from line to line. Per 21 CFR 201.66(d)(4), the first bulleted statement on each horizontal line of text shall be either left justified or separated from an appropriate heading or subheading by at least two square "ems". .
3. The sponsor should submit revised annotated font specifications following the recommendations in this review for DFL and PDP in same tabular format that they submitted in their May 2, 2016, submission.

F. Immediate Container Labels for 2-g, 15-, and 45(tubes) count SKUs

The changes described will be uniform for all SKUs. If there are differences among any of the SKUs, it will be explained in this section.

The tube label contains the following from the Drug Facts label:

- Active Ingredient
- (b) (4)
- Directions
- Warnings: If pregnant or breastfeeding, ask a (b) (4) before use
- Other information

Also, the tube label contains storage conditions, distribution information and "Made in Canada" statement with Galderma logo. Reduced labeling is acceptable as complete Drug facts are contained on the outer carton (see 21 CFR 201.66(c)).

The tube label contains reduced labeling information including proprietary name, established name and drug manufacturer, but does not contain a lot number, which are

the minimal labeling required by 21 CFR 201.10(i). Also, they do not contain expiration date per 21 CFR 201.17 and 21 CFR 211.137(d). These are necessary statements to identify certain lots of product in case there is a product recall or other issues once drug product is released into market for quality control. The expiration information is a necessary statement to inform the consumer as to safe and effective use of product. The sponsor should identify the location of the lot number and expiration date.
Also, the sponsor will need to submit revised statement of identity (see discussion under II. Reviewers' Comments (A) (2)).

As part of the 'Directions" statement, the word "once" is underlined; the sponsor should remove the underline and can bold instead for emphasis (see discussion under II. Reviewers' Comments (D) (5) (a.)).

2-g tube

1. The 2-g tube label, unlike the 15- and 45-g tubes, contains the statement "Purpose: Acne Treatment", immediately following the "Active Ingredient" statement.
2. The location of the established name including proprietary name (e.g., "Differin 0.1% adapalene Gel) appears at the bottom of the label. The sponsor should revised labeling so that the following appears for the proprietary and SOI in this order: Differin Gel, adapalene gel 0.1%

   Alongside it is a picture of (b) (4) graphic design. The picture of the (b) (4) structure is not acceptable and the sponsor should remove it (see discussion under II. Reviewers' Comments (B) (2)).
3. The location of the Galderma logo is located in the middle. This is acceptable.
4. The statement "SAMPLE (Not for Sale)" is present for this particular tube size as it will serve as a physician sample. This is acceptable.

15-g and **45-g** tubes

1. Unlike the 2-g outer carton, the tube label also, contains the statement: "**Warnings: For external use only**. Do not use on damaged skin (cuts, abrasions, eczema, sunburned)." The sponsor should delete the "-ed" after "sunburn".
2. The location of the established name including proprietary name (e.g., "Differin 0.1% adapalene Gel) appears at the top of the label. The sponsor should revised labeling so that the following appears for the proprietary and SOI in this order: Differin Gel, adapalene gel 0.1%.

   (b) (4) The (b) (4) is not acceptable and the sponsor should remove it (see discussion under II. Reviewers' Comments (B) (2)).
3. The location of the Galderma logo is located on bottom right corner. This is acceptable.

To ensure consistency and clarity, in addition to the required labeling information set forth by 21 CFR 201.10(i), the sponsor should have identical labeling information for all

SKUs that are subject to review in this application. For instance, the sponsor should include the following information for all SKUs:

- Purpose: Acne Treatment
- **Warnings: For external use only**. Do not use on damaged skin (cuts, abrasions, eczema, sunburn)

G. Lot number and Expiration Date

The lot number and expiration date are provided on the 2-, 15-g and 45-g cartons. However, they are not provided on the immediate containers (2-, 15- and 45-g tubes). The sponsor should identify the location of lot number and expiration dates for the 2-g, 15-g and 45-g tube labels with this information so that it is visible on all SKUs to the consumers.

H. Consumer Information Leaflet (CIL)

The established name including proprietary name (e.g., Differin 0.1% adapalene gel) is at the top of each page with the picture of the (b) (4) graphic design (b) (4) The picture (b) (4) is not acceptable and the sponsor should remove it (see discussion under II. Reviewers' Comments (B) (2)).

The CIL is a 2-page *Frequently Asked Questions* consisting of 13 general questions (in blue bold font) which provide similar if not more detailed information than what appears in the Drug Facts label. The responses are in gray font (see below).

The statement of identity with established and proprietary names needs to be revised (see (see discussion under II. Reviewers' Comments (A) (2)).

There is a picture of (b) (4) graphic design (b) (4) The picture of the (b) (4) structure is not acceptable and the sponsor should remove it (see discussion under II. Reviewers' Comments (B) (2)).

(b) (4)

This information is clear and concise. This is acceptable.

(b) (4)

This is different from what the prescription label suggests. The prescription label indicates that 'therapeutic results should be noticed after eight to twelve weeks of treatment." Sponsor should state that it will take up to 3 months to see results. The sponsor should revise response to this question as follows (see discussion under II. Reviewers' Comments (D) (4) (d)):

- It may take up to 3 months of daily use for results to appear.

What should I know before using the product?

- **If pregnant or breast-feeding,** ask a (b) (4) before use.
- **Keep out of reach of children.** If swallowed, get medical help or contact a Poison Control Center right away.

The sponsor should revise statement from "**If pregnant or breast-feeding,** ask a (b) (4) before use to:

- **If pregnant or breast-feeding,** ask a doctor before use. Some other retinoid drugs have been shown to cause birth defects. There is no evidence that Differin 0.1% causes birth defects when used topically as directed.

Per the clinical assessment, adapalene, unlike other retinoid products (e.g., tretinoin products), did not demonstrate an association with teratogenic effects in the form of birth defects which are clinically evident with other retinoid products. This language informs consumers, especially of child-bearing age, that adapalene was different from other retinoids in this particular safety aspect of use (see discussion under II. Reviewers' Comments (D) (4) (c)).

The sponsor should add the following bulleted statement regarding allergies:
Do not use Differin if you are allergic to adapalene and or any of the ingredients in this product (see discussion under II. Reviewers' Comments (D) (4) (d)).
The bulleted statement regarding "Keep out of reach of children" is acceptable (see discussion under II. Reviewers' Comments (D) (4) (f)).

How do I apply the product?

(b) (4)

The sponsor should revise the first bulleted statement under this question from (b) (4) to:

- Gently clean the affected areas using a mild cleanser and pat dry.

The sponsor should elaborate on the term "mild cleanser" (what makes a cleanser mild?);
The sponsor should revise the second bulleted statement to:

- Apply Differin as a thin layer to the affected areas of the skin (b) (4) If you get acne on the face, clean, dry and apply the product to the entire face. Differin is **not** a spot treatment and should not be used to treat a single pimple.

This is consistent with the prescription label for adapalene gel (see discussion under II. Reviewers' Comments (D) (5) (a)).

The sponsor should revise the third bulleted statement from (b) (4) to:

- Avoid contact with eyes, lips and mouth. **If contact occurs, immediately flush with water.**

This statement is consistent with the prescription label for adapalene gel. The second sentence is bolded for emphasis to be more salient to the consumer regarding self-triage if the product gets into the eyes, mouth and/or lips.
The sponsor should add the following statement:

- Wash hands after use.

This addition was found acceptable review (see discussion under II. Reviewers' Comments (D) (4) (d)).

The sponsor should delete the (b) (4) after "sunburn" so that he statement reads as follows:

- Do not apply the product to damaged skin (cuts, abrasions, eczema, or sunburn)

This is acceptable (see discussion under II. Reviewers' Comments (D) (4) (b)).

How often do I apply the product?

(b) (4)

The sponsor should (b) (4) Also, the sponsor should revise to the following (see discussion under II. Reviewers' Comments (D) (5) (a)):

- Apply this product (b) (4) and (b) (4) try to apply the product at the same time once each day, but best at night.

Can I use a moisturizer if my skin is dry?

- Yes.

The sponsor should revise to the following statement:

- Yes. Avoid products containing alpha hydroxy or glycolic acids which may worsen irritation.

This is acceptable (see discussion under II. Reviewers' Comments (D) (4) (d)).

What do I do if I need to be in the sun?

(b) (4)

The sponsor should revise the first bulleted statement to:

- When possible, limit sun exposure, and light from tanning beds.

This is acceptable as it follows DFL and the prescription label for adapalene (see discussion under II. Reviewers' Comments (D) (4) (d)).

The sponsor should revise the second bulleted statement to the following:

- When going outdoors, use a sunscreen as labeled. Your skin may be more sensitive while using Differin. If you must use this product during the day, allow it to dry before applying sunscreen.

This additional information is helpful to the average consumer that it is clear the reason behind avoiding/lessening exposure to the sun when using this product (see discussion under II. Reviewers' Comments (D) (4) (d).

When is my skin most likely to become irritated? And what do I do?

• Irritation (redness, itching, dryness, burning) is more likely to occur:
— In the first few weeks of use

(b) (4)

The second sentence under the first bulleted statement should be revised (b) (4) to:

- If using abrasive skin cleansers, products with drying effects or more than one topical acne medication at a time. You may want to delay starting Differin until any irritation from using other product(s) has gone away.

This is consistent with the prescription label for adapalene gel under the Precautions section-Drug Interactions subsection section of the prescription label.

The sponsor should delete the first sentence under the second bulleted sentence (b) (4) (see discussion under II. Reviewers' Comments (C) (3-4)).

The sponsor should revise the third bulleted statement from (b) (4) to:

- Irritation usually lessens after 4 weeks of continued use.

This language is consistent with the prescription language

What do I do if my skin becomes severely irritated?

• If irritation becomes severe, stop use and ask a doctor before using the product again.

The sponsor should provide clarification on what is meant by the term "severe" in relation to a severe irritation.

Can I remove unwanted facial hair by waxing while using this product?

(b) (4)

The sponsor should revise to the following bulleted statement:

- Do not use wax to remove hair in areas where the product has been applied because it may worsen skin irritation.

The existing statement is confusing and unclear and should be revised statement for clarity to emphasis that the application of the product can cause the skin to become more sensitive so such procedures such as waxing in the applied areas can potentially exacerbate skin irritation.

What ingredients are used in Differin?

• Differin contains:
The active ingredient is adapalene 0.1%. The other ingredients are: Carbomer 940, Edetate Disodium, Methylparaben, Poloxamer 182, Propylene Glycol, Purified Water and Sodium Hydroxide. May contain Hydrochloric Acid to adjust the pH.

(b) (4)

How should I store this product?

• Differin should be stored at room temperature [68° – 77°F]. Protect from freezing.
• **Do not use** the product after the expiry date marked on the crimp of the tube.

The sponsor should remove the second bulleted statement under **"What ingredients are used in Differin?"** to:

- (b) (4)

This bulleted statement does not belong in this section, but rather should be moved under the **"What should I know before using this product?"** section of the CIL. It is more appropriate in this section, as it is important safety information that the consumer should know before using the product.

This remaining information on the "**What ingredients are used in Differin**?" section and the "**How should I store this product**" section is found to be acceptable by CMC (see CMC review).

Other Questions?
- Where can I get more information?
- Phone: 1-866-735-4137

The information is consistent with DFL (see discussion under II. Reviewers' Comments (D) (8)).

III. RECOMMENDATIONS

Issue an Information Request communication to the sponsor for the submitted Differin 0.1% adapalene Gel labeling and provide the following preliminary comments. Additional recommendations may be forthcoming once all of the reviews are completed. Inform the sponsor that it must make the following labeling revisions:

Principal Display Panel (PDP) for all SKUs

1. **Statement of identity (SOI) (see 21 CFR 201.61)**
   a. For the pharmacological category, identify the product as an "acne treatment" for consistency as you have used under the Purpose section of the Drug Facts label. Use this term consistently throughout your labeling to prevent confusion.
   b. Revise SOI to the following: adapalene gel 0.1% Acne Treatment.
   c. Submit revised labeling so that the SOI is at least 25% to 50% of the most prominent printed matter on the PDP.
   d. Reformat the orientation of the proprietary name Differin Gel and SOI, "adapalene gel 0.1%, to comply with 21 CFR 201.61 (c). Your current proposed PDP labels has these terms relatively perpendicular (vertical) to the package's base, instead of relatively parallel to the base as required.
2. Remove (b) (4) as it is not appropriate. If you would like to keep this statement on the PDP, it is suggested that you should place as a statement (b) (4)
3. Remove the statement (b) (4) as this may be confusing to consumers (b) (4)
4. Provide data to support this statement (b) (4) for this proposed OTC Differin Gel 0.1% product or remove it.

5. Revise the statement [redacted] to "**One Time A Day Acne Treatment**" for clarity and consistency with the Drug Facts label and consumer information leaflet.
6. Remove the [redacted] statements for 15-g and 45-g products respectively, [redacted].
7. Remove the [redacted] graphic design from the PDP and anywhere else proposed in the labeling [redacted]

Outer Panels except the Principal Display Panel, 15- and 45-g outer cartons

1. Revise statement from [redacted] to:
   "First FDA approved over-the-counter topical retinoid* for acne treatment".
   Also, include the following statement:
   > * **Read carton and enclosed consumer information leaflet before using this product. Keep this carton and consumer information leaflet. They contain important information.**

   This may be placed in a flag prominently on the outer carton in close proximity to the "**First FDA approved over-the-counter topical retinoid* for acne treatment**" where it would be the most visible to the consumer at point of purchase.

2. These comments refer to the claims and statements present within the outline of the actual size tube figure.
   a) Refer to the comments made for the statement of identity for the PDP and revise all labels accordingly.
   b) Remove the following claims [redacted]
   c) Remove the statement [redacted] as it already appears in other areas of your proposed labeling (e.g., Drug facts label).
   d) Justify or remove the statement "Dermatologist developed [redacted]" as data are required for review and approval of such a statement for Differin Gel 0.1% marketed OTC.
   e) Remove [redacted] graphic design here and wherever it appears in labeling.

Drug Facts Label – All SKUs

1. It is recommended that the ***Active*** ingredient is as follows:
   Active Ingredient

"Adapalene, 0.1% (retinoid)*
*read consumer information leaflet"

2. ***Warnings***
   a. **Do not use**
      1) Delete the "-ed" after the term "sunburn".
      2) Add the following bulleted statement:
         - If you are allergic to adapalene or any of the ingredient in this product

   b. Revise the following statement from "**If pregnant or breast-feeding,** ask a [redacted] (b) (4) before use" **to:**
      - **If pregnant or breast-feeding,** ask a doctor before use.

   c. **When using this product**
      1) Add the following bulleted statement:
         - it may take up to 3 months of once daily use to notice results
      2) Revise the following statement from [redacted] (b) (4) to
         - limit sun exposure, including light from tanning beds, and use sunscreen when going outdoors.
      3) Add a third another sub-bullet under the "irritation (redness, dryness, burning) is more likely to occur" bulleted statement which reads as follows :
         - but, usually lessens with continued use of this product
      4) Revise the following bulleted statement from: [redacted] (b) (4) to:
         - avoid product contact with eyes, lips and mouth. If contact occurs, immediately flush affected area with water
      5) Revise the following bulleted statement from: [redacted] (b) (4) to:
         - during the early weeks of use, your acne may appear to worsen before it improves (this is normal); continue using as directed, unless you get irritation that becomes severe
      6) Revise the following bulleted statement from: [redacted] (b) (4) to:
         - do not [redacted] (b) (4) wax to remove hair in areas where the product has been applied
      7) Add the following bulleted statement:
         - Wash hands after use

   d. **Stop use and ask a doctor if**
      1) Add the following bulleted statements:
         - you become pregnant, or are planning to become pregnant, while using the product
         - you have symptoms of an allergic reaction (such as itching, rash, hives, swelling of the lips, eyelids and face, shortness of breath)
         - you see no improvement after 3 months of once daily use

3. ***Directions***
   [redacted] (b) (4)

a. Remove the underline under the word "once". We agree with emphasizing the term "once", but bold font is recommended and consistent with the labeling.
b. Revise the following statement from "Use once daily" to:
    - Use **once** daily at night
c. Revise the following statement from (b) (4) to:
    - Clean the skin gently and pat dry before applying the product
d. Revise the following statement from (b) (4) to:
    - Cover the entire affected area with a thin layer. If your acne is on the face, apply the product to the entire face.
e. Add the following bullet:
    - Do not use more than one time per day. Applying more than directed will not provide faster or better results, but may worsen skin irritation. (b) (4)
f. Revise bulleted statement from (b) (4) to:
    - Ask a doctor

Annotated Specifications for Drug Facts Labels

As requested in our April 27, 2016, labeling information request, provide the following annotated font specifications:

a. Revise the font specifications so that they meet the font specifications required under 21 CFR 201.66(d) (2). For example, the font type or size of the headings is required to be 8-point type and the subheadings not smaller than 6-point type.
b. Provide the specifications for characters per inch and leading per 21 CFR 201.66(d) (3). (e.g., annotate the specifications directly to the DFL or annotate the specifications in tabular format alongside the label).
c. Revise bullets so that they all are a solid circle or solid square bullet of 5-point type size (21 CFR 201.66 (d) (4)). Also, ensure that bullets follow format specifications per 21 CFR 201.66 throughout your proposed label.
d. The bulleted statements are difficult to read and follow from line to line. Revise the first bulleted statement on each horizontal line of text so that it is either left justified or separated from an appropriate heading or subheading by at least two square "ems" (21 CFR 201.66(d)(4)).
e. Revise such that additional bulleted statements appearing on each subsequent horizontal line of text under a heading or subheading are vertically aligned with the bulleted statements appearing on the previous line.
f. Submit revised annotated font specifications following the recommendations in this review for DFL and PDP in same tabular format that was submitted in your May 2, 2016, submission.

Immediate Container Labels

a. Revise label so that the proprietary name and SOI are as follows and appears in this order: Differin Gel, adapalene gel 0.1%
b. Delete the underline and bold the word "once".

c. Identify the location of the expiration and lot numbers on the immediate container labels (21 CFR 201.10(i) and 21 CFR 201.17).
d. For the 2-g package size, add the following statement: "**Warnings: For external use only**. Do not use on damaged skin (cuts, abrasions, eczema, sunburn)" for consistency with all labels and this is important safety information be conveyed to the consumer.
e. For the 15-g and 45-g package sizes, add the following statement: "Purpose: Acne Treatment" as you have done so for the 2-g physician sample immediate container. Delete the "-ed" after word "sunburn"
f. Remove the (b) (4) graphic design wherever it appears in the label and labeling.

Lot number and Expiration Date

Identify the location of the lot number and expiration date on the immediate containers (2-, 15- and 45-g tubes) (see recommendations under Immediate Container Labels).

Package Inserts

1. **Consumer Information Leaflet (CIL)**
   - **a.** Remove (b) (4) graphic design wherever it appears (b) (4)
   - **b.** Revise the order of the proprietary name and SOI to the following: Differin Gel, adapalene gel 0.1% Acne Treatment.
   - **c. How long will it take for Differin to work?**
     Delete the statement; (b) (4) Revise to the following statement:
     - It may take up to 3 months of daily use for results to appear.
   - **d. What should I know before using this product?**
     Revise the following statement from (b) (4) to:
     - **If pregnant or breast-feeding,** ask a doctor before use. Some other retinoid drugs have been shown to cause birth defects. There is no evidence that Differin causes birth defects when used topically as directed.
     - **Do not use** Differin if you are allergic to adapalene and or any of the ingredients in this product
   - **e. How do I apply the product?**
     1. Revise the following statement from (b) (4) to:
        - Gently clean the affected areas using a mild cleanser and pat dry.

        Clarify what is meant by a "mild cleanser" (what makes a cleanser mild?).

     2. Revise the following statement from (b) (4) to:

- Apply Differin as a thin layer to the affected areas of the skin (b) (4) If you get acne on the face, clean, dry and apply the product to the entire face. Differin is **not** a spot treatment and should not be used to treat a single pimple.

3. Revise the following statement from (b) (4) to:
   - Avoid contact with the eyes, lips and mouth. **If contact occurs, immediately flush with water.**
4. Add the following statement:
   - Wash hands after use.
5. Delete the "-ed skin" after the term "sunburn" so the statement reads as follows:
   - Do not apply the product to damaged skin (cuts, abrasions, eczema, or sunburn)

f. How often do I apply the product?

1. Revise to the following:
   - Apply this product (b) (4) and try to apply the product at the same time each day, but best at night.
2. Clarify "mild cleanser" in terms of what makes a cleanser mild.

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

Revise to the following:

- Yes. Avoid products containing alpha hydroxy or glycolic acids which may worsen irritation.

h. What do I do if I need to be in the sun?

1. Revise the first bulleted statement from (b) (4) to:
   - When possible, limit sun exposure, including light from tanning beds.
2. Revise the second bulleted statement from (b) (4) to:
   - When going outdoors, use a sunscreen as labeled. Your skin may be more sensitive while using Differin. If you must use this product during the day, allow it to dry before applying sunscreen.

h. **When is my skin most likely to be become irritated? And what to do?**

1. Under the first bulleted statement "Irritation (redness, itching, dryness burning) is more likely to occur", revise the second sub-bullet from (b) (4) to
   - If using abrasive skin cleansers, products with drying effects or more than one topical acne medication at a time. You may want to delay starting Differin until any irritation from using other product(s) has gone away.
2. Under the second bulleted statement, delete the following sub-bullet:
   - (b) (4)

3. Revise the third bulleted statement from (b) (4) to:
    - Irritation usually lessens after 4 weeks of continued use.

i. What do I do if my skin becomes severely irritated?
Clarify the term "severe" in the following:
- If irritation becomes severe, stop use and ask a doctor before using the product again.

j. Can I remove unwanted facial hair by waxing while using this product?
Revise the bulleted statement to:
- Do not use wax to remove hair in areas where the product has been applied because it may worsen skin irritation.

k. What ingredients are used in Differin?
Remove the second bulleted statement which reads:
- (b) (4)

Issue a communication to the sponsor that includes these deficiencies in order to initiate labeling negotiations.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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

/s/

YOON KONG
06/23/2016

STEVEN A ADAH
06/24/2016

FDA Social Science Review: Consumer Studies

Division of Nonprescription Drug Development

Date:	May 12, 2016
From:	Barbara Cohen, MPA, Social Scientist, DNDP
Through:	Jane Filie, MD, Clinical Team Leader, DNDP
To:	Theresa Michele, MD, Director, DNDP
Subject:	Label comprehension and self-selection studies supporting the prescription (Rx) to over-the-counter (OTC) switch for adapalene 0.1% gel for the treatment of acne

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1. Executive Summary

The targeted pregnancy self-selection study conducted by the Applicant shows that adult pregnant women will self-select to use Differin® OTC. While the DNDP clinical assumption is that overuse would be mitigated by skin irritation, this reviewer is still concerned about the potential use by adolescents, which was not assessed in the self-selection study. Additionally, while adolescents ages 12-14 are not as likely to get pregnant as older adolescents, their relatively lower label comprehension scores of statements such as "use once daily" and "ask a doctor under age 12," coupled with their potential use of this product for many years, could potentially contribute to safety concerns at later ages when they are more likely to become pregnant. Low literacy adolescents may be particularly vulnerable due to their lower comprehension of "use once daily". Moreover, the potential use of this product by women of older childbearing age for wrinkles could not be assessed in the consumer development program, but conceivably these women could also be prone to overuse for this indication. For all of these reasons, this reviewer is recommending that the "Use Once Daily" statement be enhanced so as to optimize compliance with this directive.

2. Background

Adapalene is currently marketed for prescription use for the topical treatment of acne vulgaris in adults and children 12 years of age and older in a variety of different formulations. Galderma Laboratories, L.P. has submitted a supplemental New Drug Application (sNDA), seeking approval for a full prescription to OTC switch of adapalene gel 0.1% (prescription trade name Differin®) for the treatment of acne as a once daily topical administration. The proposed OTC dosing is the same as the approved prescription dosing. If approved, this would be a first-in-class prescription to OTC switch for a topical retinoid.

One major clinical concern associated with the switch is the teratogenicity associated with the retinoic class of drugs. The teratogenicity of adapalene appears to be lower than that of other retinoids, but overall the risk in humans is unknown. To date, there are no adequate and well controlled studies in pregnant women.

At the request of the Agency, the Applicant conducted two major consumer studies (label comprehension and self-selection) to determine the comprehension of labeled warnings and the potential extent of use by pregnant women.

3. Regulatory Activity Regarding Consumer Studies

In 2013, FDA's then Division of Nonprescription Clinical Evaluation and the Applicant began discussions on the OTC switch development program. Highlights of these interactions are outlined below as they pertain to the label comprehension, self-selection, and standard of care studies.

March 12, 2013 pre-IND meeting with FDA:

- The Agency noted that there was a potential for teratogenicity, as it considered adapalene to be a retinoid. Thus, the Agency stated that the "If pregnant or breastfeeding, ask a (b) (4) before use" warning would need further evaluation, and stated that given the potential teratogenicity concerns, the pregnancy warning needed to be enhanced for the OTC market.

- The Agency noted that there was a potential for carcinogenicity as animal studies had shown an increased tumor risk with the use of pharmacologically similar drugs, namely retinoids, when exposed to UV radiation or sunlight. The Agency stated that although avoiding sunlight was not a unique element to this label, if the product was indicated for younger children and/or the sunlight exposure effects are more significant for this product than for other products, the Applicant needed to strengthen the warning. The Agency recommended that in any case, the sunlight exposure warning be tested in label comprehension with users as well as parents and caregivers.

- The Agency stated that it was interested in data on the use in the prescription setting with regards to current prescribing practices and how clinicians counsel patients who may potentially become pregnant or who are pregnant while using this product. The Agency wanted to know if clinicians co-prescribe oral contraceptives when prescribing Differin® 0.1%, whether they currently prescribe Differin® 0.1% to pregnant patients, and whether they advise patients to stop using the product if they become pregnant.

- The Agency also stated that the Applicant needed to ensure that consumers understand that they should not be using other acne medications concurrently, especially given the possibility that their acne may flare up early in the therapy and that therefore they may be more tempted to treat with a second product containing salicylic acid.

- In the Applicant's meeting background package, the proposed protocol for the label comprehension study included as a primary objective an assessment of the pregnancy/breastfeeding warning. The Agency confirmed that this was the most important objective of the study. In the protocol that was submitted, the sunlight exposure objective was a secondary communication objective. The Agency stated that this needed to be a primary objective.

- The Agency also advised the Applicant to test potentially unique warnings, directions and/or elements necessary for safe use, such as "Do not used on damaged skin", use of protective clothing over treated areas where sun exposure cannot be avoided, minimize exposure to sunlamps, weather extremes such as wind or cold may also be irritating, avoid contact with the lips, angles of the nose, and mucous membranes, caution should be exercised in using preparations containing sulfur, resorcinol or salicylic acid in combination with Differin, during the early weeks of therapy an apparent exacerbation may occur, use of waxing as a depilatory method should be avoided on treated skin.

- The Agency stated that a self-selection study was needed to support an NDA

filing for the proposed switch, with women of childbearing age, women who were pregnant, women looking to become pregnant.

In a discussion that encompassed both the self-selection and actual use studies, the Agency indicated that the indication for use, how much would be used, how often and for how long should all be assessed.

October 30, 2013 written response from FDA:

- The Agency reiterated its strong recommendation that the Applicant conduct a self-selection study to assess the likelihood of pregnancy exposures.

June 10, 2015 pre-sNDA meeting with FDA:

- The Agency emphasized again the importance of demonstrating that pregnant women would not use the product. Regarding the LCS, the Applicant confirmed that they had not submitted a revised protocol to the Agency prior to fielding the study, but that the Agency's comments were incorporated into the revised protocol.

4. Consumer Studies

To address the Agency's concerns, the Applicant conducted research and submitted reports for two consumer studies in support of the NDA for Differin® OTC. The Applicant also conducted research and submitted reports for two other "standard of care" studies in support of the NDA for Differin® OTC. However, these standard of care studies will only be discussed nominally here due to significant Agency concerns with their methodology.

4.1 Label Comprehension Study – Design and Conduct

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

1. "Use once daily" and
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%; the Applicant stated that these objectives did not represent serious safety concerns, but that increased irritation could occur if the product was used on damaged skin or more than once daily and therefore the labeled statements provide important information about proper use. The Applicant declined to assess the pregnancy warning as a primary objective; the Applicant also declined to assess the sun exposure warning as a primary objective (note: the pregnancy warning was not tested at all, while the tanning bed component of the sun exposure warning was tested as a secondary objective.)

Ten secondary objectives were assessed:

1) For the treatment of acne, clears up pimples and blemishes.
2) Ages 12 and older.
3) Do not use wax to remove hair in areas where the product has been applied.
4) When using this product avoid unnecessary sun exposure, including tanning beds, and use a sunscreen when going outdoors (tanning beds only was tested.)
5) When using this product, moisturizers may be used to relieve dry skin.
6) When using this product, irritation is more likely to occur in the first few weeks of use.
7) Under 12, consult a physician.
8) When using this product, during the early weeks of use your acne may appear to worsen before it improves. This is not a reason to stop using.
9) Stop use and ask a doctor if irritation becomes severe.
10) When using this product, irritation (redness, itching, dryness, burning) is more likely to occur if using more than one topical acne medication at a time.

Study Demographics

The study was conducted in April, 2014 with a total of 586 unique respondents. The study population included males and females, ages 12 to70, in eight geographically dispersed sites in the United States – Chicago, IL; Dallas, TX; Springfield, MO; Tampa, FL; Louisville, KY; Seattle, WA; Baltimore, MD; Los Angeles, CA.

Appendix 4 displays a profile of the study population. Below is a summary of key demographic issues:

Literacy

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

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

Although the Cohort 1 had poor low literacy representation, there were sufficient numbers of low literates in Cohorts 1 and 2 combined for FDA to detect and analyze any differences between normal and low literacy respondents overall.

Age

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 to24-year-old age group. As Appendix 4 illustrates, only 33 respondents in the entire study were between the ages of 18 and 24.

Race/ethnicity

With regard to racial/ethnic representation, overall 69.4% were white, 19.4% were black and 11% were Asian, Native American or other ethnicities. Overall, there were 9% Hispanics in the study; this contrasts with the estimated U.S. Hispanic population of 18%. Furthermore, 10.6% of adolescents in the study were Hispanic; this contrasts with the estimated U.S. adolescent population of 24% Hispanic.[1] Therefore, it appears that Hispanics were significantly under-represented in the study population.

The study population was all comers, as recruited from site database lists; respondents were not recruited for having acne. Recruitment of all comers is acceptable, according to the FDA guidance for industry - Nonprescription Label Comprehension Studies, anyone should be able to understand a typical Drug Facts Label (DFL), even if they personally do not suffer from the condition. The Applicant did not specifically recruit caregivers of young children, although it is reasonable to expect that they naturally appeared in the study

[1] U.S. Census Bureau, Population Division. The data for 2010 to 2014 are based on the population estimates released for July 1, 2014. Data beyond 2014 are derived from the national population projections released in December 2014.

population. In fact, the protocol for scheduling instructions reminded subjects that "*due to the nature of the study, we will not be able to accommodate unattended small children during their visit. If small children are brought to the site, the subject should bring another adult to supervise the child*." However, because there was no data collected on caregivers, it is not possible to assess whether they were more or less likely to comprehend key statements on the label.

Although the Applicant did not specifically recruit acne sufferers, respondents were asked if they had used OTC acne products within the past 12 months. Of the total study population, 38.7% had used OTC acne products. Table 1 displays the breakout by age. In the 12 to 14-year-old age group, 52.6% of study respondents used acne products; 66.6% of 15 to 17-year-old study respondents used them. These relatively higher rates of adolescent usage of OTC acne products lead us to examine adolescent comprehension closely with regard to the study findings.

Table 1: Label Comprehension Study – Have used acne products in past six months, by age (n=586)

Age	12-14	15-17	18-34	35-44	45-64	65+	Total
Yes, used	52.6%	62.6%	31.0%	27.7%	15.5%	--	38.7%
No, have not used	47.4%	36.7%	69.0%	72.3%	83.7%	100.0%	60.9%

Source: Applicant's NDA submission

Potential participants were recruited over the phone from site databases and screened using standard inclusion/exclusion criteria. Qualified participants were then directed to a local facility for a one-on-one interview. Participants who were 12 years and older were required to sign an assent and to have a parent in attendance to sign a consent form and give written parental permission to participate in the research study. The health literacy of each participant was then assessed by administering either the Rapid Estimate of Adult Literacy in Medicine (REALM) or the Rapid Estimate of Adolescent Literacy in Medicine to adolescents. Adult subjects who scored 60 or less on the REALM were classified as low literate and those scoring 61 or above were classified as normal literate. For teens, subjects testing below current grade level were identified as low literate and subjects testing at or above current grade level were identified as normal literate.

Following the administration of the REALM, participants were presented with the Differin® OTC package and given an opportunity to review the labeling (See Appendix 1 for the DFL used in the study) at his/her own pace. The label stayed with the participant as they were asked the label comprehension questions so that they could refer back to it if they desired. Participants were asked a series of open- ended questions, including questions involving a variety of hypothetical scenarios.

For each question, the Applicant utilized the follow-up probe of "why do you say that?" within the question to not only provide insights into participant thinking, but also to mitigate responses when participants decided to change their mind. Because the interviewers utilized paper questionnaires in which they had to write in longhand any incorrect responses provided by the participant (by contrast, correct responses were coded), this could have served to cue participants that an answer they provided was incorrect when the interviewer did a lot of writing. For instance, this questionnaire started off with two easy questions (regarding the indication and the scenario of a 16-year-old using the product), in which the participants probably were fairly comfortable with their answers while observing that the interviewers were not writing anything after they provided their answers. This might have also served to cue participants when the interviewers were writing after they provided their responses, and therefore they may have been more prone to rethink their original answers.

However, in this particular study, I have examined the mitigations and determine them to be not of concern, because generally responses were characterized as "incorrect" either initially or subsequently if participants said that the person in the scenario should not use the product at all, or if participants had another interpretation that led to extremely cautious use. Therefore, from a safety perspective, I do not have a concern here about the responses being characterized as "incorrect" and then being mitigated to be "correct" upon further reflection of the participant. However, for the reasons cited above, I would have a concern if this methodology was generally utilized in other studies.

4. 2 Label Comprehension Study – Results

Table 2 – LCS Results for Primary Objectives

(Question #) Primary Objective		General Population (Cohort 1) N=515		
		n	PE%	LB%, UB%
(Q7)	**Do Not Use** On damaged skin (cuts, abrasions, eczema, sunburned)	502	97.5	95.7, 98.7
(Q5)	**Directions:** Use once daily	494	95.9	93.8, 97.5

Source: Tabulated Data

Source: Applicant's study report

Use Once Daily

As Table 2 shows, comprehension of the primary objective of "Use once daily" for the general population was 95.9%, with a 2-sided 95% exact lower confidence bound (LCB) of 93.8%. This LCB exceeded the target threshold of 85%, but as previously noted, Cohort 1 had relatively few LL participants (11%).

As Table 3 illustrates, the comprehension rates for the objective "Use once daily" differed significantly between literacy levels; NL (normal literacy) participants had a comprehension

rate of 96.5% and LL (low literacy) participants had a comprehension rate of 86.9% (Fisher's exact p-value<0.0001).

Table 3: Label Comprehension Study Results – Use Once Daily

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)

Source: Adapted from study report Table 10-6. Includes participants from the General Population who tested as low literate (n=59) as well as low literate participants enrolled through targeted recruitment (n=71)

As Table 4 illustrates, the comprehension did not differ significantly between genders (Fisher's exact p-value=0.86), but for both genders, NL participants scored higher than LL participants.

Table 4: Label Comprehension Results - "Use Once Daily" by Gender and Literacy

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)

Source: FDA Statistics utilizing Applicant's data

As Table 5 shows, focusing on adolescent comprehension of "Use Once Daily," there was a significant (Fisher's exact p-value=0.006) difference in comprehension between NL adolescents (95.7%) and low literacy adolescents (84.9%). The differences that did exist by literacy level were similar across genders (Zelen test p-value=1.00).

Table 5: Label Comprehension Results - "Use Once Daily": NL vs LL Adolescents (Age 12 to 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) (90.8)	95.3 (81/85) (88.4)	84.9 (62/73) (74.6)	83.9 (26/31) (66.3)	85.7 (36/42) (71.5)

Source: FDA Statistics utilizing Applicant's data

Table 6 displays comprehension of "Use Once Daily" by age range. Adolescents ages 12 to 14 had significantly lower comprehension (87.4%) than any other age group except age 65+. This is of concern in light of the data displayed in Table 1 that showed more than half the adolescents in that age range have used an acne products in the past six months.

Table 6: Label Comprehension Results – "Use Once Daily" by Age

Age	12-14	15-17	18-34	35-44	45-64	65+
Demonstrated comprehension	87.4% 118/135	98.0% 144/147	96.4% 81/84	96.9% 63/65	96.1% 124/129	88.5% 23/26

Source: Applicant's NDA Submission

Table 7: Label Comprehension Results – "Use Once Daily" by Adolescent Age and Literacy

Age Group	12-14 % (n/N)	15-17 % (n/N)
Normal Literacy	91.9 (91/99)	99.1 (109/110)
Low Literacy	75.0 (27/36)	94.6 (35/37)

Source: FDA Statistics utilizing Applicant's data

Table 7 shows that although total low literacy adolescent comprehension (point estimate) was 84.9%, when looking at the low literacy adolescents ages 12-14, that comprehension of "Use Once Daily" was as low as 75.0%.

Do not use on damaged skin

Table 2 shows that comprehension of the primary objective "Do not use on damaged skin" for the general population was 97.5% with a 2-sided 95% exact LCB of 95.7%, which exceeded the established threshold of 85%.

As Table 8 shows, for "Do not use on damaged skin", NL participants had a comprehension rate of 97.4% and LL participants 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).

As Table 9 shows, comprehension of "Do not use on damaged skin" did not differ significantly between genders or literacy groups.

It is unknown whether the wording of the relevant question overly cued most participants as to the correct answer when otherwise they might not have answered correctly. The LCS question that was asked was: "*Carl has a cut on his face and wonders if he should apply the product to the damaged skin. What if anything does the label say about this*?" The wording of this question directly cued the answer, because of the explicit mention of damaged skin, which is the exact phrase that appears on the DFL. "*A cut on the face*" would have been a sufficient enough phrase to convey the concept. Thus, the comprehension scores of this question may be upwardly biased.

Table 8: Label Comprehension Study Results – Do Not Use on Damaged Skin

Primary Objective	Normal Literacy % (n/N) (LCB)	Low Literacy % (n/N) (LCB)
Do Not Use: On damaged skin (cuts, abrasions, eczema, sunburned)	97.4 (444/456) (95.5)	99.2 (129/130) (95.8)

Source: Applicant NDA Submission

Table 9: Label Comprehension Study Results - "Do Not Use on Damaged Skin" by Gender and Literacy

Primary Objective	Normal Literacy % (n/N) (LCB)		Low Literacy % (n/N) (LCB)	
	Female	Male	Female	Male
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)

Source: Applicant NDA Submission, FDA Statistics utilizing Applicant data

Table 10 shows the normal and low literacy scores for the secondary communication objectives.

Table 10: Label Comprehension Study Results: Secondary Communication Objectives, NL vs LL

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

Secondary Objectives		N	P.E.	N	P.E.
(Q1)	**Use of the medication:** For the treatment of acne, clears up acne pimples and acne blemishes, helps prevent new acne pimples and acne blemishes from forming	456	100.0	128	98.5
(Q2)	**Directions:** Ages 12 and older	453	99.3	122	93.8
(Q11)	**When using this product** Do not use wax to remove hair in the areas where the product has been applied	450	98.7	126	96.9
(Q3)	**When using this product** Avoid unnecessary sun exposure, including tanning beds, and use a sunscreen when going outdoors (only tested the "including tanning beds" portion of this warning; all other wording is monograph)	444	97.4	124	95.4
(Q6)	**When using this product** Moisturizers may be used to relieve dry skin	443	97.1	112	86.2
(Q10)	**When using this product** Irritation (redness, itching, dryness, burning) is more likely to occur in the first few weeks of use	431	94.5	112	86.2
(Q12)	**Directions:** Under 12 years of age, consult a physician	430	94.3	111	85.4
(Q4)	**When using this product** During the early weeks of use your acne may appear to worsen before it improves. This is not a reason to stop using	407	89.3	98	75.4
(Q9)	**Stop use and ask a doctor if** irritation becomes severe	359	78.7	93	71.5
(Q8)	**When using this product** Irritation (redness, itching, dryness, burning) is more likely to occur if using more than one topical acne medication at a time	294	64.5	67	51.5

(Source: Applicant's Study Report)

Avoid unnecessary sun exposure

Regarding the secondary objective of "Avoid unnecessary sun exposure, including tanning beds, and use sunscreen when going outdoors," the Agency had advised that the sunlight exposure component of the warning be tested because this product's active ingredient, adapalene, is not generally recognized as safe and effective under the OTC monograph and because the effects of sun exposure while using this product would be of particular concern. However, the Applicant declined to do so, on the premise that this is labeling language consistent with the monograph and therefore did not need to be assessed. The Applicant only tested the component of the warning regarding avoidance of tanning beds: "*Melissa has acne and has been using this product. She is planning to go to the tanning bed today. What, if anything, does the label say about this?"* As Table 10 illustrates, this tested extremely well, with no significant differences in comprehension between literacy levels.

In this particular instance, DNDP's clinical reviewers are not significantly concerned with potential significant phototoxicity or photocarcinogenicity after reviewing the relevant data. However, the failure to test comprehension of this statement is a study deficiency; the Applicant's rationale for not including this as a primary objective would not be acceptable to the Agency in a variety of other contexts. Moreover, sun exposure from sunlight may lead to significant irritation and discomfort; therefore, it may be helpful to modify the statement.

Under 12 years old, consult a physician

Another key secondary objective of interest regarding the potential for pediatric misuse is "Under 12 years old, consult a physician." Normal literacy participants were significantly more likely to comprehend this statement than LL participants (94.3% vs 85.4%). There were no significant differences between genders. Of particular concern is that, as Table 11 illustrates, ages 15 to 17 (94.6%) and ages 18 to 34 (96.4%) were significantly more likely to comprehend this objective than ages 12-14 (85.9%). It is possible that adolescents in the 12 to 14-year-old age ranges would provide or share the product on their own with younger siblings, either without looking at a label or without understanding the label.

Additionally, there was a methodological issue with this question. Following the first two questions in the study – questions that assessed comprehension of the indication and comprehension of the statement "for ages 12 and older"- the interviewer stated: *"The next few questions describe possible situations that could occur in real life. Please assume that each question has all the information in it for you to make a decision and that each person mentioned in the scenario is 12 years of age or older, unless otherwise specified".* This wording could have had the effect of cueing the participants that the cutoff of age 12 was significant in some way. Although the relevant question of concern - *"Anna's 10 year old son has developed acne on his face. Her son would like to start using this product to treat his acne. According to the label, what if anything should Anna do?"* - was the last in a series of ten questions asked after the interviewer made this statement, the placement of this objective's assessment at the end of the study provided study participants with numerous opportunities to look at the label before they were asked to answer the comprehension question assessing this objective. Therefore, the comprehension scores on this question could have been upwardly biased.

Table 11: Label Comprehension Results – "Under 12 Consult a Physician" by Age

Age	12-14	15-17	18-34	35-44	45-64	65+
Demonstrated comprehension	85.9% 116/185	94.6% 139/147	96.4% 81/84	92.3% 60/65	95.3% 123/129	84.6% 22/26

Source: Applicant's NDA Submission

Other Secondary Objectives

The LCS had other secondary objectives that did not for the most part test well. These statements dealt with usage to both minimize and cope with skin irritation. According to the DNDP clinical reviewer, there are minimal clinical concerns associated with incorrect comprehension of these statements; the assumption is that consumers will simply stop using the product if the irritation is too severe. Additionally, a verbatim review reveals that most of the incorrect responses either expressed caution or a conservative approach beyond that advocated by the DFL, or that there was confusion about the different factors – sunburn, eczema, other medications - that could contribute to irritation. Therefore, the comprehension scores do not represent a safety concern.

Other Comments About the Proposed Labeling

The Applicant has proposed a Consumer Information Leaflet (CIL) but this has not been assessed in comprehension testing.

4.3 Label Comprehension Study – Conclusions and Discussion

This study had some significant deficiencies. It did not test comprehension of the pregnancy statement and did not assess comprehension of avoiding sunlight while using. Moreover, methodological issues led to probable overestimates in comprehension of "do not use on damaged skin" and "under 12 years of age, ask a physician". Finally, the study population was comprised of very few females ages 18 to 24, and Hispanics were underrepresented particularly in the adolescent population.

Additionally, some of the findings are of concern, particularly with regard to the 12 to14-year-old age range and with regard to low literates. As Table 1 illustrates, 12 to 14-year-olds are most likely to use acne products, yet as Tables 6 and 11 illustrate, 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.

As Table 3 illustrates, "use once daily" did not test as well among low literates as it did among normal literates.

Although low literates and 12 to14 year olds tested significantly lower than other normal literates 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. On the other hand, there is the issue of the potential study biases, which could have artificially inflated all of the scores.

The issue of adolescent Hispanics being underrepresented in the study is somewhat of a concern, particularly with the "use once daily" statement. There is some discussion in the literature about Hispanics who are of limited English proficiency confusing "once" with its Spanish translation, "eleven".[2] [3]

Finally, as noted, 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, the DNDP clinical team would need to weigh in on whether this potentially inflated comprehension is of concern when consumers use the product.

4.4 Targeted Self-Selection Study – Design and Conduct

The primary objective of the targeted self-selection study 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, the Agency 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 low literacy augmented cohort, consisting of an additional 51 low literacy subjects.

The Applicant established a target threshold of 90% for the precaution "ask a healthcare professional before use", which was compared to the lower bound of the two-sided exact 95% confidence interval for correct self-selection. For Differin® OTC, the Applicant asserted that there was no clinical rationale for the proposed target threshold as teratogenicity was not an issue; therefore, their 90% threshold determination was based solely on the Agency's stated concern during the development discussions.

Adult recruitment for the self-selection took place via mall intercepts at 25 sites across the United States. Women were recruited for the study if they appeared to fall into at least one of the following four groups: 1) between the ages of 18 and 50, 2) with noticeable acne, 3) visibly pregnant, 4) accompanied by a baby under 18 months. If the interviewing screener confirmed that they were 1) pregnant and/or breastfeeding, and 2) with acne (all self-reported), they were invited to take part in the study. Pregnant subjects were not asked

[2] March 26 1997. Institute for Safe Medication Practices, Acute Care Medication Safety Alert.
[3] 2013 National Social Science Proceedings. Volume 52 1. National Technology and Social Science Conference, "Eleven Pills a Day? Linguistic Diversity in America", Kathleen Kreamelmeyer, Ball State University

about which trimester of pregnancy they were currently in.

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

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

4.5 Targeted Self-Selection Study – Results

As stated previously, in addition to only two adolescents in the entire study, there were also only 37% subjects who were pregnant. Additionally, Appendix 6 shows that it appears as if the study was not fielded uniformly across sites, as 16% (4/25) of the sites (Los Angeles, CA; Ontario, CA; Fort Worth, TX and Tallahassee FL) recruited 43% (39/91) of pregnant study subjects.

Of the 91 subjects, 80 out of 242 subjects were pregnant-only in the study, and an additional 11 subjects were both pregnant and breastfeeding. This is a significant issue with the study, because in development discussions regarding the labeled statement, FDA had focused its concerns on pregnant women. The relatively small sample size of pregnant women in the study leads to difficulty in drawing conclusions from age analyses of this subgroup in the general population.

In Cohort 1, 74.4% [2-sided exact 95% CI of (68.4%, 79.8%)] of the subjects correctly stated that they would ask a healthcare professional before using the product. The Applicant was not able to demonstrate that pregnant or breastfeeding women could adequately self-select to use the product. This conclusion is based on the following: the LCB is 68.4%, over 20 percentage points below the target threshold of 90%; furthermore, the correct self-selection rate is statistically significantly lower than the 90% threshold since the confidence interval, around the observed rate, lies completely below the 90.0% target threshold equivalent to $p<0.001$. This suggests that a substantial proportion of pregnant or breastfeeding women would not consult a healthcare professional before using the product.

Table 11 shows the general population (Cohort 1) results by age, literacy, and pregnancy/ breastfeeding status.

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Table 12: 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: FDA Statistics utilizing Applicant's data

Because the Agency was more concerned about pregnant women using Differin® and less concerned with breastfeeding women, we conducted a subgroup analysis of the pregnant-only women in Cohort 1. As Table 12 shows, pregnant-only women correctly stated that they would ask a health professional before use 70.0% (56/80) of the time, with a 2-sided exact 95% CI of (58.7%, 79.7%). The Applicant was not able to demonstrate that pregnant women could adequately self-select to use the product based on the following: The LCB is over 30 percentage points below the target threshold of 90%; furthermore, the correct self-selection rate is statistically significantly lower than the 90% threshold since the confidence interval, around the observed rate, lies completely below the 90.0% target threshold equivalent to $p<0.001$. This suggests that a substantial proportion of pregnant women would not consult a healthcare professional before using the product.

Because of the concern that younger pregnant-only women might be more likely to use the drug, we looked at self-selection by age. Table 13 displays the variation in the observed correct self-selection rates across age groups for the women who were pregnant-only in Cohort 1. The rates did not differ significantly across the age groups (Fisher's exact p-value=0.26). Of note however, due to the relatively small number of pregnant-only women in the study, there is relatively low statistical power to detect a difference in self-selection rates across age groups in this general population cohort.

Table 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: FDA Statistics utilizing Applicant's data

Table 14 shows the augmented low literacy (Cohort 2) results by age and pregnancy/breastfeeding status. Table 14 only reflects the LL women who were recruited specifically for this augmented cohort. It does not include the LL women in Cohort 1.

Table 14: Correct self-selection rates for LL, by Age and Pregnancy/Breastfeeding

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

Source: FDA Statistics utilizing Applicant's data

Table 15 shows the variation in correct self-selection rates for the 39 LL women in the study who were pregnant only, excerpted from the two cohorts each displayed in Tables 12 and 13, respectively. For these low literacy women, there were significant differences in correct self-selection across age groups (Fisher's exact p-value=0.06), with 18 to 24-year- old LL females having the lowest correct self-selection rates among women under age 45.

Table 15: Pregnant-only Low Literacy 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: FDA Statistics utilizing Applicant's data

Table 16 displays the different reasons that pregnant study subjects gave for making an incorrect self-selection decision.

Table 16: Self-Selection Results - Pregnant-Only Reasons For Incorrect Self-Selection

Age	RACE	ETHNIC	Education	Literacy	Reason for selecting to use Differin
45 - 54	Other	NOT HISPANIC OR LATINO	High school	NL	Because it is specifically made for pregnant women.
25 - 34	African-American/Black	NOT HISPANIC OR LATINO	High school	LL	Because it doesn't look safe for me to use.
25 - 34	Caucasian/White	NOT HISPANIC OR LATINO	High school	LL	Because all medicines say that.
25 - 34	African-American/Black	NOT HISPANIC OR LATINO	Some college	NL	Well most of the time my mid-wife lets me pick what's right for my skin I bring it in to her and she tells me after a week of me using that if it's good or not for me to use.
45 - 54	African-American/Black	NOT HISPANIC OR LATINO	College grad	LL	The box says it contains Hydrochloric Acid so I want to see if it will hurt my child. I don't know what that is so I don't know if I can use it.
35 - 44	African-American/Black	NOT HISPANIC OR LATINO	Some College	LL	I've never heard of adapalene.
25 - 34	Caucasian/White	NOT HISPANIC OR LATINO	Some College	LL	It's just an acne treatment and not going anywhere near my baby.
35 - 44	Caucasian/White	NOT HISPANIC OR LATINO	Some College	NL	It's a face treatment. It's washable and seems safe. The only problem would be is if it had an odor to it. Other than that, it should be fine.
35 - 44	Caucasian/White	NOT HISPANIC OR LATINO	High school	NL	Because there are some things I feel I can use my instinct on and this is something like that.
25 - 34	Asian or Pacific Islander	NOT HISPANIC OR LATINO	High school	NL	Because it is just to take away acne.
25 - 34	African-American/Black	NOT HISPANIC OR LATINO	High school	NL	Because I'm not allergic to anything.
25 - 34	Caucasian/White	NOT HISPANIC OR LATINO	High school	NL	Looking at the ingredients, they don't seem harmful and I don't have sensitive skin and I don't see what it has to do with me being pregnant, it doesn't seem harmful.
35 - 44	Caucasian/White	NOT HISPANIC OR LATINO	Some College	NL	This product seems okay to use, I don't see why I would have any problems.

25 - 34	Caucasian/White	NOT HISPANIC OR LATINO	High school	NL	There are no harmful ingredients in this so I would use it and like I said the product doesn't have bad side effects.
25 - 34	Caucasian/White	NOT HISPANIC OR LATINO	High school	LL	I thought it would be okay to use because I don't think it can hurt me or the baby.
25 - 34	Caucasian/White	NOT HISPANIC OR LATINO	Some College	LL	I don't think it would effect my pregnancy.
35 - 44	African-American/Black	NOT HISPANIC OR LATINO	Some College	NL	It doesn't seem like product that is harmful.
25 - 34	Caucasian/White	NOT HISPANIC OR LATINO	High school	NL	The fact that it said once a day was reassuring, my doctors said I was safe using acne cream. I wasn't allergic.
45 - 54	Caucasian/White	NOT HISPANIC OR LATINO	College grad	NL	I have used many products like this before so I believe it will be fine.
25 - 34	Caucasian/White	NOT HISPANIC OR LATINO	High school	NL	Because it says to ask a health provider.
45 - 54	Caucasian/White	NOT HISPANIC OR LATINO	College grad	NL	I said I didn't know if it was okay for me to use because I am pregnant. I don't see why it would be harmful but I'm going to ask my doctor.
35 - 44	Caucasian/White	NOT HISPANIC OR LATINO	High school	NL	Because a lot of things say to talk to your healthcare provider when you're pregnant.
25 - 34	Caucasian/White	NOT HISPANIC OR LATINO	Some College	LL	Because on the package it says to ask your doctor if you are pregnant.
25 - 34	Caucasian/White	NOT HISPANIC OR LATINO	High school	LL	I need to ask a doctor.
25 - 34	Other	HISPANIC OR LATINO	High school	LL	Did not see pregnancy warning.
25 - 34	Caucasian/White	NOT HISPANIC OR LATINO	Less than High School	LL	I guess I just kind of scanned through it, and I should probably read more thoroughly than what I do.
25 - 34	Asian or Pacific Islander	NOT HISPANIC OR LATINO	Less than High School	LL	I skimmed over the warning and must have missed it.
35 - 44	African-American/Black	NOT HISPANIC OR LATINO	High school	LL	What does my face have to do with my pregnancy.
35 - 44	African-American/Black	NOT HISPANIC OR LATINO	High school	LL	It's just a skin care product.
25 - 34	Other	HISPANIC OR LATINO	High school	NL	Because as long as I'm not putting it inside my body, I think it's not harmful.
45 - 54	Caucasian/White	NOT HISPANIC OR LATINO	High school	NL	Just didn't even think I couldn't use this on my face.

Source: Data from Applicant NDA Submission

4. 6 Targeted Self-Selection Study – Conclusions and Discussion

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

Verbatims reveal that incorrect pregnant self-selectors – regardless of literacy level - 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.

Of note, the study did not address concerns about women who might become pregnant while using the product, which the Agency had asked the Applicant to assess. For example, an arm of the study might have been conducted in women of childbearing age, and for those who self-selected to use the product, they could have been asked what if anything they would do if they subsequently found out they were pregnant. However, self-selection studies are not necessarily designed for subjects to predict this type of future behavior. This is typically more easily suited to be assessed in the actual use study, (and it was) but ideally in a study that would have lasted longer than the duration of this particular actual use study. This would have allowed for more time for subjects to become pregnant and to document how – if at all - they followed up with their physicians about use of Differin OTC as a result.

4.7 Standard of Care Studies

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

Physician Standard of Care Study

Objective of Physician Standard of Care Study

The objective of the Physician Standard of Care Study was to respond to the Agency's request for data by providing information on prescribing, counseling, and patient

management by physicians who prescribe adapalene 0.1% gel. The Applicant states (Response to FDA Request dated 29 February 2016) that the sample size (n=150) was intended to provide qualitative insights these behaviors, but that it was not intended to be a pivotal or quantitative study.

All physicians in this study self- reported that they had prescribed adapalene-containing products (Differin® and/or Epiduo®) for acne in the past six months.

Design and Conduct of Physician Standard of Care Study

Physician prescribing and counseling practices with regard to adapalene were not explored in this study. Physicians were not asked specifically about counseling that they provide regarding adapalene 0.1% gel or even adapalene overall. This was supposed to have been a major objective of the study.

Furthermore, there was relatively little discussion of the study's design and conduct in the Applicant's NDA submission; the Agency submitted four separate Information Requests to the Applicant regarding the Physician Standard of Care Study. Below is a summary of what was contained in the Applicant's responses:

The panel was managed by a medical market research company that recruits and collects data on special populations of healthcare providers. This company has access to medical specialties by accessing an online American Medical Association database. Physicians may be included in the database if they were recruited for a specific study and want to participate in future studies. The database contains over 500,000 physicians in varying specialties in 50 states. Random sampling (not stratified by specialty) was conducted. The targets set were n=75 for dermatologists and n=75 for primary care providers as a whole. PCPs were split evenly for family med/general practice, internal medicine and pediatrics with just a small number of OBGYN physicians targeted, since it was anticipated that not many OBGYNs prescribe acne medications. There were no key demographic or practice type targets set for enrollment. There was no special recruitment of physicians who typically were resistant to marketing research or who were very busy, but most physicians reported seeing 2500 or more patients per year. Galderma was not identified in either the invitation to the survey or on the survey itself. None of the physicians were compensated by Galderma or used by Galderma as staff or consultants. Physicians were compensated $75 for their participation.

Physicians from 31 states were represented in the actual survey responses. Appendix 7 displays the physician population variables. Of note, 75% of the PCPs surveyed were either from the midwest or the south, and only 8% had been in practice less than 10 years. However, 49% of the dermatologists surveyed were from the northeast, and 38% had been in practice less than 10 years. The Applicant did not provide any data to validate the representativeness of the sample for these criteria.

Because the online panel was proprietary and there was such a significant delay in obtaining even the above information, and because the Applicant did not offer data or references to confirm the validity and generalizable nature of the sample to the actual prescribing population for adapalene, FDA has not been able to comprehensively assess the extent to

which this sample may or may not be at all generalizable.

Additionally, an analysis of the survey questionnaire yields the following observations:

1) Physicians were not asked specifically about their perceptions of adapalene 0.1%.

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

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

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

For readers who may wish to accept that the study is of sufficient rigor for purposes of providing insights, a subject-level analysis of the physician respondents reveals that almost 90% of the physicians voiced one concern or another about prescribing topical retinoids. Table 10 shows the Applicant reported results for each of the relevant questions. However, the Agency's subject level analysis pinpointed where there were overlaps and where there were differences about which specific physicians voiced concerns about which specific questions. When the data is examined on a subject level basis, it becomes apparent that only 12.6% of physicians surveyed had no concerns regarding any of the safety issues asked about. In other words, the overwhelming majority of physicians (almost 90%) had some type of concern about prescribing topical retinoids to their female patients of childbearing age.

Table 17: Standard of Care Study: Pregnancy Related Counseling to Topical Retinoid Patients

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

Source: Applicant NDA Submission, FDA Statistics utilizing Applicant data (subject level physician analysis)

Patient Standard of Care Study

Objective of Patient Standard of Care Study

As the Applicant has stated, the objective of the Patient Standard of Care Study was to assess how patients use topical retinoids in real world practice.

Design and Conduct of Patient of Care Study

It is difficult to evaluate the extent of pregnancy counseling in females of childbearing age who were prescribed Differin®, as there were only 31 of these patients. This is not a robust sample size for analysis.

Because there was relatively little discussion of the study's design and conduct in the Applicant's NDA submission, the Agency submitted four separate Information Requests to the Applicant regarding the Patient Standard of Care Study. Below is a summary of what was contained in the Applicant's responses:

In the Response to FDA Information Request dated 04 January 2016, the Applicant stated that a preliminary sampling was conducted of patients, ages 13 and older; from that group of patients, a computer algorithm was applied to randomly select patients who would be sent an invitation to participate in a survey. Of those who were randomly selected to receive an invitation and who responded, there were inclusion and exclusion screening criteria: male or female of any race, ages 13 +, self-reported use of adapalene 0.1% gel, tretinoin or tazarotene prescription medication within the past 12 months (the retinoids of interest were masked in a list of acne medications so that the patients entering the study did not know which medications would ultimately result in their being invited to complete the survey). Patients were compensated $25 for the survey. None of the patients were compensated by Galderma or used by Galderma as staff or consultants, and Galderma was not identified or referenced in any way in the questionnaires.

In the Response to FDA Information Request dated January 26 2016, the Applicant stated that subjects were recruited from the panel database, which was made up of over 3 million consumers and developed over many years through email and telephone campaigns, online advertisement, digital banner advertisements, media buying, search engines, etc. From the panel of 3 million there were approximately 66,000 patients sent invitations to the study, based on known inclusion and exclusion criteria and random sampling. From those patients, there was an overall response rate of 15% (9898): of these, 6627 were screening failures due to not meeting the inclusion or exclusion criteria; 1543 incompletes, and 1492 after the quota was full. The number of completes was 233.

In the Response to FDA Information Request dated February 3, 2016, the Applicant clarified that adolescents and teens were recruited through the same mechanism as adults; adolescents 13 years of age and younger must have had parental consent and verification before being included in the panel, and adolescents 14 to17 years of age were able to register under the same guidelines as adults.

In the Response to FDA Information Request dated February 9, 2016, the Applicant clarified that the medical marketing research company actually utilized three online panels managed by three different other companies in order to gather a broad range of consumers for this study. Of the three panels, the largest had 6.5 million consumers, followed by one with 1 million consumers and one with thousands (unstated). The crosswalk of these numbers to the 3 million originally cited by the Applicant, to how exactly the final 233 respondents recruited through the above means were representative and generalizable to the overall population of retinoid users, was neither explicitly or implicitly clarified by the Applicant.

Because the online panels were proprietary and there was a significant delay in FDA obtaining even the above information, and because the Applicant did not offer data or references to confirm the validity and generalizable nature of the sample to the actual population for whom adapalene is prescribed, FDA has not been able to comprehensively assess the extent to which this sample may or may not be at all generalizable.

Additionally, an analysis of the survey questionnaire yields the following observations:

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

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

Due to the methodological questions surrounding both the physician and patient Standard of Care studies, the Agency has not utilized these studies in its regulatory decision-making and therefore will not be reviewed in any more detail.

5. Conclusions and Recommendations

The studies 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. However, it appears from the LCS that adult women of childbearing age (over the age of 24, since so few females between the ages of 18 to24 were in the study population) understand in theory how to use the product (once a day) so as not to lead to significant overuse. 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. Moreover, the clinical team believes that irritation that is typically caused by overuse would be a naturally self-limiting factor to ultimately prevent significant overuse.

Because adolescents were not assessed in the self-selection study, because the pregnancy statement was not asked about in the LCS, and because adolescents are the major purchasers of products for acne, the relatively lower comprehension of particularly low literacy adolescents is still a concern of mine, even if the numbers are within the acceptable range. It is possible the adolescents could significantly overuse the product and also use it for a long enough period of time due to acne duration at that age that - even if they read the DFL initially upon purchase - they might not recall the statement to consult a doctor if/when they become pregnant when using the product. The relatively low comprehension of the age group of 12 to14 year olds is particularly concerning, because they also didn't understand as well as the older age groups the statement to "ask a doctor under age 12." It is quite possible that girls of this age could purchase this product on their own and provide it to even younger siblings who could use it for years at a time if needed. In doing so, any patterns of over usage that are established could carry over to when they become of childbearing age.

The other issue for which consumer behavior is difficult to predict is that in which females of childbearing age use the product not for acne but, off label, for wrinkles. In that instance adolescent usage and their associated relatively lower comprehension is not as much of a

concern, since they would not be the target audience for this indication. However, it's quite possible that females of childbearing age, for instance, ages 35 to44, might start using this product for long periods of time. And although it appears from the LCS that females of this age understand "once daily" usage very well for an acne indication, it's unclear whether they would comprehend it in the same way for off label usage.

Therefore, at a minimum I encourage the Applicant to reinforce further in the labeling the "once a day" aspect and to possibly even incorporate additional wording (either in the DFL or CIL) to implicitly nudge consumers toward use as directed and/or explicitly discourage overuse. Explanations as to why overuse will not lead to quicker results may be helpful.

The other issue is the existence, placement, and wording of the pregnancy statement. This was a subject of extensive discussion at the April 15, 2016 Nonprescription Drugs Advisory Committee meeting. Regarding its existence, I strongly advocate that a pregnancy statement remain on the DFL if for no other reason that many consumers are aware of this statement on the Drug Facts Label. To delete it altogether would imply to consumers that this product is inherently safer than many products on which it currently appears. Regarding the placement of the pregnancy statement on the DFL, that has been tweaked over the course of the consumer studies program (See Appendices 1-3). It would be interesting to ask the Applicant why it has been altered. There may be an optimum placement for that statement. Regarding the wording of the statement, since the self-selection study clearly shows that pregnant women will self-select to use this drug with the current labeled statement, the Agency should consider revising it to a more strongly worded statement.

Regarding the breastfeeding component of the pregnancy statement, I support leaving it on the DFL as well. Again, many women are aware of this statement on Drug Facts Labels and, even though there does not appear to be any data suggesting that the amount in breastmilk is harmful, the absence of such a statement might suggest to some women that there is no trace amount in breastmilk. As an aside, in recognition of the complexity of OTC labeling consistent with different consumers' and physician' perceptions of - and comfort - with different levels of risk, pregnancy/breastfeeding is a topic that is ripe for further research as to the optimal way of communicating about this with brevity on a DFL.

Also, because it appears from the self-selection study that breastfeeding women will use this product, I recommend that a statement about hand washing after application be incorporated into the CIL.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix 4: Demographics of Population in LCS

	General Population (Cohort 1)			**Low Health Literacy (Cohort 2 and LL from Cohort 1)**			**Total Unique Respondents**	
	#	%		#	%		#	%
Male	211	41.0		69	53.1		247	42.2
Female	304	59.0		61	46.9		339	57.8
Age 12-17	250	48.5		73	56.2		282	48.1
18-24	27	5.2		9	6.9		33	5.6
25-34	47	9.1		7	5.4		51	8.7
35-44	60	11.7		9	6.9		65	11.1
45-54	68	13.2		15	11.5		78	13.3
55-64	42	8.2		11	8.5		51	8.7
65+	21	4.1		6	4.6		26	4.4
Caucasian/White	375	72.8		66	50.8		407	69.5
African American/Black	86	16.7		49	37.7		114	19.5
Native American Asian, Pacific Islander	13	2.5		2	0.8		14	2.4
Other	41	8.0		13	10.0		51	8.7
Hispanic	45	8.7		12	9.2		53	9.0
Non Hispanic	468	90.9		117	90.0		531	90.6
Normal Literacy	456	88.5		--	--		456	77.8
Low Literacy	59	11.5		130	100		130	22.1

Source: Applicant Study Report

Appendix 5: Demographics of Population in Self Selection Study

	General Population (Cohort 1) (n=242)			**Low Health Literacy (Cohort 2 and LL from Cohort 1; n=112)**			**Total Unique Respondents (n=293)**	
	#	%		#	%		#	%
Pregnant	80	33.1		39	34.8		96	32.8
Breastfeeding	151	62.4		66	58.9		184	62.8
Both	11	4.5		7	6.3		13	4.4
Age 12-17	2			1			2	
18-24	97	40.4		48	43.2		111	5.6
25-34	98	40.8		45	40.5		124	8.7
35-44	41	17.1		16	14.4		51	11.1
45-54	4	1.7		2	1.0		5	13.3
55-64	0	--		0	--		0	8.7
65+	0	--		0	--		0	4.4
Caucasian/White	140	57.9		57	50.9		168	57.3
African American/Black	49	20.2		27	24.1		60	20.5
Native American Asian, Pacific Islander	10	4.2		6	5.4		11	3.7
Other	43	17.8		22	19.6		54	18.4
Hispanic	46	19.0		25	22.3		53	19.5
Non Hispanic	196	81.0		87	77.7		531	80.5
Normal Literacy	181	74.8		--	--		181	61.8
Low Literacy	61	25.2		112	100		112	38.2

Source: Applicant Study Report

Appendix 6: Self Selection Study: Pregnant Women Recruited By Site

Site #: Location	n (%) N=109
Site 01: Buffalo, NY	1 (0.9)
Site 03: Philadelphia, PA	3 (2.8)
Site 05: Cleveland, OH	4 (3.7)
Site 06: Indianapolis, IN	3 (2.8)
Site 07: Atlanta, GA	6 (5.5)
Site 08: Dallas, TX	6 (5.5)
Site 09: Louisville, KY	9 (8.3)
Site 10: Raleigh, NC	5 (4.6)
Site 11: Tampa, FL	2 (1.8)
Site 12: Denver, CO	4 (3.7)
Site 13: Seattle, WA	3 (2.8)
Site 14: Los Angeles, CA	8 (7.3)
Site 15: Tucson, AZ	2 (1.8)
Site 16: Aurora, CO (adolescent site)	2 (1.8)
Site 17: San Francisco, CA	2 (1.8)
Site 18: Ontario, CA	8 (7.3)
Site 19: Fort Worth, TX	13 (11.9)
Site 20: Houston, TX	1 (0.9)
Site 21: Oklahoma City, OK	5 (4.6)
Site 22: Fayetteville, AK	2 (1.8)
Site 23: Tallahassee, FL	10 (9.2)
Site 24: Spartanburg, SC	4 (3.7)
Site 25: Baltimore, MD	3 (2.8)
Site 26: New York, NY	3 (2.8)

Source: FDA Statistics using Applicant data

Appendix 7: Physician Population Variables

Population Variables	Question	Responses	Primary Care Physicians (Pediatrics, Family Medicine, Internal Medicine, OB/GYN) (n=76)	Specialists (Dermatologists) (n=75)
		75+	45 (59.2%)	71 (94.7%)
	% Patients with Acne (Q.5)	Mean score - Total	14.08	21.69
	% Patients Acne Severity (Q.6)	Mean score - Mild	48.74	32.89
		Mean score – Moderate	37.45	44.03
		Mean score – Severe	13.82	23.08
Practice location variables*	Geographic location (Q.2)	Suburban	49 (64.5%)	43 (57.3%)
		Urban	23 (30.3%)	32 (42.7%)
		Rural	4 (5.3%)	0 (0.0%)
	Census Regions/ Divisions** (State)	Division 1: New England	4 (5.3%)	13 (17.3%)
		Division 2: Middle Atlantic	7 (9.2%)	16 (21.3%)
		Region 1: Northeast Total	**11 (14.5%)**	**29 (38.7%)**
		Division 3: East North Central	28 (36.8%)	6 (8.0%)
		Division 4: West North Central	3 (3.9%)	2 (2.7%)
		Region 2: Midwest Total	**31 (40.8%)**	**8 (10.7%)**
		Division 5: South Atlantic	18 (23.7%)	8 (10.7%)
		Division 6: East South Central	4 (5.3%)	4 (5.3%)
		Division 7: West South Central	4 (5.3%)	4 (5.3%)
		Region 3: South Total	**26 (34.2%)**	**16 (21.3%)**
		Division 8: Mountain	5 (6.6%)	2 (2.7%)
		Division 9: Pacific	3 (3.9%)	20 (26.7%)
		Region 4: West Total	**8 (10.5%)**	**22 (29.3%)**
Volume variables	# of Patients per year (Q.3)	< 500	0 (0.0%)	0 (0.0%)
		500 to < 1000	1 (1.3%)	4 (5.3%)
		1000 to < 2500	19 (25.0%)	9 (12.0%)
		2500 to < 5000	33 (43.4%)	28 (37.3%)
		≥ 5000	23 (30.3%)	34 (45.3%)

Population Variables	Question	Responses	Primary Care Physicians (Pediatrics, Family Medicine, Internal Medicine, OB/GYN) (n=76)	Specialists (Dermatologists) (n=75)
Demographic variables	Gender (Q.43)	Male	55 (72.4%)	50 (66.7%)
		Female	21 (27.6%)	25 (33.3%)
	Age (Q.44)	< 30	0 (0.0%)	1 (1.3%)
		30-39	7 (9.2%)	25 (33.3%)
		40-49	24 (31.6%)	16 (21.3%)
		50-59	32 (42.1%)	23 (30.7%)
		60-69	12 (15.8%)	9 (12.0%)
		70+	1 (1.3%)	0 (0.0%)
		Refused	0 (0.0%)	1 (1.3%)
	Race (Q.45)	Caucasian	63 (82.9%)	55 (73.3%)
		Asian / Pacific Islander	11 (14.5%)	11 (14.7%)
		African American	1 (1.3%)	1 (1.3%)
		Native American	0 (0.0%)	1 (1.3%)
		Hispanic	0 (0.0%)	1 (1.3%)
		Indian	0 (0.0%)	1 (1.3%)
		Refused	1 (1.3%)	5 (6.7%)
	Ethnicity (Q.46)	Hispanic – Yes	0 (0.0%)	2 (2.7%)
		Hispanic – No	75 (98.7%)	67 (89.3%)
		Refused	1 (1.3%)	6 (8.0%)
	Length of time practicing (Q.47)	1 year to < 5 years	2 (2.6%)	14 (18.7%)
		5 years to < 10 years	4 (5.3%)	14 (18.7%)
		10 years to < 15 years	14 (18.4%)	9 (12.0%)
		15 years to < 20 years	21 (27.6%)	7 (9.3%)
		20 years to < 25 years	14 (18.4%)	11 (14.7%)
		≥ 25 years	21 (27.6%)	18 (24.0%)
		Refused	0 (0.0%)	2 (2.7%)
Practice variables	Practice Setting (Q.1)	Private Practice	63 (82.9%)	52 (69.3%)
		Clinic	11 (14.5%)	14 (18.7%)
		Hospital	1 (1.3%)	8 (10.7%)
		University/Academic	1 (1.3%)	1 (1.3%)
	Age range of Patients (Q.4)	Under 13	48 (63.2%)	60 (80.0%)
		13-17	63 (82.9%)	68 (90.7%)
		18-34	63 (82.9%)	74 (98.7%)
		35-54	50 (65.8%)	74 (98.7%)
		55-74	47 (61.8%)	73 (97.3%)

Source: Applicant Response to Information Request

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/s/

BARBARA R COHEN
06/09/2016

JANE FILIE
06/11/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 9, 2016
Requesting Office or Division:	Division of Nonprescription Drug Products (DNDP)
Application Type and Number:	NDA 020380/S-010
Product Name and Strength:	Differin Gel (Adapalene) Gel, 0.1%
Product Type:	Single Ingredient
Rx or OTC:	OTC
Applicant/Sponsor Name:	Galderma
Submission Date:	May 2, 2016, and May 4, 2016
OSE RCM #:	2015-2691
DMEPA Primary Reviewer:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of NDA 020380/supplement-10 submission, this review evaluates the proposed container labels and carton labeling for Differin Gel for areas of vulnerability that could lead to medication errors.

NDA 020380, Differin (Adapalene) Gel, 0.1%, was first approved on May 31, 1996 for the topical treatment of acne vulgaris. The Applicant is now seeking Rx (prescription) to over-the-counter (OTC) switch to market Differin Gel for the treatment of acne under NDA 020380/supplement-10, for the OTC treatment of acne in adults and children 12 years of age and older. Galderma also markets Differin (Adapalene) Gel, 0.3%, under NDA 021753, as an Rx product for the topical treatment of acne vulgaris in patients 12 years of age and older.

Galderma requested a review of the proposed proprietary name, Differin Gel, under NDA 020380/supplement-10 on September 22, 2015. DMEPA found the proposed name, Differin Gel, acceptable on November 9, 2015.[1]

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

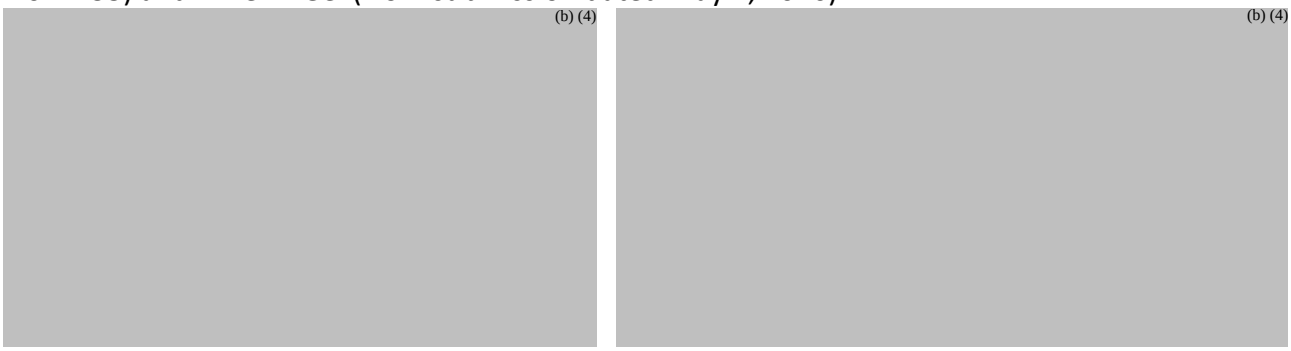
The proposed Differin Gel container labels and carton labeling contains a graphic (b) (4) image throughout the container labels and carton labeling; however, this graphic image does not appear to intervene the proprietary name so we do not anticipate that this proposed graphic image presentation would contribute to medication errors. We note that the Rx Differin (Adapalene) Gel, 0.3% container label does not have a graphic (b) (4)

[1] Gao, T. Proprietary Name Review for Differin Gel NDA 020380/S-010. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 NOV 9. RCM No.: 2015-1541586.

image and its overall container label presentation differs to the proposed Differin Gel container label (see Figure 1). Moreover, because of the difference in marketing status, Rx Differin (Adapalene) Gel, 0.3% and the proposed Differin Gel for OTC use would likely not be stored in pharmacy shelves in adjacent areas.

Our search of FAERS and ISMP did not identify postmarketing medication error issues associated with the container labels and carton labeling for Rx Differin. Therefore, our review of the proposed container labels and carton labeling for Differin Gel determined they are acceptable from a medication error perspective.

Figure 1. Differin (Adapalene) Gel, 0.3% (from Annual Report-7, submitted 9/2/2015 for NDA 021753) and Differin Gel (from submission dated May 4, 2016)



4 CONCLUSION & RECOMMENDATIONS

We conclude the proposed container labels and carton labeling for Differin Gel are acceptable from a medication error perspective.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Differin Gel that Galderma submitted on May 2, 2016.

Table 2. Relevant Product Information for Differin Gel	
Initial Approval Date	N/A
Active Ingredient	Adapalene
Indication	For the treatment of acne
Route of Administration	Topical
Dosage Form	Gel
Strength	0.1%
Dose and Frequency	(b) (4)
How Supplied	2 g sample tube 15 g tube 45 g tube
Storage	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 4, 2016, we searched the L:drive and AIMS using the terms, Differin, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified four (4) Differin labels and labeling reviews for the prescription product.[2,3,4,5] The information in these reviews was not relevant to the proposed OTC product Differin Gel container labels and carton labeling evaluation. We have not reviewed labels and labeling for Differin Gel.

[2] Mena-Grillasca CM. Label and Labeling Review for Differin NDA 021753/S-007. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 APR 28. RCM No.: 2014-300.

[3] McMillan T. Label and Labeling Review for Differin NDA 021753/S-004. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 JAN 4. RCM No.: 2011-4412.

[4] Maslov Y. Label and Labeling Review for Differin NDA 020748. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010 DEC 15. RCM No.: 2010-1826.

[5] Cantin L. Label and Labeling Review for Differin NDA 022502. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010 FEB 3. RCM No.: 2009-1820.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On January 4, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Newsletter Community Newsletter Nursing Newsletter
Search Strategy and Terms	Match Exact Word or Phrase: Differin

D.2 Results

Our search of the ISMP newsletters did not yield any results.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on January 4, 2016, using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[6]

Table 3: FAERS Search Strategy	
Date Range	**April 1, 2014 – January 1, 2016** (Last FAERS search performed for OSE review 2014-300 (NDA 021753/S-007), dated April 28, 2014)
Product	**Differin** [product name] **Differin Gel** [product name]
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)

E.2 Results

Our search identified 14 cases, but after further evaluation, we did not identify any medication error cases that were relevant for this review and could be addressed by labels and labeling revisions.

[6] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

E.3 List of FAERS Case Numbers

N/A

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

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/s/

GRACE JONES
06/09/2016

CHI-MING TU
06/09/2016

Clinical Inspection Summary

Date	4/25/16
From	Sharon Gershon, Pharm.D.
To	Jane Filie, Medical Team Leader Ryan Rafaelli, Medical Officer Lara Akinsanya, Regulatory Health Project Manager Division of Non Prescription Drug Products
NDA #	20380 S010
Applicant	Galderma Laboratories, L.P.
Drug	adapalene 0.1% Acne Gel - Differin®
NME	No
Therapeutic Classification	Priority
Proposed Indication	Over-the-counter treatment of acne
Consultation Request Date	November 13, 2015
Summary Goal Date	May 1, 2016
Action Goal Date	July 10, 2016
PDUFA Date	July 10, 2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATION

The study was conducted at 31 trial sites in the United States. All data and study records were returned, processed and stored by the Contract Research Organization (CRO) (b) (4) OSI directed an inspection of the CRO with a focus on the study records of two study-pharmacy sites with highest enrollment: Site #17 (Kroger, Houston, 80 subjects) and Site #28 (Ralph's, Los Angeles, 88 subjects). The field investigator reviewed records for 10 to 20 subjects at two additional Sites: #05 and #13. No regulatory violations were found during the inspection of the CRO, and no major deficiencies were found during the audit of records from the four pharmacy sites. This inspection was classified as NAI. OSI recommends the data be considered acceptable in support of the NDA.

II. BACKGROUND

Galderma Laboratories, L.P. is proposing the Rx-to-OTC switch of Differein® (adapalene 0.1%) gel for the topical treatment of acne. The switch of Differin® gel to over-the-counter would represent the first retinoid-like product available over-the-counter for the treatment of acne. Galderma submits Protocol #13049 Pivotal Actual Use Study for Adapalene 0.1% Gel P to evaluate the use of Differin® in an unsupervised over-the-counter (OTC) environment. This actual use study was intended to gather data about the usage of this retinoid like product due to FDA's concerns regarding off-label use or potential use in women who are pregnant or breastfeeding.

This trial was a six-week use, open-label, single–arm, multi-center, actual use study among consumers who self-reported having acne. This study was performed at 31 pharmacy sites in the U.S. Overall, 1277 subjects were entered into the study and 947 were included in the actual use population.

The following study was used to demonstrate efficacy for this application: Protocol No.13049 Pivotal Actual Use Study for adapalene 0.1% P gel.

The study objective was to understand how Differin (adapalene 0.1%) gel is used in an unsupervised OTC environment.

Reasons for Site Selection: Protocol No.13049 was conducted at 31 pharmacy sites in the U.S. The Review Division selected inspections at the two pharmacy sites with highest enrollment. OSI directed an inspection of the two pharmacy sites with highest enrollment; these records were located at the CRO.

III. RESULTS:

Name of Firm, Address	Protocol No.	Inspection Dates	Final Classification
(b) (4)	Protocol No.13049 CRO	(b) (4)	NAI
Kroger Store 12400 Fm 1960 Rd W. Houson, TX 77065	Protocol No. 13049 Site #17 80 subjects	February 17 – 24, 2016	NAI
Ralph's 3410 W. 3rd Street Los Angeles, CA 90020	Protocol No. 13049 Site #28 88 subjects	February 17 – 24, 2016	NAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

(b) (4)

This CRO inspection was conducted as a data audit for NDA 20380 S010 [Differin® (adapalene 0.1%) Acne Gel]. The inspection audited Protocol No. 13049 Pivotal Actual Use Study (AUS) for adapalene 0.1% gel referenced as Project "Juno" dated 1/29/15. This was the initial inspection of the CRO.

The study was conducted at 31 pharmacy trial sites throughout the United States. All data and study records were returned, processed, and stored (b) (4) located in (b) (4) OSI directed an inspection of the CRO with a focus on the two pharmacy sites with highest enrollment: Site #17 (Kroger, Houston, 80 subjects) and Site #28 (Ralph's, Los Angeles, 88 subjects). The field investigator reviewed records for 10 to 20 subjects at two additional Sites 05 and 13.

During the CRO inspection the field investigator covered the following areas: history of the CRO, operations and CRO oversight of the study, SOPs relating to adverse event reporting, data archiving and site selection; recruitment ; monitoring; authority and administration of the study; sponsor and IRB communications; IRB approvals; protocol training and financial disclosure forms.

(b) (4) signed a master services agreement with the sponsor Galderma Laboratories giving them responsibility for primary oversight of the study. (b) (4) also signed an agreement with The Kroger Co. located in Cincinnati, OH who owned all the retail pharmacy sites that were used as study sites for this trial. The first subject was consented on 1/23/15 and the final subject contact was on 5/29/15. A total of 947 subjects signed the Informed Consent document and 938 subjects completed the study. Reasons for subject discontinuations were not provided in the EIR.

The general format of the study was that subjects would visit study site pharmacy locations and the pharmacist at that location would call the Central Medical Operations Group (CMOG) located at (b) (4) who would screen and decide if the subject was eligible to enroll into the study. There was one Principal Investigator for the study. He was located at (b) (4) and signed the Form 1572. All monitoring was done by the CRO.

Study Records: Sites #17 (Kroger Store, Houston, TX), #28 (Ralph's, Los Angeles), #5 and #13.

The inspection reviewed inclusion and exclusion criteria, protocol adherence, informed consent documents, monitoring, drug accountability records, and verified data between source documents and data listings.

The field investigators reported that source documents were organized and legible. Each subject had a paper binder with Visit one information in the left pocket and Visit two information in the right pocket.

Each site had a log that contained all protocol deviations that occurred during the trial. Periodic site visits occurred every two months. Each site had a trial master file that had sections for study instructions, product distribution, enrollment, training, staff signatures and responsibilities, monitor log, used product log, shipping transmittals, and a CD with printouts from the electronic data capture (EDC) system. Several discrepancies or inaccuracies were found between the source documents and the eCRF entries. These were discussed with management at the end of the inspection. Examples are included below.

Although no Form FDA 483 was issued, several data discrepancies were noted during the review of records from four sites. These data discrepancies were discussed with the CRO at the conclusion of the inspection. For example:

- For Subject 28-081, the informed consent document (ICD) had initials as B-I, whereas the enrollment log documented the initials as ESS.
- For Subject 05-018, the ICD listed initials as BJA whereas the enrollment log documented initials as BJJ.
- The data listings for Site #28 indicated that Subject 28058 bought one tube of product on 3/19/2015 and another tube on 4/24/15, whereas the subject enrollment log did not show an additional purchase on 4/24/15.
- The subject summary for Subject 28028 documented the subject was a screen failure whereas the subject enrollment log indicated Subject 28028 was “NC” or subject refused to consent.
- For Subject 13001, the subject diary documented that the product was applied at 7:30 am on 3/11/15 whereas the eCRF documented the time as 7:30 pm on this same date.
- For Subject 05005 the subject diary reported “face burns” on 2/20/15 and “skin feels burned” on 3/18/15, whereas the AE log for Subject 05005 reported the subject experienced “dry skin”, “redness of skin”, “skin sensitivity”, “increased blemishes”, and “peeling skin”.

The discrepancies noted are unlikely to impact the integrity of the data for this NDA. The study appears to have been conducted adequately, and the data submitted by the Sponsor may be used in support of the respective indication.

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Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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CC:

Central Doc. Rm. NDA #20380 S010
DNDP/ Division Director/Teresa Michele
DNDP/ Medical Team Leader/Jane Filie
DNDP/ Medical Officer/Ryan Raffaelli
DNDP/Chief Regulatory Project Manager/Lara Akinsanya
OSI/Office Director (acting)/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Susan Thompson
OSI/DCCE/GCP Reviewer/Sharon Gershon
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

SHARON K GERSHON
04/25/2016

SUSAN D THOMPSON
04/25/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

A D D E N D U M

From:	Mona Khurana, M.D., Medical Officer
	Division of Pediatric and Maternal Health
	Office of Drug Evaluation IV
Through:	Hari Cheryl Sachs, M.D., Medical Team Leader
	John J. Alexander, M.D., M.P.H. Acting Deputy Director
To:	Division of Nonprescription Drug Products
Proprietary Name:	Differin Gel, 0.1%
Active Ingredient:	Adapalene
Drug Category:	Topical synthetic retinoid-like
Sponsor:	Galderma Laboratories, L.P.
Subject:	Prior approval efficacy supplement for Rx to OTC switch
PDUFA Goal Date:	July 10, 2016

Materials Reviewed

- Sponsor's response to February 3, 2016 Information Request from the Division of Nonprescription Drug Products (DARRTS Reference ID 3882447)

On February 3, 2016, the Division of Nonprescription Drug Products (DNDP) issued the following Information Request (IR) to the sponsor via electronic mail:

Provide us with any available clinical trial and post-marketing safety data you have in pediatric patients 9 years to less than 12 years of age exposed to approved adapalene-containing single-ingredient (Differin 0.1% Gel , 0.1% Lotion, 0.1% Solution, 0.1% Cream, 0.3% Gel) or combination (Epiduo gel and Epiduo gel Forte) drug products. Present post-marketing safety data from your global pharmacovigilance database for all reports (serious non-fatal reports and serious fatal reports) with the reported MedDRA SOC and Preferred Terms in decreasing order of frequency. Using the same format, provide tabular summaries of all serious reports stratified by sex and formulation. Provide the full narratives for all serious reports. Separate U.S. from ex-U.S. cases.

DPMH Comments: The purpose of this IR was to obtain any information available to the sponsor from their clinical trial database and post-marketing experience that could help inform the efficacy and safety of topical adapalene drug products in pediatric patients 9 years to less than 12 years of age.

The sponsor submitted their responses to FDA on February 8, 2016.

The sponsor provided efficacy and safety data from a single efficacy trial conducted in patients 9 years to 12 years of age. The sponsor stated their available clinical trial data involving pediatric patients down to 9 years of age are limited to this single trial (Study RD.06.SRE.18155) which they conducted in 2011 to fulfill their pediatric study requirements under the Pediatric Research Equity Act (PREA) related to the approval of Epiduo (0.1% adaplene and 2.5% benzoyl peroxide) in 2008.[1] The sponsor submitted the data from Study RD.06.SRE.18155 as a supplemental new drug application (sNDA) which was approved February 1, 2013.[2] This approval led to expansion of the pediatric indication down to 9 years of age. The sponsor has not conducted any other studies which include patients 9 years to less than 12 years of age.

DPMH Comments: The sponsor did not provide additional details about the design and conduct of Study RD.06.SRE.18155, but this reviewer retrieved additional details about the study design from the FDA reviews for NDA 22320/S-004.[3,4] The study was multi-center, randomized, double-blind, and vehicle-controlled in design and enrolled 285 patients.[3] The study evaluated once daily topical application for up to 12 weeks. The primary efficacy criteria consisted of the following: (1) success rate defined as the percent of patients rated Clear or Almost Clear with at

[1] December 8, 2008 Approval Letter for NDA 22-320 (accessed at Drugs@FDA on February 26, 2016)

[2] February 1, 2013 Approval Letter for NDA 22320/S-004 (DARRTS Reference ID 3252048)

[3] November 14, 2012 Medical Officer Review of NDA 022320/S-004 (Jane Liedtka; DARRTS Reference ID 3218328)

[4] April 4, 2012 Clinical Pharmacology Review of NDA 022320/S-004 (Chinmay Shukla; DARRTS Reference ID 3215443)

least 2 grades reduction in baseline Investigator's Global Assessment score at Week 12; and (2) change from baseline in total lesion counts at Week 12. Results showed a significantly higher success rate in the Epiduo group than the vehicle gel group (47.2% vs. 15.4%; p<0.001) and a significantly greater mean change in total lesion count from baseline through Week 12 (-27.6 vs. -3.6; p<0.001). When comparing these results with those from the two pivotal studies used to support the original approval in older pediatric patients, the Medical Officer Review noted that patients in the 9 year to 11 year age group experienced a larger overall treatment effect than their older pediatric counterparts and speculated that this may reflect the greater percentage of patients who were treatment naïve at the time of study entry.

Pharmacokinetic (PK) assessments were not carried out in Study RD.06.SRE.18155. The Division of Dermatologic and Dental Products (DDDP) clinical pharmacology[4] and clinical reviewers[3] concluded that, based on available relative bioavailability data suggesting systemic exposure of topical 0.1% adapalene is low and the lack of systemic adverse events that were considered study drug-related in Study RD.06.SRE.18155, additional PK assessments in the 9 year to 11 year age group would not be needed.[3]

From a safety standpoint, the sponsor stated that a total of 184 adverse events (AEs) were reported in 122 pediatric patients during Study RD.06.SRE.18155.

DPMH Comments: These numbers differ slightly from those noted in the DDDP MO Review of NDA 022320/S-004 (see Table 1).

Table 1. Reported AEs in Study RD.06.SRE.18155

Study Population	***Epiduo Group (n=142)***	***Vehicle Gel Group (n=143)***	***Total (n=285)***
Age			
9 years old	*25 (17.6%)*	*15 (10.5%)*	*40 (14.0%)*
10 years old	*45 (31.7%)*	*49 (34.3%)*	*94 (33.0%)*
11 years old	*72 (50.7%)*	*79 (55.2%)*	*151 (53.0%)*
Patients with at least 1 AE‡	*67 (47.2%)*	*45 (31.5%)*	*--*
Total Number of AEs	*48*	*1*	*49*
Study Drug Related AEs	***29 (20.4%)***	***1 (0.7%)***	*--*
Deaths	*0 (0.0%)*	*0 (0.0%)*	*--*
Serious AEs	*0 (0.0%)*	*1 (0.7%)*	*--*
Mild AEs	*53 (37.3%)*	*32 (22.4%)*	*--*
Severe AEs	*1* (0.7%)*	*1**(0.7%)*	*--*
Adverse Dropouts	*2† (1.4%)*	*0 (0.0%)*	*2 (0.7%)*

*AEs: adverse events;‡ patients may be counted twice; *facial skin irritation; **arteriovenous malformation which was unrelated to study drug; † one report of erythema on Day 31 and one report of skin irritation on Day 10*

(Source: created by this reviewer from the November 14, 2012 MO review of NDA 022320/S-0043[3]*)*

The DDDP MO Review[3] included the following safety observations:

- *Topical safety was adequately evaluated in Study RD.06.SRE.18155 and included an assessment for local tolerability*
- *The difference in percent of study drug related AEs between the Epiduo and vehicle gel arms was notable (20.4% vs. 0.7%)*
    - *When examined by System Organ Class (SOC), all study drug related AEs were in the Skin and Subcutaneous Tissue Disorder SOC. See Table 2.*
- *A majority of patients in the Epiduo arm initially had stinging/burning (62.1%), dryness (56.4%), and scaling (55.7%). A large minority had erythema (42.9%). For most patients, these signs and symptoms were of mild severity and resolved despite continued treatment.*
- *The spectrum of AEs seen in this study was similar to that seen in the pooled pivotal studies supporting the initial U.S. approval in older pediatric patients. Skin irritation was seen more commonly in the younger age group (5.6% vs. 1.2% in the pooled pivotal studies) but dry skin and dermatitis were less commonly reported in the younger patients (2.8% and 0.7%, respectively) than in the older pediatric patients in the pooled pivotal studies (7.4% and 3.2%, respectively) and pruritus was not noted at all.*

Table 2. System Organ Class and Preferred Term Classification of the Study Drug Related AEs Reported in Study RD.06.SRE.18155

System Organ Class/Preferred Term[a]	Epiduo Gel (N=142) n, %	Vehicle Gel (N=143) n, %
Total Number of AE(s)	**48**	**1**
Total Number (%) of Subjects with AE(s)[b]	**29 (20.4)**	**1 (0.7)**
Skin and subcutaneous tissue disorders	**29 (20.4)**	**1 (0.7)**
Skin burning sensation	13 (9.2)	0
Skin irritation	8 (5.6)	0
Skin discomfort	5 (3.5)	0
Dry skin	4 (2.8)	0
Erythema	3 (2.1)	0
Skin hypopigmentation	1 (0.7)	0
Dermatitis	1 (0.7)	0
Sunburn	1 (0.7)	1 (0.7)

[a] Multiple occurrences within a System Organ Class by a subject were counted once per System Organ Class. Multiple occurrences of a Preferred Term by a subject were counted once per Preferred Term.

[b] A subject was counted once even if the subject experienced more than one adverse event during the study.

MedDRA dictionary version 11.0.

Data source: SRE.18155, Table 14.3.3.6.1

(Source: Page 41 of November 14, 2012 Medical Officer Review of NDA 022320/S-004[3])

The sponsor also provided post-marketing safety data from their global pharmacovigilance database. The sponsor searched their database for cases reported with use of Differin or Epiduo in patients 9 years to 11 years of age and retrieved 58 reports, including two serious AEs. The narratives for these two reports are as follows:

Narrative (CA15000379; Canada): A report was received on 29-JAN-2015 from a consumer concerning an 11-year-old female patient who had been using Tactuo (Epiduo) Pump (adapalene 0.1%, benzoyl peroxide 2.5%) for acne for one week and a half then experienced redness, swelling and passed out. She tried to take corrective Benadryl (diphenhydramine) but it did not

help. She was hospitalized and went back home recovering. She stopped using the product. This report was considered as serious due to the hospitalization.

DPMH Comments: Erythema is a labeled event which is listed in the Warnings and Precautions section (Subsection 5.2: Local Cutaneous Reactions) in Epiduo labeling. Swelling is also a labeled event which is listed in the Adverse Reactions section (Subsection 6.2: Postmarketing Experience) in Epiduo labeling. Although "passed out" is an unlabeled event, little clinical details are provided in the narrative to make an assessment of this AE as being drug related.

Narrative (US-GDP-0511824; United States): The report was received on 01-APR-2005 from a pediatrician reporting her 11 year old female patient's reaction to Differin Cream (adapalene, 0.1%). The patient had been using Differin Cream, nightly for acne, since the beginning of February 2005. On 30-MAR-2005 the patient was seen by the doctor as she developed five ecchymotic spots (round purplish discoloration) on her face. The patient was seen by the doctor the next day and presented with five additional spots. Patient discontinued Differin Cream on 31-MAR-2005. The doctor believed that it was a drug reaction. Physician described event as looking like echymotic purple spots that when pressed didn't disappear. The physician believed this to be erythema multiforme. At the time of the report the patient has not recovered. The follow up information was received from the doctor on 11-APR-2005. The doctor stated that the patient has not come back or called the office after the initial report. The spots were only on the patient's face. The patient did not receive any corrective treatment and she did not take any concomitant medications for her acne (like antibiotics) only Differin. The patient did not have fever. Corrective treatment: Physician saw patient on 31-MAR-2005 and instructed patient to stop using the Differin Cream.

DPMH Comments: Erythema multiforme is an unlabeled event. Although the narrative states the physician believed the rash to be erythema multiforme, limitation of the rash to the face suggests the patients may have experienced a localized application site reaction which is a labeled event. Additional evidence is needed to establish an association between adapalene use and erythema multiforme before labeling revisions would be considered to add this as an AE.

The remaining non-serious AEs retrieved by the sponsor were almost entirely related to application site reactions consistent with the know safety profile of adapalene for which product labeling is currently labeled.

The sponsor did not state in their response to the IR whether or not they had conducted a review of the medical literature to identify additional reports of adapalene-related AEs in younger pediatric patients. A literature review was not included in their IR response.

Discussion and Conclusions

The sponsor's response to DNDP's clinical IR does not change DPMH's recommendations as provided in the February 18, 2016 memorandum.[5]

The sponsor's available clinical trial experience with topical adapelene use in pediatric patients down to 9 years of age is limited to a single efficacy trial (Study RD.06.SRE.18155) which evaluated Epiduo, a topical product containing adapalene in combination with benzoyl peroxide.

The Epiduo sNDA (NDA 022320/S-004) was approved in 2013 and led to expansion of the pediatric indication down to 9 years of age. DDDP's approval of the sNDA to expand pediatric use of Epiduo appears to have been based on a partial extrapolation approach which bridged the safety and efficacy findings from the single pediatric efficacy trial (Study RD.06.SRE.18155) in younger pediatric patients to existing data in the adapalene development program for adults and older pediatric patients. No additional PK data were requested or required in the younger pediatric cohort to support approval. Notably, the younger pediatric patients experienced a larger overall treatment effect than their older pediatric counterparts, which DDDP speculated may reflect the greater percentage of patients who were treatment naïve at the time of study entry. The spectrum of AEs seen in the younger pediatric patients was similar to that seen in the pooled pivotal studies supporting the initial U.S. approval in older pediatric patients. The post-marketing safety data provided by the sponsor in response to DNDP's IR for AEs specific to younger pediatric patients are consistent with the known safety profile for adapalene from the clinical development program in adults and older pediatric patients and do not raise concerns at this time that a unique safety signal exists in younger pediatric patients.

Although the sponsor has no clinical trial data evaluating topical adapalene alone in patients down to 9 years of age, a partial extrapolation strategy similar to that used for the Epiduo sNDA could be considered for single-ingredient topical adapalene drug products. DPMH defers to DDDP colleagues as to whether or not the clinical data from Epiduo sNDA may be used to support expansion of use for single-ingredient adapalene drug products down to 9 years of age and, if not, what additional supportive data would be needed. Such expansion of use may first need to be considered for the prescription topical adapelene drug products, which are all currently labeled down to 12 years of age, before considering expansion of use for the proposed OTC product. Notably, OTC topical acne drug products currently marketed under the Final Monograph are not required to restrict use to a specific age group in the Drug Facts Label (DFL) (56 FR 41003 at 41020; August 16, 1991).

[5] February 18, 2016 DPMH Memo under sNDA 020380/S-010 (Mona Khurana; DARRTS Reference ID 3888999)

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

/s/

MONA K KHURANA
04/07/2016

HARI C SACHS
04/08/2016
I agree with these recommendations.

JOHN J ALEXANDER
04/08/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
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Division of Pediatric and Maternal Health Memorandum

Date: March 28, 2016 **Date Consulted:** November 5, 2015

From: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health, and

Melissa Tassinari, PhD, Senior Clinical Advisor,
Division of Pediatric and Maternal Health

Through: Lynne Yao, MD, Director
Division of Pediatric and Maternal Health

To: Division of Nonprescription Drug Products

Drug: Differin (adapalene) Gel, 0.1%

Proposed OTC Indication:
- For the treatment of acne
- Clears up acne pimples and acne blemishes

NDA: 020380/S-010

Applicant: Galderma Laboratories, L.P

Subject: Efficacy supplement for complete Rx to OTC switch

Materials Reviewed:
- NDA 020380/S-010 efficacy supplement, submitted September 10, 2015.
- Differin (adapalene) Gel, 0.1% labeling, last approved September 5, 2007.
- PMHS consult reviews dated July 27, 2006, and October 11, 2006.
- OSE Postmarketing Safety Reviews, dated March 18, 2004, and September 8, 2006.

Consult Question:
"Please review the attached and referenced material, and any published literature, for pregnancy-related concerns, including teratogenicity issues, following exposure to topical adapalene, a topical synthetic retinoid. The Division of Dermatology and Dental Products (DDDP) has serious reservations about marketing the product OTC due to the risk of teratogenicity and lack of a learned intermediary in that setting. An Advisory Committee meeting is to be held in early March 2016. We request your expertise in preparation for the Advisory Committee meeting and to help us determine whether adapalene may be used by OTC [over-the-counter] consumers without advice/oversight from a learned intermediary."

INTRODUCTION

On September 10, 2015, Galderma Laboratories, LP, submitted an efficacy supplement for a complete Rx to OTC switch of Differin (adapalene) 0.1% which is currently approved in the Rx setting for the treatment of acne vulgaris. Division of Nonprescription Drug Products (DNDP) consulted the Division of Pediatric and Maternal Health (DPMH) to review the pregnancy data for a review of teratogenicity issues with adapalene use and whether a learned intermediary is need for advice/oversight in the OTC setting.

BACKGROUND

Adapalene Regulatory History

In May 1996, Differin (adapalene), 0.1% gel was approved as a once daily topical treatment of acne vulgaris in patients 12 years of age and older. The 0.1% gel is currently classified as a pregnancy category C drug. No teratogenic effects were seen in offspring of rats administered oral adapalene up to 120 times the maximum recommended daily cutaneous human dose (MRHD). [1] When adapalene was administered cutaneously, there were minimal increases in supernumerary ribs and no other adverse developmental effects observed in offspring of rats and rabbits at doses up 120 and 150 times the MRHD, respectively.

Drug Description

Adapalene is a retinoid-like compound, a naphthoic acid derivative, which has partial retinoid activity. Adapalene selectively binds to retinoic acid nuclear receptors RARβ and –γ, but not to cytosolic receptors. Systemic absorption of adapalene 0.1% gel through human skin is low, with <0.25 ng/mL of parent substance found in the plasma of acne patients following chronic topical application.[1] In a pharmacokinetic study of adapalene 0.1% gels in adults under maximal use conditions (2 g applied continuously for 30 days), the C_{max} ranged from 0.20 to 0.31 ng/mL and the $AUC_{0\text{-}24h}$ was 3.47 ng.h/mL. [2] In a similar pharmacokinetic study of maximal use in adults and adolescents, the C_{max} was 0.17 ng/mL and the $AUC_{0\text{-}24h}$ was 2.90 ng.h/mL.

[1] Differin (adapalene) Gel, 0.1% labeling, last approved September 5, 2007.
[2] Module 5.3.5.3. Integrated Summary of Safety, section 4.2.2.5.

Retinoic Acid Embryopathy

Retinoids are teratogenic when there is significant systemic exposure in humans and animals. Retinoic acid embryopathy most consistently affects development of the following four structures:[3]

- Craniofacial defects that may include: facial asymmetry, microtia and/or anotia with stenosis of the external ear canal, posterior helical pits, facial nerve palsy ipsilateral to malformed ear, narrow sloping forehead, micrognathia, flat depressed nasal bridge, ocular hypertelorism, and mottling of teeth
- Cardiovascular defects that may include: conotruncal malformations, including transposition of the great vessels, tetralogy of Fallot, truncus arteriosus communis, supracristal ventricular septal defect, aortic arch interruption, retroesophageal subclavian artery, aortic arch hypoplasia, and hypoplastic left ventricle, and
- Central nervous system defects that may include: hydrocephalus, microcephaly, structural errors of cortical and cerebellar neuronal migration and gross malformations of posterior fossa structures, and
- Thymic and parathyroid abnormalities.

Teratogens and Teratogenic Potential

A teratogen is a drug, chemical, or exposure that has the capacity under certain conditions to produce abnormal development in an embryo or fetus.[4] Whether a drug is considered a teratogen depends on several factors, including the physical and chemical nature of the drug (e.g., whether the drug crosses the placenta); the fetal exposure resulting from the maternal dose as well as the duration, frequency, and route of administration of that dose; maternal and fetal metabolic integrity; and gestational timing of fetal exposure. A teratogen generally increases the rate of specific malformations above the background rate for that malformation when the embryo or fetus is exposed to the drug at specific times during gestation.[5] These factors are evaluated along with other available relevant information. The evidence must be biologically plausible when determining whether a drug or exposure is a human teratogen.

The first trimester of pregnancy is considered a sensitive time for the embryo and developing fetus, as it is the time of many key developmental processes of organogenesis. Exposure to a teratogen during the first trimester of pregnancy may result in spontaneous abortion (i.e., miscarriage) or major structural congenital malformation (e.g., orofacial cleft, neural tube defect, heart defect).[6] Exposure to a teratogen during the late first trimester, second

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[3] E.J. Lammer, D.T. Chen, R.M. Hoar, N.D. Agnish, P.J. Benke, J.T. Braun, et al. Retinoic acid embryopathy. N Engl J Med (1985), pp. 837–841.

[4] See the guidance for FDA reviewers on *Evaluating the Risks of Drug Exposure in Human Pregnancies*, available at http://www fda.gov/downloads/Drugs/.../Guidances/ucm071645.pdf.

[5] Holmes LB. Human Teratogens: Update 2010. Birth Defects Research (Part A): Clinical and Molecular Teratology, 2011;91:1-7.

[6] Bleyl SB, Schoenwolf GC. "What is the Timeline of Important Eventes During Pregnancy That May Be Disrupted by a Teratogenic Exposure?," Chapter 2. In: Hales B, Scialli A, Tassinari M. (eds.). Teratology Primer. Second Edition. Teratology Primer. 2010.

trimester, and/or third trimester may also lead to abnormal organ differentiation, growth and function.

Major congenital malformations are defined as those that are life-threatening, require treatment or major surgery, present significant disability, or have significant cosmetic impact. In the United States, the estimated annual rate of major congenital malformations is approximately 2-4% of live births.[7,8,9] The etiologies of most congenital malformations are unknown. However, maternal medical conditions, such as diabetes and hypertension, contribute to the development of some congenital malformations. [10] Chemically-induced congenital malformations, including those associated with drug products, probably account for less than 1% of all congenital malformations, but are important because they are potentially preventable.[11] Prenatal exposures to drugs or other chemicals can also lead to damage that impacts the normal development of function. For example, developmental neurotoxic effects may cause changes in brain structure and chemistry (i.e., neurotransmitter signaling) which produce long-lasting effects on the developing brain. Studies in humans and animals have documented impaired intellectual function and various behavioral abnormalities that resulted from prenatal exposure to drugs.[12]

Drugs are evaluated for their teratogenic potential during the drug development process in a series of animal reproductive and developmental toxicity studies. By design, these studies cover all aspects of reproduction.[13] Typically, one of the studies performed is the embryofetal toxicity study that assesses the potential for teratogenicity. This study consists of multiple dose groups that are administered the study drug during the period of organogenesis (implantation through palate closure). The data from these dose groups are compared to data from an internal control group of animals. Usually, three doses are studied and selected to provide exposures that, at the low dose, at or near the exposure of the anticipated human therapeutic range and at the high dose, are an exposure sufficient to elicit some maternal toxicity in the pregnant female animal. This provides a dose response that allows for an evaluation of teratogenic risk (potential) for the drug. Based on an integrated review of data that includes the reproductive and developmental toxicity data, the general toxicity data, and available pharmacokinetic data, a drug may be determined to have teratogenic potential in humans.

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[7] CDC. Update on Overall Prevalence of Major Birth Defects – Atlanta, Georgia 1978 -2005. MMWR Weekly, Jan 11 2008; 57 (01):1-5.

[8] Nelson K, Holmes LB. Malformations due to presumed spontaneous mutations in newborn infants. N Engl J Med. 1989 Jan 5;320(1):19-23.

[9] Correa A, Cragan JD, Kucik JE, Alverson CJ, Gilboa SM, Balakrishnan R, Strickland MJ, Duke CW, O'Leary LA, Riehle-Colarusso T, Siffel C, Gambrell D, Thompson D, Atkinson M, Chitra J. Reporting birth defects surveillance data 1968-2003. Birth Defects Res A Clin Mol Teratol. 2007 Feb;79(2):65-186.

[10] Cragan JD, Friedman JM, Holmes LB, et al. Ensuring the Safe and Effective Use of Medications During Pregnancy: Planning and Prevention Through Preconception Care. Matern Child Health J 2006;10:S129-S135.

[11] Uhl K, Trontell A, Kennedy D. Risk minimization practices for pregnancy prevention: understanding risk, selecting tools. Pharmacoepidemiol Drug Saf 2007 Mar;16(3):337-48.

[12] Voorhees CV. "Effects on Brain and Behavior," Chapter 5. In: Hales B, Scialli A, Tassinari M. (eds.). Teratology Primer. Second Edition. Teratology Primer. 2010.

[13] See ICH S5 for a complete discussion of the reproductive and developmental studies.

DISCUSSION

Review of Published Literature and Adapalene

Pregnancy

Review of the Reprotox database noted two articles that described adapalene use during pregnancy. The first, by Autret *et al*., is a case report of anophthalmia with maternal use of topical adapalene 0.1% gel 0.3 mg daily from one month prior to conception through 13 weeks gestation.[14] At a 22 week ultrasound of the developing fetus, anopthalmia, agenesis of the optic chiasm and fetal growth restriction are found. The findings lead to termination of the pregnancy. The authors of the case report state that the findings are not usually associated with retinoid exposure and cannot establish causality. The authors of ReproTox concluded that the findings may be coincidental. This case is also mentioned in the TERIS database.

The second article, by Panchaud *et al.,* is a collaborative study of the European Network of Teratology Information Services to evaluate the rate of congenital malformations following first trimester topical retinoid exposure.[15] Outcome information was collected from 235 pregnancies exposed to topical retinoid drug and compared to 444 unexposed matched controls. The study captured 143 exposures to tretinoin, 52 exposures to isotretinoin, 24 exposures to adapalene, 10 exposures to retinoic acid, 1 exposure to motretinide, and 5 exposures to combination retinoids. No significant differences were demonstrated between the topical retinoid exposed group and the unexposed matched controls for major or minor malformations, or for spontaneous abortions. No retinoid embryopathy was demonstrated for any of the drugs. The rate of elective termination was 3 times higher in the topical retinoid exposed group compared to the unexposed matched control group; however, the authors report that no termination was motivated by a major malformation.

DPMH also conducted a search of published literature in PubMed and Embase, and no specific information on adverse pregnancy outcomes was found to further inform the safety of adapalene use during pregnancy. However, given that adapalene shares a mechanism of action similar to other retinoids, its use during pregnancy is often avoided. Many dermatologic review articles have discussed topical acne drugs and use in pregnant women. These review articles conclude that use of topical retinoids, including adapalene, should be avoided during the first trimester of pregnancy, with proper counseling of the patient and consideration of alternative treatments.[16, 17, 18] Table 1 provides a comparison across the topical retinoids on known data for risk when used in pregnancy.

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[14] Autret E, Berjot M, Jonville-Bera AP, Aubry MC, Moraine C. Anophthalmia and agenesis of optic chiasm associated with adapalene gel in early pregnancy (letter). Lancet 1997;350:339

[15] Panchaud A, Csajka C, Merlob P, Schaefer C, Berlin M, De Santis M, Vial T, Ieri A, Malm H, Eleftherious G, Stahl B, Rousso P, Winterfeld U, Rothuizen LE, Buclin T. Pregnancy outcome following exposure to topical retinoids: A multicenter prospective study. J Clin Pharmacol 2012;52:1844-1851.

[16] Murase JE, Heller MM, and DC Butler. Safety of Dermatologi Medicinationsn in Pregnancy and Lactation.. Part I Pregnancy. J Am Acad Dermatol. March 2014;70:401.e1-14.

[17] Tyler K.H., Zirwas M.J. Pregnancy and Dermatologic Therapy. J Am Acad Dermatol 2013; 68:4 (663-671).

[18] Akhavan A., Bershad S. Topical acne drugs: Review of clinical properties, systemic exposure, and safety. American Journal of Clinical Dermatology 2003 4:7 (473-492).

Table 1: Summary of Topical Retinoid Products in Pregnancy Based on Published Literature†

Name	Molecule	Data	Pregnancy Category
Adapalene	derived from naphthoic acid	Risk with first trimester exposure. Very low systemic absorption, one report of congenital eye anomaly associated with use	C
Tazarotene	acetylenic retinoid	Risk with exposure during any time in pregnancy. Minimal absorption, Caused retinoid-like anomalies in animals.	X
Tretinioin	all-trans-retinoic acid	Risk with first trimester exposure. Multiple case reports of associated teratogenicity, but controlled study failed to confirm; avoid first trimester use given availability of alternatives.	C

† Excerpted from Leachman SA, Reed BR. The Use of Dermatologic Drug Use in Pregnancy and Lactation. Dermatol Clin 24 (2006):167-197, and Tyler K.H., Zirwas M.J. Pregnancy and Dermatologic Therapy. J Am Acad Dermatol 2013; 68:4 (663-671).

Lactation

DPMH conducted a search of published literature in PubMed and LactMed databases[19] regarding the use of adapalene during breastfeeding, and no data were found. LactMed, however, stated that due to the low systemic exposure after topical administration, there is likely a low risk to the breastfed infant.

Reviewer Comment

In 1997, Autret et al., described the rare and severe case of anophthalmia as the first demonstration of malformation following maternal use of adapalene in the first trimester. No further cases of congenital malformation have been described in the published literature. Based on the limited available information from published literature, no potential risk to the fetus from maternal adapalene use during pregnancy, or to the breastfed infant with adapalene exposure via breastmilk can be established.

[19] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Applicant's Review of the Pharmacovigilance Database

Clinical Development Program

In the Integrated Summary of Safety (5.3.5.3), the Applicant states that the experience from clinical trials of unintended adapalene 0.1% exposure during early pregnancy was considered an event to be carefully followed from initial reporting to outcome. The exception was the Actual Use Study 100931, where pregnancy was reported as an adverse event (AE). Pregnancy outcomes are reported for 15 of 18 adapalene exposures during pregnancy:

- For Actual Use Study 100931, there were 4 pregnancies: one terminated based on personal reasons, and the remaining three are lost to follow up.
- For Japan Study 27005, there was 1 pregnancy reported in the *placebo* treatment group, with an outcome of elective abortion based on personal reasons.
- For Japan Study 27006 for long-term safety, there were 14 pregnancies reported with the following pregnancy outcomes. None of the live births included congenital malformation.
    - 9 normal births
    - 2 premature births
    - 1 miscarriage at ~13 weeks, patient withdrawn from study 1 day after positive pregnancy test, after 27 days on drug
    - 1 intra-uterine death, patient withdrawn from study 4 days after positive pregnancy test, after 84 days on drug; stillbirth ~ 6 months after positive pregnancy test; associated serious AEs of threatened premature labor, premature separation of placenta, disseminated intravascular coagulation, and intra-uterine death.
    - 1 elective abortion 5 days after positive pregnancy test.

There were no pregnancies reported in the integrated efficacy and safety studies (C-89-61, 9105-CD271G-EV, CR 88051, CR 89064, C-89-32), the Maximal Use PK Trial (Study 18254), or Japan registration Study 27003.

Postmarketing Surveillance

Based on the most recent PSUR submitted in September 2014 (cutoff date July 1, 2014), the Applicant reported a total of 280 cases of pregnancies exposed to adapalene 0.1% gel/cream/solution/lotion and 0.3% gel. There were 41 cases from clinical trials and 239 from postmarketing surveillance.

These numbers were updated in the review by Dr. E. Gnasia[20] from February 2015 (cutoff date September 30, 2014) for a total of 332 pregnancies exposed to adapalene, including those from Epiduo (adapalene 0.1%/benzoyl peroxide 2.5%). There were 56 pregnancies reported during clinical trials and 276 from postmarketing surveillance. Information from the majority (90%) of pregnancy cases were prospectively collected (before the outcome was known, including results of prenatal testing). Of these 332 adapalene-exposed pregnancies,

[20] Module 5.3.6. Elisabeth Gnasia, MD, PhD. Review of exposures to topical adapalene gel, cream, lotion during pregnancy. External expert in medical genetics and teratology, Registre des malformations en Rhône-Alpes (REMERA). February 2015.

there were 28 ongoing and 135 lost to follow up. Therefore, outcomes are known for 169 pregnancies: 109 healthy infants, 18 elective abortions, 23 miscarriages, and 19 other abnormal outcomes. The applicant's table below provides the breakdown by clinical and postmarketing surveillance.

Table 2: Applicant's Table: Distribution of Pregnancy Outcomes Collected through Clinical Trials or Postmarketing Surveillance*

Outcome / source	PMS	Clinical trials
Ongoing	27	1
Lost to Follow-up	126	9
Healthy baby	83	26
Elective abortion	7	11
Miscarriage	16	7
Other abnormal outcomes	17	2
Total	**276**	**56**

*From Applicant's submitted review, Module 5.3.6., by E. Gnasia, February 2015, page 3.

Reviewer Comment
Despite the Applicant's intention to follow adapalene exposures during pregnancy, 40% of the known pregnancies in the pharmacovigilance database are lost to follow up. Based on the known pregnancy outcomes with adapalene exposure, the estimated rate of miscarriage (13.6%, 23/169) is not increased over the 15-20% rate of miscarriage in the U.S. general population. The "other abnormal outcomes" referred to in Table 2 is further discussed below under Abnormal Pregnancy Outcomes.

This reviewer finds the inclusion of pregnancy outcomes from Epiduo (adapalene 0.1%/benzoyl peroxide 2.5%) acceptable for the assessment of risk with adapalene use during pregnancy. The benzoyl peroxide component contributes no risk of congenital malformation such that these pregnancy outcomes may reasonably provide information on risks associated with adapalene exposure during pregnancy. Per ReproTox and TERIS, animal studies with benzoyl peroxide demonstrated no increased risk of congenital malformations and there are no human data to inform any potential risks.

Abnormal Pregnancy Outcomes
In the applicant's submitted review of adapalene-exposed pregnancies, conducted by Dr. E. Gnasia, an expert in medical genetics and teratology, 19 of the 332 pregnancies with adapalene-exposure were found with "other abnormal outcomes". Dr. Gnasia analyzed all the reported cases with respect to possible causal association between drug and exposure and

pregnancy outcome. The role of adapalene could not be determined in some cases because 1) other explanations were identified, 2) the type of anomaly observed was not compatible with the time of exposure during pregnancy, or 3) the information was too scarce to lead to any conclusion (consumer case). Table 3 below is the listing of abnormal pregnancy outcomes from Dr. Gnasia's review.

The applicant's submitted review also includes some description of a rationale that certain outcomes are not likely secondary to adapalene exposure during pregnancy:

- Multiple fetal abnormalities (Case US-GD-0310567): multiple malformations reported are not sufficiently documented, "but this type of association of severe defects usually cannot be attributed to a known cause or risk factor."
- Scimitar syndrome (cardiovascular defect) (Case CH-GDP-0511972): case of multiple malformations from Switzerland; "an association of a complex cardiac defect with Scimitar syndrome (right partial anomalous pulmonary venous return with hypoplastic right lung and sequestration of the inferior lobe) and abnormal cardiac rhythm, Dandy Walker malformation (cystic dilation of IVth cerebral ventricle, agenesis of cerebellar vermis and enlargement of posterior cerebral fossa), right ectopic kidney, right inguinal hernia and glanular hypospadias. These defects do not evoke a known monogenic syndrome, but the nature of malformations indicates that the teratogenic event, if any, took place at least 3 weeks after conception, i.e., 5 weeks after LMP. Because the treatment was stopped before the period of development of the affected organs in this child, the systemic passage of topical retinoids is very low, and the observed association of malformations is not the one normally attributable to retinoids, the role of adapalene in the occurrence of the malformations observed in this child can be excluded."
- Convulsion, areflexia (Case FI20000002): "functional anomaly from Finland is not described in full detail: abnormal trampling with feet, absence of primitive reflex and inability to swallow. The MRI shows no anomaly. This description may be related to a genetic recessive disease called spinal muscular atrophy, the second most common lethal, autosomal recessive disease in Caucasians after cystic fibrosis. Its phenotype is caused, in many cases, by disruption of the telomeric copy of a duplicated gene called SMN1 for 'survival motor neuron'. The gene is missing in a majority of SMA patients, and small intragenic mutations in the gene have been associated with spinal muscular atrophy. Approximately half of the severely affected SMA1 patients are also missing both homologs of a neighboring gene, the neuronal apoptosis inhibitory protein (NAIP). The diagnosis can be confirmed by molecular biology."

Table 3: Abnormal Pregnancy Outcomes†

Outcome	Case ID	PMS	Clinical trials	Prospective/ retrospective	Total
Malformations					
Hydrops fetalis	BR14003185	1		Prospective	1
Talipes	NL14001284	1		Retrospective	1
Polymalformative syndrome (fetal malformation, brain malformation, corpus callosum agenesis, congenital foot malformation, malformation venous)	FR13003020	1		Retrospective	1
Neurofibromatosis type I	US-GDP-12415335	1		Retrospective	1
Fallot tetralogy	BR-GDP-11410861 FR-GDP-11412410	2		1 Prospective 1 Retrospective	2
Dandy Walker syndrome	AT-GDP-10409257	1		Retrospective	1
Congenital Hand malformation	CH-GDP-09406029	1		Retrospective	1
Chromosomal deletion (2Q37)	US-GDP-09406176	1		Retrospective	1
Vacterl syndrome	FR-GDP-08403799	1		Retrospective	1
Scimitar syndrome (cardiovascular defect)	CH-GDP-0511972	1		Retrospective	1
Multiple fetal abnormalities (cleft lip, cleft palate, congenital central nervous system anomaly, congenital gastric anomaly, congenital cardiovascular anomaly, congenital intestinal malformation)	US-GD-0310567	1		Retrospective	1
Multiple congenital abnormalities: congenital optic nerve anomaly, congenital eye disorder, congenital central nervous system anomaly)	FR19960020	1		Retrospective	1
Aarskog syndrome	FR19970008	1		Retrospective	1
Kidney malformation, single umbilical artery	FR199636045	1		Retrospective	1
Functional anomalies					
Respiratory distress, renal failure, hydronephrosis, anasarca	USCTMX0101		1	Retrospective	1
Others					
Placenta abruptio, fetal death	JP-GDP-0411379		1	Prospective	1
Premature baby	CH-GDP-11412563	1		Retrospective	1
Convulsion, areflexia	FI20000002	1		Retrospective	1
Total		17	2		19

† From Applicant's submitted review, Module 5.3.6., Elisabeth Gnasia, MD, PhD. Review of exposures to topical adapalene gel, cream, lotion during pregnancy. February 2015. Table 3, page 4.

Reviewer Comment

This reviewer finds that not all cases considered abnormal pregnancy outcomes were associated with major congenital malformations. First, the separately reported cases of premature birth and fetal death due to placenta abruption were not due to major congenital malformations although may still be potential adverse fetal outcomes. Second, cases due to genetic causes should be excluded (i.e., Neurofibromatosis type I, Chromosomal deletion 2Q37, VACTERL syndrome, and Aarskog syndrome). Six of the remaining 12 cases have other possible explanations (e.g., concomitant medications, timing of exposure, insufficient information) that make it difficult to determine a possible association with drug exposure. This reviewer finds six cases (3.5%, 6/169) that had first trimester exposure and a type of malformation observed that might be expected for a drug that acts like a retinoid. However, no pattern of malformations was observed in this small sample. The estimated background rate of major congenital malformations is 2-4% in the U.S. general population.

Summary

The Applicant has provided a total of 169 reported pregnancy outcomes following exposure to adapalene. Based on the small number of known outcomes, and small number of possible malformations (as assessed by the applicant and DPMH), it is difficult to clearly establish an association between adapalene and major congenital malformations. At this time, the possible malformations did not occur consistently or in a high frequency to clearly establish a pattern. Continued monitoring of adapalene exposed pregnancies may provide additional information.

CONCLUSION

In the review of the published literature and the human safety data provided by the Applicant, DPMH considered the following points:

- Adapalene 0.1% has a low systemic absorption following topical administration.
- Nonclinical studies in rats and rabbits administered adapalene cutaneously at doses up 120 and 150 times the MRHD did not demonstrate retinoid embryopathy.
- Reports of a small number of malformations from adapalene-exposed pregnancies do not support a clear determination of drug-associated risks.
- The experience of oral retinoids and retinoid embryopathy has many practitioners advising alternative acne treatments for pregnant patients.

There is no robust safety signal to clearly establish an association between adapalene and an increase in incidence for major congenital malformations. In addition, there is a large safety margin between human systemic exposure and the animal exposure associated with adverse developmental outcomes. However, healthcare practitioners continue to associate adapalene with potential retinoid embryopathy and, therefore, prescribe alternative treatment for pregnant women. As DNDP determines whether adapalene gel will proceed to the OTC setting, the risk benefit of adapalene must be weighed with the availability of other products that are already OTC that do not have the same potential risk.

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/s/

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance, Epidemiology and Drug Utilization Review

Date:	March 14, 2016
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Product Name(s):	Differin (adapalene) Gel, 0.1 %
Subject:	Nonprescription Drugs Advisory Committee (NDAC)

Application Type/Number: NDA 20380/IND 116864

Applicant/Sponsor: Galderma

OSE RCM #: 2015-2278

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EXECUTIVE SUMMARY

Galderma has proposed an RX-to-OTC switch of adapalene gel 0.1% (Differin) which will be discussed at an April 15, 2016, Nonprescription Drug Advisory Committee (NDAC) meeting. The Division of Nonprescription Drug Products (DNDP) has requested that the Divisions of Pharmacovigilance (DPV II) and Epidemiology (DEPI I) review abnormal pregnancy outcomes, (with a focus on congenital anomalies) associated with adapalene (Differin) and other topical retinoids in the FDA Adverse Events Reporting System (FAERS) database and the medical literature. Additionally, DNDP requested a review of all serious adverse events associated with adapalene, with a focus on off-label use on large body surface areas (BSA). DEPI II was also requested to provide utilization data on adapalene-containing products with a focus on single-ingredient versions for insight into current use as well as context for the safety profile of adapalene.

DPV identified 18 serious cases of adapalene associated abnormal pregnancy outcomes. These cases included miscarriage (9), congenital anomalies (5), abortion (2), preterm birth (1), and hemorrhage (1). Three of the five congenital anomaly cases reported one isolated anomaly [limb malformation, club feet, and Dandy Walker (DW) malformation]. 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. 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. However, there was an insufficient basis for reasonably concluding that adapalene caused the episode of hepatitis, and we therefore did not identify any new adapalene-associated safety signals. We will continue routine monitoring of FAERS and the medical literature for additional cases of hepatitis and unlabeled events associated with adapalene.

Drug utilization patterns for adapalene products in the U.S. outpatient retail pharmacy setting were also assessed. Single-ingredient adapalene utilization decreased 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. According to an office-based physician surveys database, the most common diagnosis associated with the use of adapalene-containing products was "Acne, Not Elsewhere Classified." The diagnosis data was consistent with the most common indication reported in FAERS associated with adapalene.

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.

1 INTRODUCTION

Galderma has proposed an RX-to-OTC switch of their product adapalene gel 0.1% (Differin). This would entail a first-in-class switch for a topical retinoid, a drug class with known teratogenicity risks (Lammer 1985). Currently, adapalene is classified as FDA pregnancy category C. The label states that adapalene should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

DNDP consulted the Division of Pharmacovigilance (DPV II) and the Division of Epidemiology (DEPI) on October 15, 2015, to review the FDA Adverse Event Reporting System (FAERS), the medical literature, and epidemiological studies assessing the relationship between adapalene, topical retinoids, and abnormal pregnancy outcomes. Additionally, DNDP is interested in a review of all serious adverse events associated with adapalene, specifically off-label use on large body surface areas (BSA).

1.1 BACKGROUND

Adapalene is a synthetic retinoid used in acne. It is marketed for topical use as a gel (0.1%, 0.3%) cream (0.1%), lotion (0.1%), and combination adapalene/benzoyl peroxide (0.1%/2.5%). Oral adapalene is teratogenic in animals and transdermal absorption of adapalene has been shown in volunteers after daily application of 0.1% adapalene gel by detection of small amounts in the feces, although no circulating adapalene was detected. There is little known about the risk to the fetus of topical adapalene in pregnant women.

1.2 REGULATORY HISTORY

See Appendix D

1.3 PRODUCT INFORMATION

Product Name	Dosage form/Strength	Indication(s)
	Single-ingredient adapalene	
Differin®	**45 and 75 gram tube** Strength: adapalene 0.1% gel	Topical treatment of acne vulgaris
	Combination-ingredient adapalene	
Epiduo®	**45 gram tube or pump** Strength: adapalene 0.1% and benzoyl peroxide 2.5% gel	Topical treatment of acne vulgaris in patients 9 years of age and older.
Epiduo® Forte	**15, 30, 45, 60, and 70 gram pump** Strength: adapalene 0.3% and benzoyl peroxide 2.5% gel	Topical treatment of acne vulgaris

1.4 PRODUCT LABELING

Topical Retinoid Products	Pregnancy Category	Location in label	Labeling*
Adapalene (Differin) 0.1%	C	Precautions	No teratogenic effects were seen in rats at oral doses of 0.15 to 5.0 mg/kg/day adapalene (up to 20 times the maximum recommended human dose (MRHD) based on mg/m comparisons). However, adapalene administered orally at doses of ≥ 25 mg/kg, (100 times the MRHD for rats or 200 times MRHD for rabbits) has been shown to be teratogenic. Cutaneous teratology studies in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day (24 times the MRHD for rats or 48 times the MRHD for rabbits) exhibited no fetotoxicity and only minimal increases in supernumerary ribs in rats. There are no adequate and well-controlled studies in pregnant women. Adapalene should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Alitretinoin (Panretin)	D	Warnings	Panretin® gel could cause fetal harm if significant absorption were to occur in a pregnant woman. 9-cis-Retinoic acid has been shown to be teratogenic in rabbits and mice.
Bexarotene (Targretin)	X	Contraindications/ Precautions	Targretin gel 1% may cause fetal harm when administered to a pregnant woman.
Tazarotene (Tazorac, Fabior)	X	Contraindications/ Warnings and Precautions	Tazorac Cream may cause fetal harm when administered to a pregnant woman. Tazarotene elicits teratogenic and developmental effects associated with retinoids after topical or systemic administration in rats and rabbits.
Tretinoin (Retin-A, Renova, Tretin-X, Retin-A Micro	C	Precautions	Topical tretinoin has not been shown to be teratogenic in rats and rabbits when given in doses of 100 and 320 times the topical human dose, respectively (assuming a 50 kg adult applies 250 mg of 0.1% cream topically). However, at these topical doses, delayed ossification of a number of bones occurred in both species.
*Not the complete labeling pertaining to pregnancy			

1.5 PREVIOUS OSE REVIEWS

There have been several post-marketing safety reviews for adapalene. These reviews are summarized below.

- May 18, 2004. The Division of Drug Risk Evaluation (DDRE) reviewed reports of pregnancy exposure and birth defects with topical adapalene in the Adverse Event Reporting System (AERS) and the literature. Five cases of congenital anomalies in association with topical adapalene were identified, three of which were considered potential cases of retinoid-specific birth defects. One case was published in the literature (Autret 1997). It was concluded that the cases did not suggest a compelling safety signal for retinoid-specific birth defects in association with topical adapalene at that time. No labeling changes were recommended (Brinker 2004).

- September 8, 2006. DDRE evaluated the drug Sponsor's submission of pregnancy exposure information for adapalene topical products. One additional case not included in the 2004 review was identified, but it described multiple organ system anomalies that were not consistent with the usual picture of retinoid embryopathy. DDRE recommended adding pregnancy outcome information to the label, consistent with other pregnancy category C topical retinoids (Pitts 2006).

- July 24, 2009. In response to a request by the Division of Dermatology and Dental Products (DDDP), DPV reviewed reports of phototoxicity with adapalene when used concomitantly with tetracycline or doxycycline. One report in a 16 year old patient on multiple medications was identified, but it could not be determined if the adapalene and tetracycline were being used concurrently, or if they were used at the time of the photosensitivity reaction. No action was recommended as a result of the review (Salaam 2009).

- August 30, 2010. In accordance with the Pediatric Research Equity Act (PREA), DPV reviewed post-marketing reports of adverse events associated with the use of Epiduo (adapalene 0.1%/benzoyl peroxide 2.5%) in patients 16 years of age and younger. DPV recommended adding hypersensitivity-related adverse event information to the Contraindications and Postmarketing Experience sections of the Epiduo label (Salaam 2010).

- January 12, 2012. In accordance with non-NME (new molecular entity) 915, DPV reviewed post-marketing reports of adverse events associated with the use of adapalene 0.1% topical lotion, but did not identify any potential safety issues at that time (Weintraub 2012).

- March 8, 2012. In accordance with PREA, DPV reviewed post-marketing reports of adverse events associated with adapalene lotion 0.1% in patients 16 years of age and younger. DPV identified idiopathic intracranial hypertension (IIH) as a potential safety signal to be reviewed separately (Weintraub 2012).

- June 7, 2012. As a result of the review of March 8, 2012, DPV reviewed topical retinoids (adapalene, adapalene/benzoyl peroxide, alitretinoin, bexarotene, tazarotene, tretinoin,

tretinoin/clindamycin, tretinoin/flucinolone acetonide/hydroquinone, tretinoin/mequinol) in association with IIH. Based on the limited number of cases, most of which were poorly documented, there was insufficient evidence to suggest an association between topical retinoids and IIH (Weintraub 2012).

2 METHODS AND MATERIALS

2.1 DRUG UTILIZATION

Proprietary drug utilization databases available to the Agency were used to conduct this analysis. (See Appendix B for detailed descriptions of the databases).

2.1.1 *Determining Settings of Care*

The IMS Health, IMS National Sales Perspectives™ (NSP) database was used to determine the various retail and non-retail channels of distribution for single-ingredient adapalene and combination adapalene/benzoyl peroxide products. For single-ingredient adapalene products, approximately 91% of boxes were distributed to outpatient retail pharmacy settings, 6% to non-retail pharmacies, and 3% to mail-order/specialty pharmacies from December 2014 through November 2015. For combination adapalene/benzoyl peroxide products, approximately 95% of boxes were distributed to outpatient retail pharmacy settings, 3% to non-retail pharmacies, and 2% to mail-order/specialty pharmacies from December 2014 through November 2015. As a result, U.S. outpatient retail pharmacy utilization patterns were examined. Non-federal hospital and clinic settings were not included in this analysis.

2.1.2 *Data Sources Used*

The National Prescription Audit (NPA™) database was used to obtain the nationally estimated number of dispensed prescriptions for single-ingredient adapalene and combination adapalene/benzoyl peroxide products from U.S. outpatient retail pharmacies, December 2010 through November 2015, annually. We also examined the number of dispensed prescriptions stratified by the top 10 prescribing specialties for the study period.

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

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

2.2 CASE DEFINITION

CDER standards for assessment of embryofetal toxicity studies (which would assess teratogenicity) were outlined in ICH CICHS5A in 1993. This Guidance includes study design elements (dosing, group size, species selection, etc.). In 2005, the Agency outlined a human specific guidance in *FDA Reviewer Guidance on Evaluating the Risks of Drug Exposure in Human Pregnancies* (FDA Guidance 2005). This Guidance document recommends epidemiological studies as the best method of evaluating a causal relationship between a drug exposure during pregnancy and congenital anomalies. Discussion regarding the utility of 'Case Reports' and 'Epidemiologic Studies' in the assessment of teratogenic risk with drug exposure during pregnancy in this FDA Guidance is provided below.

> Case Reports: Although an individual case report, by itself, can never prove causality, a series of similar reports of a distinct abnormality or group of abnormalities can establish a strong association or signal the need for further research. Most signals based on case reports will need to be further investigated using other pharmacoepidemiologic studies.
>
> Epidemiologic Studies: Formal epidemiology studies provide the best means of evaluating whether a gestational exposure adversely affects the developing infant. Epidemiology studies can identify associations between a given drug exposure and abnormalities in the newborn, and they can quantify the strength of such associations.

As noted in the Guidance and the literature - including the overview of drug-induced teratogenicity provided by Motherisk Program (Diav-Citrin 2016) – most proven human teratogens result in a spectrum - or syndrome – of adverse effects and not one isolated birth defect. Thus, with interest in a new signal for teratogenic risk with adapalene or any other agent, any review of spontaneous reports would include an assessment for a known or unique clustering of birth defects.

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

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

Spontaneous adverse event reports submitted to the Agency are collated and accessed via the FDA Adverse Event Reporting System (FAERS) database. Since adapalene is a retinoid and a

specific *retinoid embryopathy* has been described (Lammer EJ 1985), reports were reviewed not only for a rare event in the newborn population but also the clinical features of *retinoid embryopathy*: craniofacial anomalies (microtia or anotia, accessory parietal sutures, narrow sloping forehead, micrognathia, flat nasal bridge, cleft lip and palate, and ocular hypertelorism), cardiac defects (primarily conotruncal malformations), abnormalities in thymic development, and alterations in central nervous system development.

Inclusion Criteria

- Temporal relationship in a patient using at least one single ingredient topical retinoid: adapalene, tretinoin, alitretinoin, tazarotene, bexarotene *AND*
- Use in a female exposed to at least one of the abovementioned retinoids while pregnant regardless of duration of exposure *AND*
- Any abnormal pregnancy outcome [reports of pregnancy with one or more of the following outcomes: spontaneous abortion, induced abortion, premature or post-term birth (regardless of fetal outcome, congenital anomaly, peri-natal or post-perinatal complication, stillbirth (intrauterine death), or ectopic pregnancy] reported regardless of cause or potential confounding factors

Exclusion Criteria

- None

2.3 FAERS SEARCH STRATEGY

The FAERS database was searched with the strategy described in Table 2.3.1.

Table 2.3.1. FAERS Search Strategy*	
Date of search	November 17, 2015
Time period of search	1/1/1969 - November 17, 2015
Search type	FBIS Quick Query
Product Terms	Active ingredient- Active ingredient-Adapalene†, Alitretinoin, Tazarotene, Bexarotene, Tretinoin (single ingredient)
Outcome(s)	Serious (Death, Hospitalization, Life-threatening, Disability, Congenital Anomaly, Other Serious)
MedDRA Search Terms	SOC (System Organ Class) • Congenital, familial, and genetic disorders • Pregnancy, puerperium and prenatal conditions SMQ (standardized MedDRA Queries) • Congenital and neonatal arrhythmias • Congenital biliary disorders • Congenital, familial, and genetic disorders • Congenital, familial, neonatal, and genetic

	disorders of the liver • Foetal disorders
* See Appendix C for a description of the FAERS database. †reports of adapalene were searched from 04/01/2006 - November 17, 2015 as an update from two previous reviews (Brinker 2004, Pitts 2006)	

2.4 FAERS SEARCH STRATEGY FOR ALL ADAPALENE EVENTS

In addition to the search strategy in Table 2.3.1, the FAERS database was searched to identify all serious cases of adapalene associated adverse events (Table 2.4.1).

Table 2.4.1 FAERS Search Strategy*	
Date of search	November 17, 2015
Time period of search	1/1/1969 - November 17, 2015
Search type	FBIS Quick Query
Product Terms	Active ingredient-Adapalene
Outcome	Serious
* See Appendix A for a description of the FAERS database.	

Data mining was also used to identify any unlabeled adverse events.

Table 2.4.2 Data Mining Search Strategy*	
Data Refresh Date	September 20, 2015
Product Terms	Adapalene
Empirica Signal Run Name	Generic (S)
MedDRA Search Strategy	All adverse events, retrieved at the MedDRA PT level
EB05 Threshold for Review	EB05≥2
*See Appendix C for description of Data Mining of FAERS using Empirica Signal	

2.5 PHARMACOEPIDEMIOLOGY EVALUATION METHODS

The reviewer conducted a PubMed search for epidemiological studies using a combination of generic drug names of topical retinoids and subheadings for drug adverse effects, and restricted to articles with full text and published in English. The search algorithm is described in the Table 2.5.1:

Table 2.5.1 Literature Search Strategy for Epidemiological Studies	
Data Refresh Date	December 12, 2015
Database	PubMed@FDA
Search Terms	("adapalene"[All Fields] OR "Retinoids"[All Fields] OR "Isotretinoin"[All Fields] OR "Retinaldehyde"[All Fields] OR "Tretinoin"[All Fields] OR "tazarotene"[All Fields] OR "motretinide"[All Fields]) AND ("adverse effects"[Subheading] OR "complications"[Subheading] OR "poisoning"[Subheading] OR "Pregnancy"[All

	Fields]) AND ("topical"[All Fields] OR "acne"[All Fields]) AND ("loattrfull text"[sb] AND English[lang])
Years included in search	All
Types of studies retrieved for further review	Cohort studies, RCTs, Meta-Analysis

Initially, 1,120 publications were returned from PubMed. After reading the abstracts and then full texts when necessary and excluding the studies that are reviews, case reports or case series, and those without the interest of exposures (topical retinoids) or outcomes (adverse effects), the reviewer identified five studies on pregnancy outcomes, two studies on other serious adverse effects, and eight on local skin adverse effects. In total, 15 studies were included in this review (Appendix G, Section 8.2, Table 1).

2.6 PHARMACOVIGILANCE LITERATURE SEARCH STRATEGY

The medical literature was searched with the strategy described in Table 2.6.1 to identify any additional case reports not reported in FAERS.

Table 2.6.1. Literature Search Strategy	
Date of search	December 15, 2015
Database	PubMed@FDA, EMBASE, Web of Science, Scifinder, EBSCOhost, TOXNET (TOXLINE and DART)
Search Terms	(teratogenicity OR teratogens [mesh] OR teratogens [tw] OR teratogenesis OR "congenital anomalies" OR embryotox* OR fetotox* OR "drug induced abnormalities" OR "abnormalities, drug-induced" [mesh] OR "congenital malformation" OR "congenital malformations" OR "congenital abnormalities" [mesh] OR "congenital abnormalities" OR "congenital abnormality" OR "birth defect" OR "birth defects" OR "congenital defect" OR "congenital defects" OR "congenital anomaly" OR pregnancy OR pregnant OR pregnancies OR "maternal exposure" OR "prenatal exposure") AND adapalene
Years included in search	All
Filters	Human

3 RESULTS

3.1 DRUG UTILIZATION

U.S. Outpatient Pharmacy Utilization Data

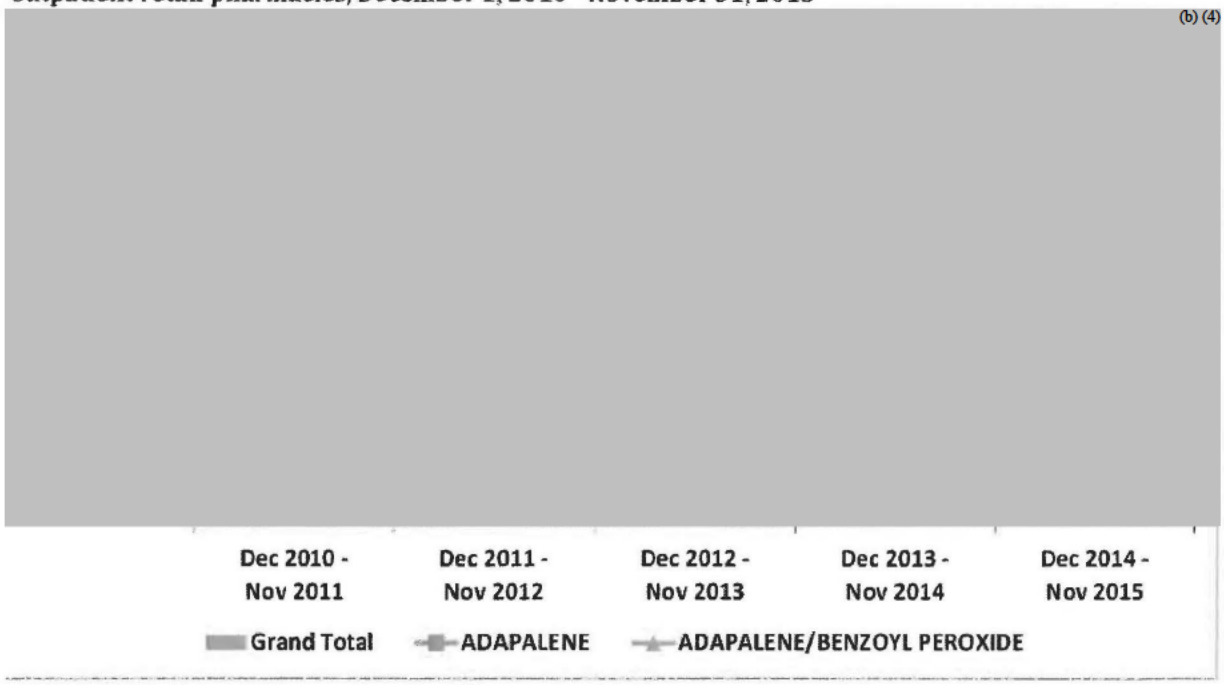
3.1.1 *Dispensed Prescriptions*

Figure 1 displays the nationally estimated number of dispensed prescriptions for single-ingredient adapalene and combination adapalene/benzoyl peroxide products from U.S. outpatient

retail pharmacies from December 2010 through November 2015, annually. The total number of dispensed prescriptions increased from approximately (b) (4) prescriptions in the 12-month period ending in November 2011 to (b) (4) prescriptions in the 12-month period ending in November 2015, accounting for a 7% increase overall.

Single-ingredient adapalene products decreased by 16% from (b) (4) prescriptions dispensed in the 12-month period ending in November 2011 to approximately (b) (4) prescriptions dispensed in the 12-month period ending in November 2015. Conversely, combination adapalene/benzoyl peroxide products increased by 37% from approximately (b) (4) prescriptions dispensed in the 12-month period ending in November 2011 to (b) (4) prescriptions dispensed in the 12-month period ending in November 2015.

Figure 1. Nationally estimated number of dispensed prescriptions for adapalene products from U.S. outpatient retail pharmacies, December 1, 2010 - November 31, 2015



Source: IMS National Prescription Audit (NPA). Dec 2010 - Nov 2015. Extracted December 2015. File: NPA 2015-2278 Adapalene TRx by MAT 12-29-15.xlsx

3.1.2 *Dispensed Prescriptions by Prescribing Specialty*

Table 1 in Appendix A shows the nationally estimated number of dispensed prescriptions by the top 10 prescribing specialties for single-ingredient adapalene and combination adapalene/ benzoyl peroxide products from U.S. outpatient retail pharmacies, December 2010 through November 2015, cumulative. Dermatology was the top prescribing specialty for both adapalene and adapalene/benzoyl peroxide products at 48-49% of dispensed prescriptions followed by Physician Assistants at 15%-17% of dispensed prescriptions and Pediatricians at 10%-16% of dispensed prescriptions, respectively.

3.1.3 *Patients by Age and Sex*

Table 2 in Appendix A shows the nationally estimated number of unique patients who received a dispensed prescription for single-ingredient adapalene and combination adapalene/benzoyl peroxide products from U.S. outpatient retail pharmacies, stratified by patient age and sex, from December 2010 through November 2015, annually. The total number of patients slightly increased from approximately (b) (4) patients in the 12-month period ending in November 2011 to approximately (b) (4) prescriptions in the 12-month period ending in November 2015. Patients with a dispensed prescription for single-ingredient adapalene products decreased by 16% from approximately (b) (4) patients in the 12-month period ending in November 2011 to (b) (4) patients in the 12-month period ending in November 2015. Combination adapalene/ benzoyl peroxide products increased by 26% from approximately (b) (4) patients in the 12-month period ending in November 2011 to (b) (4) patients in the 12-month period ending in November 2015.

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.

3.1.4 *Diagnosis Data by Patient Sex and Age*

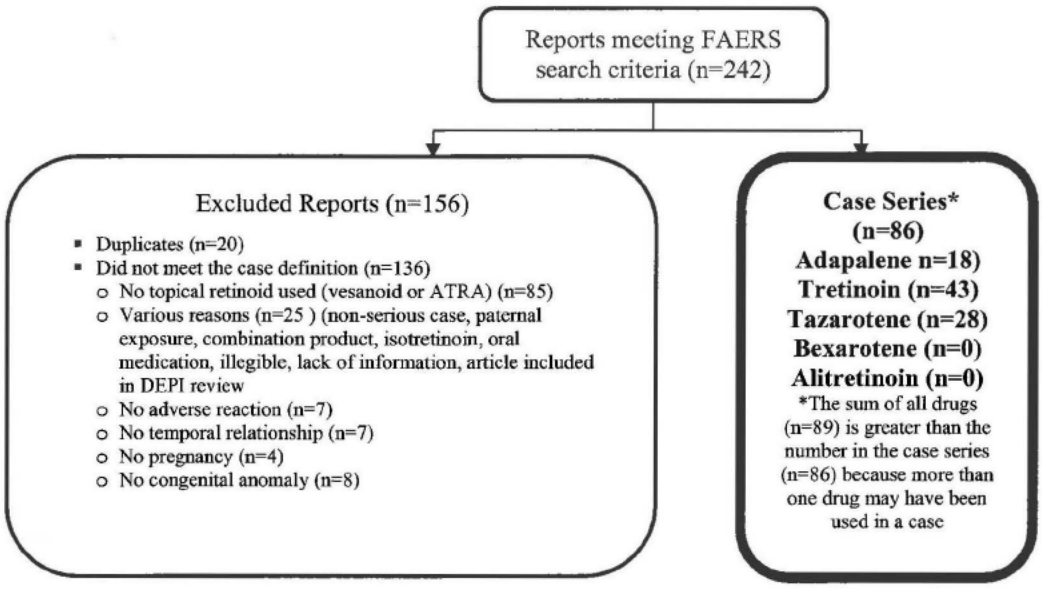
Table 3 and 3a in Appendix A show diagnoses associated with the use[1] of single-ingredient adapalene and combination adapalene/benzoyl peroxide products, stratified by patient sex and age, as reported by U.S. office-based physician surveys from December 2010 to November 2015, cumulative. For single-ingredient adapalene products, the majority of drug use mentions were in patients aged 12-45 years. Among women aged 12-45 years, "Acne, Not Elsewhere Classified (NEC)" (ICD-9 code 706.1) was the top diagnosis code associated with the use of single-ingredient adapalene containing products at 99% of drug use mentions, followed by "Rosacea" (ICD-9 code 695.3) at 1% of drug use mentions. Similar trends by diagnoses were noted among male patients aged 12-45 years and overall for combination adapalene/benzoyl peroxide products. Of note, the number of drug use mentions for adapalene as reported by office-based physician surveys for use by pediatric patients aged 0-11 and adults 46 years or older were below the acceptable count allowable to provide a reliable estimate of national use.

3.2 FAERS Case Selection

The FAERS search retrieved 242 reports. After applying the case definition in Section 2 and accounting for duplicate reports, 86 cases were included in the case series of abnormal pregnancy outcomes reported with adapalene, alitretinoin, tazarotene, bexarotene, and tretinoin (see Figure 3.2.1).

Figure 3.2.1 FAERS Case Selection

[1] "Drug uses" - refer to the mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. "Drug uses" does not necessarily result in prescription being generated but are the projected number of times a given drug was mentioned during an office visit.



Adapalene is discussed separately below and Table 3.2.1 summarizes the remaining 68 FAERS cases of abnormal pregnancy outcomes reported with tretinoin, tazarotene, bexarotene, and alitretinoin for this case series.

Appendix F lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers for the 86 cases in this case series.

ADAPALENE AND ABNORMAL PREGNANCY OUTCOMES (n=18)

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

Congenital Anomalies (n=5)

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

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

Case#10084260 Netherlands 2014
A female patient with a history of high blood pressure, one previous abortion, previous healthy child, and tobacco user gave birth to a baby with club foot on both sides. Amniocentesis did not

show any chromosomal defects. Concomitant medications included folic acid, ferrous sulphate, and adapalene 0.1% gel for acne during the first 14 weeks of pregnancy. No additional information was provided.

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

Case# 6636807 France 2008

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

Reviewer's comments: The case lacks specific information regarding time and duration of exposure to the numerous medications and products. VACTERL Syndrome is not known to be associated with retinoid exposure and may be genetic.

Case#7059072 US 2009

A 28-year-old female with a history of penicillin and seasonal allergies, gestational diabetes, and five previous pregnancies, one child, had a fetus with a genetic defect, 2q37 deletion. The pregnancy was terminated. She used adapalene gel 0.3% for 21 weeks into her pregnancy.

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

Case#7703133 AUT 2010

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

Reviewer's comments: Dandy Walker (DW) Malformation is a congenital human brain malformation involving the cerebellum and the fluid-filled spaces around it. The etiology of DW malformation is poorly understood but is presumed to be multifactorial, with genetic forms accounting for the majority of patients (Pichiecchio 2016). DW has not been associated with a teratogenic treatment in the literature, except for one article which describes 2 newborns with multiple malformations including a DW malformation with oral isotretinoin. The malformation is isolated and a very rare manifestation of retinoid embryopathy. The only congenital anomaly case identified in a DPV 2006 review consisted of a DW malformation. It was concluded that there were some cardiac and brain anomalies; however, the overall range of anomalies identified were inconsistent with retinoid exposure (Pitts 2006).

Table 3.2.1 summarizes the 68 FAERS cases of abnormal pregnancy outcomes reported with tretinoin, tazarotene, bexarotene, and alitertinoin for this case series.

Table 3.2.1 Descriptive characteristics of abnormal pregnancy outcomes reported with topical retinoid (tretinoin, tazarotene, bexarotene, alitretinoin) use, received by FDA from January 1, 1969 –November 17, 2015 (n=68)

Age (years) (n=37)	Age Range: 16-43 Median: 31 Mean: 30		
Source	Domestic: 51 Foreign: 17		
Initial FDA received date (year)	1985:1 1986:1 1988:1 1989:5 1990:1 1991:2 1992:2 1993:2 1994:6	1995:1 1996:2 1997:3 1998:2 1999:2 2000:2 2003:2 2004:4 2005:9	2006:2 2007:1 2008:6 2009:2 2010:2 2011:2 2013:2 2014:2 2015:1
Report Type	Expedited: 64 Direct: 4 Periodic: 0		
Retinoid used*	Tretinoin (strength unknown): 16 Tretinoin 0.05%: 14 Tretinoin 0.1%: 4 Tretinoin: 0.025%: 4 Tretinoin 0.01%: 2 Tretinoin 0.035%:1 Tretinoin: 0.5%: 1 Tretinoin: 0.02%: 1	Tazarotene: 0.05%: 11 Tazarotene (strength unknown): 5 Tazarotene 0.1%:5 Tazarotene 0.01%: 5 Tazarotene 1%: 2	
Indication for use	Acne: 28 Psoriasis: 3 Stretch marks: 1 Rash: 1 Unknown: 35		
Trimester of exposure	1st: 40 1st and 2nd: 5 3rd: 1	"early": 2 entire pregnancy: 3 unknown: 17	

Table 3.2.1 Descriptive characteristics of abnormal pregnancy outcomes reported with topical retinoid (tretinoin, tazarotene, bexarotene, alitretinoin) use, received by FDA from January 1, 1969 –November 17, 2015 (n=68)

Congenital anomalies reported ≥2 or more times* See table for line listing of all congenital abnormalities reported	• Miscarriage:24 • Congenital heart defect (patent ductus arteriosis, TAPVD, coarctation of the aorta, transposition of the great vessels, hypoplastic left heart syndrome, double aortic arch, pericardial defect, dextroposition of the heart, ventricular septal defect, patent foramen ovale):11 • Brain defects (microcephaly, anencephaly, holoprosencephaly, spina bifida, oxycephaly, widely spaced horns of the lateral ventricles, absent corpus callosum):10 • Cleft lip, cleft palate, moderately high palate, bifid uvula, abnormal lip/palate:9 • Hand or finger malformations:7 • Microtia, small ear canals, low ears, hearing loss, deformed ear: 5 • Hypertelorism or hypotelorism:3 • Chromosomal abnormality (Triploidy or Trisomy 18):2 • Craniofacial deformity: 2 • Gastroschisis:2 • Hernia:2			
Concomitant Meds Categorized by FDA Pregnancy Category*	**B** loratadine diphenhydramine macrodantin erythromycin clindamycin benzyl alcohol cefadroxil azithromycin oxybutynin ipratropium	**C** fluticasone nasal venlafaxine APAP with codeine trimethoprim topical benzoyl peroxide Dimetapp psoralen triamcinolone scopolamine TAC triamcinolone acetonide, carboxymethyllcellulose hydroxychloride albuterol inhaler gabapentin carisoprodol hyoscyamine gamma globulin beclomethasone escitalopram dexamethasone hydrocodone amitriptyline sumatriptan methadone	**D** doxycycline tetracycline lorazepam ibuprofen	**X** estazolam
Elective abortion	8			

*Patient may have had more than one retinoid used, congenital anomaly, and/or concomitant medication

TOPICAL TRETINOIN, TAZAROTENE, BEXAROTENE, AND ALITRETINOIN AND ABNORMAL PREGNANCY OUTCOMES (n=68)

DPV identified 68 serious cases of abnormal pregnancy outcomes associated with single ingredient topical retinoids (alitretinoin, bexarotene, tazarotene, tretinoin). The cases occurred in patients with a median age of 31 years and the majority (75%) were domestic reports. Most patients did not have a contributing medical history or it was unknown. Forty-four cases were reported in association with tretinoin, the most common strength [when known (n=14)] was 0.05%. Twenty-eight occurred with tazarotene, the most common strength [when known (n=11)] was 0.05%. In three cases, patients were using 2 different strengths of tretinoin. There were no cases associated with alitretinoin or bexarotene. The most common indications were acne (28), psoriasis (3), and stretch marks (2).

Of the 68 cases, the most frequently reported event was miscarriage (24) followed by a congenital heart defect (11), brain defects (10), and cleft palate (8). The majority of exposures (n=40) occurred in the first trimester, first and second (n=5), or the entire pregnancy (3). There were eight elective abortions and four cases which resulted in a fetal death. The four cases of death included a stillborn, death from hypoplastic left heart syndrome, lethal skeletal dysplasia, and an infant delivered by cesarean section complicated by malpresentation and severely impacted vertex requiring significant traction at the time of delivery to release infant's head from maternal pelvis.

Twenty-three cases reported at least one concomitant medication. The majority of concomitant medications were listed as FDA pregnancy category B or C. Four cases reported a concomitant FDA category D medication, of which one case included two FDA category D medications and one FDA category X medication (estazolam).

ADAPALENE and ALL SERIOUS ADVERSE EVENTS

Table 3.2.2 summarizes the most frequently reported serious adverse events associated with adapalene from 1/1/1969 to November 17, 2015.

Table 3.2.2. Most Frequently Reported MedDRA PTs with N ≥ 4 for adapalene, received by FDA from 1/1/1969 –November 17, 2015 sorted 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

Table 3.2.3 summarizes data mining results for adapalene as of September 20, 2015.

Row	**PT**	**N**	**EB05**	**Labeled^ (Yes/No), Location or Other Category**
1	Skin irritation	24	46.071	Yes, P, AR, PI
2	Skin burning sensation	22	37.852	Yes,
3	Skin exfoliation	36	33.124	Yes, AR
4	Dry skin	59	20.517	Yes, P, AR
5	Pain of skin	9	20.139	Yes, PM
6	Eyelid oedema	15	18.998	Yes, AR
7	Acne	30	10.659	IR

Row	PT	N	EB05	Labeled^ (Yes/No), Location or Other Category
8	Erythema	38	9.228	Yes, P, AR
9	Dermatitis	65	6.879	Yes, AR
10	Skin hyperpigmentation	6	6.043	Yes, AR
11	Abortion induced**	9	3.407	No
12	Abortion spontaneous**	14	3.169	No
13	Scar	8	2.966	DR
14	Exposure during pregnancy**	10	2.458	No
15	Condition aggravated	22	2.181	DR
16	Maternal exposure during pregnancy**	14	2.144	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, PM=Post Marketing

Reviewer Comments on Severity and Frequency of Adverse Events

From the time of approval (May 31, 1996) through November 17, 2015, there were 237 serious reports associated with adapalene in FAERS. Twenty-six drug-event combinations (DEC) were reported four or more times. Eight of the most frequently reported DECs were labeled. Three were disease or indication related (Condition Aggravated, Acne, Scar) and two were uninformative (Drug Ineffective, Product Use Issue) (Table 3.2.2). The six pregnancy-related DECs are reviewed in the adapalene and abnormal pregnancy outcomes section.

A review of the 237 reports identified 127 serious, unduplicated cases associated with adapalene in FAERS. The majority of use was with the 0.1% strength (n=65), followed by 0.3% (n=23), 0.01% (n=1), 0.2%, (n=1), and 0.05% (n=1) (one patient used two strengths subsequently). When known (n=102), the majority of indications were for acne (n=96). Three cases reported more than one indication. Off-label indications (n=9) were reported as keratosis follicular (1), pigmentation disorder (1), skin rejuvenation (1), therapeutic skin care (1), skin discoloration (1), whitening freckles (1), hyperpigmentation (1), follicular mucinosis (1), or skin aging (1). In the hyperpigmentation case, the patient reported using adapalene "rarely" on the upper part of the body. The one case of adapalene for off-label use on a large BSA is described below.

Unlabeled events (alopecia, headache, depression, intracranial pressure increased, and vision blurred) and a case of off-label use on a large BSA were selected for further review.

UNLABELED PTs (n=5)

Alopecia (n=9)

There were nine cases of alopecia in patients ranging in age (n=7) from 16 to 45 years. Eight were direct reports and one was a 15-day report. Six patients were taking adapalene for acne, and the indication for the remaining three patients was unknown. Mean time to onset (n=7) was 152 days. There was only one case which reported a specific concentration which was 0.1% adapalene. Patterns of hair loss varied, including all over the scalp, diffuse hair loss, hair thinning/hairline receding, abnormal hair loss, hair loss, hair loss at temples and forehead, and beard hair loss.

One patient saw a dermatologist, but it was unclear whether alopecia was the primary reason for the visit. Concomitant medications were reported in four cases as benzoyl peroxide/clindamycin gel, fexofenadine, esomeprazole (labeled for alopecia), and recent isotretinoin use (labeled for alopecia). One patient reported a positive rechallenge (confounded by isotretinoin), three patients reported a positive dechallenge, three reported a negative dechallenge, and the outcome for the two remaining cases was unknown. Eight cases did not report any past medical history and four did not report any concomitant medication.

Reviewer comment: One case of thinning of the hair and receding of the hairline, included in the nine cases above, was reviewed by DPV in association with a PREA review (Weintraub 2012). It was concluded at that time that the case was confounded by concomitant esomeprazole labeled for alopecia. The positive rechallenge case was confounded by recent isotretinoin use. Eight cases did not report any past medical history and four did not report any concomitant medication and the contribution of adapalene to these cases could not be established. DPV will continue to monitor for adapalene associated alopecia.

Headache (n=6)

The majority of headache cases were in association with intracranial pressure increased. Please see section below titled "Intracranial Pressure Increased" for additional information.

Depression (n=4)

A 28-year-old female who had previously taken tretinoin cream 0.05% experienced depression. Tretinoin was discontinued and she started taking adapalene gel 0.1%. After two weeks, she felt sad and hopeless. She reported that "off both of these medications she was fine." No other concomitant medication or medical history was reported. A 40-year-old female with a history of depression (on venlafaxine) complained of "deterioration" of depression while on adapalene. A 16-year-old with no psychiatric medical history was treated with adapalene 0.3% for acne. Seven months later, he experienced lack of concentration at school, trouble focusing, trouble sleeping, anxiety, and depression. Adapalene was discontinued and he recovered approximately two weeks later. Concomitant medication included Clindoxyl [clindamycin/benzoyl peroxide (not labeled for depression)] was ongoing. Another report was from a female (age unknown)

who received adapalene for approximately 45 days and reported depression among several other symptoms including stress, anxiety, nausea, dizziness, yeast infection, rashes, dark patches on tongue, bruising, and hair loss. No concomitant medication, past medical history or outcome information was reported.

Reviewer comment: Adapalene is not labeled for depression. Of the four cases, there was one possible case in a 16-year-old with a positive dechallenge (reviewed in Weintraub 2012). One case is confounded by underlying depression. Additionally two cases do not report past medical history or concomitant medications. These cases do not support a safety signal at this time. DPV will continue routine surveillance to monitor for additional cases of depression.

Intracranial Pressure Increased (n=4)

The four cases identified as intracranial pressure increased were included in the 2012 review of IIH and there have been no new cases at this time. In the March 2012 review, DPV (Weintraub 2012) reviewed topical retinoids including adapalene and concluded that based on the limited number of cases, most of which were poorly documented, there was insufficient evidence to suggest an association between topical retinoids and IIH at that time.

Vision Blurred (n=4)

The majority of the cases of blurred vision were associated with intracranial pressure increased.

ADVERSE EVENTS OF SPECIAL INTEREST (n=1)

Off-label use on a large BSA (n=1)

Case#9067293 France 2015 Literature (Lerisson, 2014)
A 55-year-old female with Darier disease and no other medical history or other treatment was treated with acitretin (oral retinoid) long term. In May 2010, her liver tests were normal. In (b) (6) ((b) (6) months later), she developed an acute mixed pattern hepatitis characterized by ALT 107 IU/L, AST 67 IU/L, alkaline phosphatase 319 IU/L gamma-glutamyltransferase 81 IU/L, and bilirubin 7.1 micromol/L. The hepatitis was attributed to acitretin because it was her sole medication, other causes of hepatitis were excluded (negative tests for recent viral hepatitis A, B, C, E and auto-antibodies), an ultrasound showed normal liver and biliary tract, and she had a positive dechallenge. Approximately 10 months later, she was treated with adapalene 0.1% cream daily for the relapse of Darier disease. Overall, 15 tubes of 30 g adapalene were applied on approximately 15% of her body surface from January 2012 to September 2012 (8 months). She developed asthenia, nausea, and dyspepsia. The clinical exam was normal and there was no jaundice or other manifestations of liver disease. Liver tests were: ALT 403 IU/L, AST 205 IU/L, alkaline phosphatase 203 IU/L, gamma-glutamyltransferase 105 IU/L, serum bilirubin 11.8 micromol/L Serum albumin was 34.5 g/l, gammaglobulin 14 g/l, INR 1.00, prothrombin time 100% of normal value and blood cell counts were normal. Tests were negative for recent infections (hepatitis virus A, B, C, E, cytomegalovirus, Epstein-Barr virus and Herpes simplex virus, antibodies to mitochondria, smooth muscle and nuclei, transglutaminase). Serum levels of iron, copper and ceruloplasmin were normal. Ultrasonographic and MRI examinations showed

normal liver and biliary tract patterns. A liver biopsy was performed because liver tests improved slowly. Histological examination revealed a normal architecture without fibrosis, inflammation, steatosis, hepatosiderosis, cholangitis, or endothelial lesion. Her liver tests progressively improved upon discontinuation of adapalene and returned to near normal seven months later.

Reviewer's comment: Hepatitis is an unlabeled event for adapalene, but labeled for oral retinoids. This case supports a probable association between adapalene and hepatitis based on temporality, clinical presentation, laboratory values, positive dechallenge, and absence of other causes of hepatitis. The use of a large dose of adapalene on her lesions may have resulted in an increased absorption of adapalene resulting in toxicity. Studies enroll patients who have approximately 5-6% BSA involvement (Mathis 2006), whereas this patient had 15% involvement.

3.3 PHARMACOEPIDEMIOLOGY LITERATURE

3.3.1 Pregnancy Outcomes

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

Two subsequent studies also investigated the effect of topical tretinoin on pregnancy outcomes, and neither observed a positive association. Using a prospective cohort design, Shapiro et al. (Shapiro, Pastuszak et al. 1997) compared 94 first-trimester tretinoin-exposed women to 133 unexposed controls with similar maternal age, patterns of smoking, and alcohol use and reported no significant differences in the rates of live births, miscarriages, elective terminations of pregnancy, and major malformations between exposed and unexposed. However, mean birth weight was lower in exposed women compared to unexposed (3355g vs 3502g, P=0.05). Another prospective study conducted by Loureiro et al. (Loureiro, Kao et al. 2005) compared pregnancy outcomes in 106 pregnant women with first-trimester exposure to tretinoin to 389 similar controls. No significant difference was reported between the two groups for spontaneous abortion (6.6% vs. 8.5%, P=0.53), major structural defects (2.2% vs. 1.2%, P =0.62), and the prevalence of one or more retinoic acid-specific minor malformations (12.9% vs. 9.9%, P =0.51).

More recently, Panchaud and colleagues prospectively studied 235 pregnant women exposed to any topical retinoid including tretinoin (n=143), isotretinoin (n=52), adapalene (n=24), retinoic acid (n=10), or their combinations and 444 controls for pregnancy outcomes from 1992 to 2006 (Panchaud, Csajka et al. 2012). Although they observed a higher risk of spontaneous abortion (OR 1.5, 95% CI: 0.8-2.7), minor birth defects (OR 1.3, 95% CI: 0.4-3.7), and major birth defects (OR 1.8, 95% CI: 0.6-5.4) in the exposed group compared to unexposed, these increases were not statistically significant. The investigators did find a 3-fold increased risk of elective termination (OR 3.4, 95% CI: 1.5-7.8) among the exposed compared to unexposed. The authors

did not adjust for any confounding variables. The authors suggest their findings are reassuring in cases of inadvertent exposure but that the use of topical retinoids during pregnancy remains questionable.

Kaplan et al. performed a meta-analysis based on the above four published studies (Kaplan, Ozsarfati et al. 2015) to better understand any potential association between topical retinoids and adverse pregnancy outcomes. They did not detect significant increases in risks of major congenital malformations [OR=1.22, 95% CI 0.65–2.29], spontaneous abortions (OR=1.02, 95% CI 0.64–1.63), stillbirth (OR=2.06, 95% CI 0.43–9.86), elective termination of pregnancy (OR=1.89, 95% CI 0.52–6.80), low birth weight (OR=1.01, 95% CI, 0.31–3.27) or prematurity (OR=0.69, 95% CI 0.39–1.23). However, the authors pointed out the inadequate statistical power and concluded that their results do not justify the use of topical retinoids during pregnancy.

3.3.2 Other Serious Adverse Effects

3.3.2.1 Inflammatory Bowel Disease (IBD)

In a large retrospective cohort study Alhusayen et al. compared 184,824 patients ages 12-29 years treated with a topical acne medication (benzoyl peroxide, erythromycin, clindamycin, retinoic acid, or adapalene) to 1,526,946 non-exposed controls (Alhusayen, Juurlink et al. 2013). After up to 12 years of follow-up, the authors observed a borderline statistically significant increased risk of ulcerative colitis, a type of IBD, in those exposed to a topical acne medication (RR 1.19; 95% CI 1.00-1.42). While further analysis on topical retinoids specifically was unavailable, the investigators suggested a possible association between IBD and acne itself but did not rule out the possibility of topical acne medications, including retinoids, as a cause of IBD.

3.3.2.2 All-Cause Mortality

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

3.3.3 Cutaneous Adverse Effects

The most common adverse effects of topical retinoid therapy reported in the literature are related to local skin irritations including erythema, dryness, scaling, pruritus, burning, and post inflammatory hyperpigmentation (Dunlap, Mills et al. 1998, Ioannides, Rigopoulos et al. 2002,

Kawashima, Harada et al. 2008, Goh, Tang et al. 2009, Feldman, Werner et al. 2013, Tirado-Sanchez, Espindola et al. 2013). Although common and usually observed in the majority of treated patients (Rao, Ghosh et al. 2009, Tirado-Sanchez, Espindola et al. 2013), the local adverse effects are in general mild to moderate, and often transient (Dunlap, Mills et al. 1998, Ellis, Millikan et al. 1998, Phillips 2005, Kawashima, Harada et al. 2008, Goh, Tang et al. 2009, Tirado-Sanchez, Espindola et al. 2013). Among the three topical retinoid agents, adapalene is better tolerated than tretinoin and tazarotene with respect to both frequency and severity of local cutaneous adverse effects (Thielitz, Abdel-Naser et al. 2008).

3.4 PHARMACOVIGILANCE LITERATURE SEARCH

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

Reviewer's comment: The article did not report whether or not the mother was using concomitant medications. The authors stated that microphthalmia had been observed among 81 rabbit fetuses exposed to very high doses of topical adapalene, and that tretinoin is known to cause microphthalmia and anophthalmia in mice. Additionally, they concluded that this was the first published observation of a severe malformation in a baby born to a mother who used adapalene gel in early pregnancy. This case was described in a previous DPV review (Brinker 2004).

4 SUMMARY AND DISCUSSION

4.1 DRUG UTILIZATION

In order to provide post-marketing utilization patterns as well as context for the adverse event profile, drug utilization patterns for adapalene products were assessed. In the U.S. outpatient retail setting, use of single-ingredient adapalene products decreased by 16% 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. Combination adapalene/benzoyl peroxide products increased by 37% from approximately 867,000 prescriptions dispensed or 545,000 unique patients to 1.2 million prescriptions dispensed or 689,000 unique patients during the same time. Dermatology was the top prescribing specialty for single-ingredient and combination adapalene/benzoyl peroxide products for the review period. Women aged 12-45 years accounted for the majority of use for single-ingredient and combination adapalene containing products. According to an office-based physician survey database, the most common diagnosis associated with the use of single-ingredient and combination adapalene containing products was "Acne NEC."

4.2 FAERS ANALYSIS

Topical retinoid associated abnormal pregnancy outcomes

DPV identified 18 serious cases of adapalene associated abnormal pregnancy outcomes. These cases included miscarriage (9), congenital anomalies (5), abortion (2), preterm birth (1), and hemorrhage (1). When known (n=12), adapalene 0.1% strength (n=8) was used more frequently than 0.3% (n=4). Three of the five congenital anomaly cases reported one isolated anomaly (limb malformation, club feet, and DW malformation). Additionally, there was one case of a congenital anomaly in the literature which described adapalene associated anophthalmia and agenesis of the optic chiasma. This literature case was described in a previous DPV review (Brinker 2004). Of the five congenital anomaly cases, three fetuses were aborted. It is unknown if the abortions were a direct result of the congenital anomaly after inadvertent exposure to adapalene. DPV cannot be certain because there may have been other reasons that were not reported. A patient's perception of risk to the fetus may have contributed to this outcome, but it is unknown to what extent.

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%.

Retinoids are a family of compounds with structures that resemble those of Vitamin A (retinol) and adapalene is a synthetic analog of retinoic acid. Tretinoin was the first topical retinoid used for the treatment of acne; adapalene and tazarotene are third-generation. Retinoids are known teratogens when used systemically and retinoic acid embryopathy has been well described in the literature. Adapalene 0.1% gel is currently an FDA pregnancy category C and use in pregnancy is not contraindicated. The other topical retinoids have varied pregnancy categories [tretinoin (category C), tazorotene (category X), alitretinoin (category D), and bexarotene (category X). Although there is data that oral adapalene is a teratogen in animals, it is not clear that the animal studies predict the risk in pregnant women, especially for the dose and duration they take the medication.

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

4.3 EPIDEMIOLOGY

Findings from five studies assessing pregnancy outcomes do not suggest an increased risk of teratogenicity in the offspring among women exposed to a topical retinoid agent during first-trimester of pregnancy (Kaplan, Ozsarfati et al. 2015); Appendix G, Section 8.2.1, Figure 1. Although an increased risk of IBD (Alhusayen, Juurlink et al. 2013) and all-cause mortality were reported (Weinstock, Bingham et al. 2009) among users of topical retinoids, both findings were difficult to interpret and inconclusive. None of the reviewed studies specifically assessed adapalene.

1. Evidence for a causal association between topical retinoid exposure and risk of birth defects is inconclusive.

While the risk of adverse pregnancy outcomes observed from the four original studies and one meta-analysis does not appear increased among women exposed to topical retinoids during early pregnancy (Kaplan, Ozsarfati et al. 2015), those studies have multiple limitations and their findings should be interpreted with caution. For example, one limitation to these studies is small sample size (range= 200-700 women). Given the low prevalence of birth defects, the studies were underpowered to detect significant increases in defect risk. In addition, methodological issues may threaten the validity of these studies. For example, the reliance on prescription records for exposure (Jick, Terris et al. 1993) could cause a non-differential exposure misclassification which could likely bias the risk estimate towards the null. Also, studies using voluntary calls or phone interviews for exposure details and information on pregnancy outcomes (Shapiro, Pastuszak et al. 1997, Loureiro, Kao et al. 2005, Panchaud, Csajka et al. 2012) are prone to 1) self-selection bias due to voluntary study participation, and 2) outcome misclassification due to potential differences in reporting of study outcomes in the exposed versus unexposed. Among cohort studies, the potential for differential loss-to-follow-up between exposed and unexposed (Shapiro, Pastuszak et al. 1997) can also introduce selection bias either towards or away from the null.

Limited confounding adjustment due to the lack of data may have resulted in biased risk estimates. Therefore, although the combined findings from a meta-analysis does not show a positive association between topical retinoid therapy and adverse pregnancy outcomes (Kaplan, Ozsarfati et al. 2015), the potential for confounding in each individual study does not preclude a possible increased risk of birth defects. Given the lack of information on differences between exposed and unexposed in several of the reviewed studies, the extent of confounding in each study is unclear.

The finding of an increased risk of elective termination among the exposed in a most recent multi-center study (Panchaud, Csajka et al. 2012), Appendix G, Section 8.2.1, Figure 2) is noteworthy but difficult to interpret. The authors explained that it is possible that patients' or providers' perceptions of fetal risk might have contributed to this finding. Alternatively, it may reflect an increased risk of a real pregnancy complication (such as a defect) ultimately leading to termination.

2. Evidence for associations between topical retinoids and other serious adverse events is limited and unclear.

In addition to teratogenicity, several serious adverse effects including IBD, depression and suicidal behavior, lipid abnormalities, and deteriorated bone health have been reported in patients treated with systemic isotretinoin (Digiovanna 2001, De Marchi, Maranhao et al. 2006, Reddy, Siegel et al. 2006, Roodsari, Akbari et al. 2010, Alhusayen, Juurlink et al. 2013). While these issues appear to be less likely a serious concern for topical retinoid therapy, Alhusayen et al. report an increased risk of ulcerative colitis in their study of 184,424 patients who received topical acne medication (Alhusayen, Juurlink et al. 2013). Since this is a well-powered and generally well-conducted study and the finding could be true, additional research should be conducted to explore this possible causal association. .

The unexpected increased risk of all-cause mortality reported from the large randomized controlled trial (VATTC) (Weinstock, Bingham et al. 2009), should be further investigated. The investigators argue that a causal association is questionable due to minimal systemic absorption of topical tretinoin, the lack of a dose-response association, the absence of a specificity of cause of death, and the failure in showing an interaction with smoking; however, the risk should not be completely ignored. For example, one possibility is that the long-term exposure (2-6 years) of topical tretinoin to the older study population (mean age: 71 years) whose immune system is relatively weak could result in an accumulation of a subtle but lethal toxicity that may cause multiple systemic consequences, and thus, increased risk of all-cause mortality.

3. Dose-effect relationship is lacking.

A consistent limitation to all of the reviewed literature is the lack of investigation into a possible dose-effect. Limited by small study populations and lacking data on dose, these studies usually only compared patients exposed to topical retinoids to those unexposed without further stratification by exposure details such as specific retinoid, medication strength, application frequency, or the size of application area. The absence of this important information not only prevents the establishment of causal association, but it may also obscure a possible threshold effect of the drug. Since the topical retinoid therapy for acne treatment could be a long-term and frequent exposure on a large body area (especially if available as an OTC medication), the plasma retinoid could be accumulated to a toxic level that is much higher than a usually less than 1% level of oral administration.

4.4 PHARMACOVIGILANCE LITERATURE

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 (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.

5 CONCLUSION

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 methodologic limitations that prevent conclusions regarding the safety of adapalene and other topical retinoids. Findings of an increased risk of ulcerative colitis and all-cause mortality are difficult to interpret.

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7 APPENDICES

7.1 APPENDIX A. DRUG UTILIZATION TABLES

Table 1. Nationally estimated number of dispensed prescriptions by top 10 prescribing specialties for adapalene products from U.S. outpatient retail pharmacies, Dec 2010 - Nov 2015

	Dec 2010 - Nov 2015	
	TRx	*Share*
	N	%
Grand Total	(b) (4)	
ADAPALENE		
DERMATOLOGY		
PHYSICIAN ASSISTANT		
PEDIATRICS		
NURSE PRACTITIONER		
FAMILY PRACTICE		
OSTEOPATHIC MEDICINE		
INTERNAL MEDICINE		
SPECIALTY UNSPECIFIED		
OBSTETRICS/GYNECOLOGY		
INTERNAL MED/PEDIATRICS		
ALL OTHERS		
ADAPALENE/BENZOYL PEROXIDE		
DERMATOLOGY		
PHYSICIAN ASSISTANT		
PEDIATRICS		
NURSE PRACTITIONER		
OSTEOPATHIC MEDICINE		
FAMILY PRACTICE		
INTERNAL MEDICINE		
SPECIALTY UNSPECIFIED		
OBSTETRICS/GYNECOLOGY		
DERMATO-PATHOLOGY		
ALL OTHERS		

Source: IMS National Prescription Audit (NPA). Dec 2010 - Nov 2015. Extracted January 2016. File: NPA 2015-2278 Adapalene by MD 1-6-16.xlsx

Table 2. Nationally estimated number of patients who received a prescription for adapalene products from U.S. outpatient retail pharmacies, stratified by patient age and sex (0-11, 12-45, 46+ yrs), Dec 2010 - Nov 2015

	Dec 2010 - Nov 2011		Dec 2011 - Nov 2012		Dec 2012 - Nov 2013		Dec 2013 - Nov 2014		Dec 2014 - Nov 2015	
	Patient Count N	*Share* %	Patient Count N	*Share* %	Patient Count N	*Share* %	Patient Count N	*Share* %	Patient Count N	*Share* %
Grand Total										(b) (4)
adapalene										
Age 0-11 years										
Female										
Male										
Age 12-45 years										
Female										
Male										
Age 46+ years										
Female										
Male										
adapalene/benzoyl peroxide										
Age 0-11 years										
Female										
Male										
Age 12-45 years										
Female										
Male										
Age 46+ years										
Female										
Male										

Source: IMS, Vector One®: Total Patient Tracker. Dec 2010 - Nov 2015. Extracted December 2015. File:TPT 2015-2278 Adapalene by gender 12-29-15.xls

**Subtotals may not sum exactly, due to rounding. Patients may have received multiple administrations of drug during the study period and due to aging of patients during the study period, patients may be counted more than once in the individual categories. For this reason, summing is not advisable and will result in overestimates of patient counts.*

Table 3. Diagnoses associated with the use* of adapalene as reported by U.S. office-based physician survey, stratified by patient sex and age (0-11, 12-45, 46+ yrs), Dec 2010 - Nov 2015

	Dec 2010 - Nov 2015		
	Uses	*Share*	95% Confidence
	(000)	%	(000)
adapalene	[redacted]		(b) (4)
Female			
Age 0-11 yrs			
7061 ACNE NEC			
0780 MOLLUSCUM CONTAGIOSUM			
Age 12-45 yrs			
7061 ACNE NEC			
6953 ROSACEA			
Age 46+ yrs			
7061 ACNE NEC			
6953 ROSACEA			
7090 DYSCHROMIA			
Unknown Age			
7061 ACNE NEC			
Male			
Age 0-11 yrs			
7061 ACNE NEC			
0780 MOLLUSCUM CONTAGIOSUM			
Age 12-45 yrs			
7061 ACNE NEC			
7062 SEBACEOUS CYST			
7048 HAIR DISEASES NEC			
Age 46+ yrs			
7061 ACNE NEC			
Unknown Age			
Unknown sex			

Source: Encuity Research, LLC., TreatmentAnswers™ with Pain Panel, Dec 2010 - Nov 2015. Extracted December 2015. File: PDDA 2015-2278 Adapalene by gender AgeDx4 1-6-16.xls

**"Drug uses" - refer to the mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. "Drug uses" does not necessarily result in prescription being generated but are the projected number of times a given drug was mentioned during an office visit.*

NEC - Not Elsewhere Classified NOS - Not Otherwise Specified

Table 3a. Diagnoses associated with the use* of adapalene/benzoyl peroxide as reported by U.S. office-based physician survey, stratified by patient sex and age (0-11, 12-45, 46+ yrs), Dec 2010 - Nov 2015

	Dec 2010 - Nov 2015		
	Uses	*Share*	95% Confidence Interval
	(000)	%	(000)
adapalene/benzoyl peroxide	(b) (4)		
Female			
Age 0-11 yrs			
7061 ACNE NEC			
0780 MOLLUSCUM CONTAGIOSUM			
Age 12-45 yrs			
7061 ACNE NEC			
Age 46+ yrs			
7061 ACNE NEC			
7020 ACTINIC KERATOSIS			
7048 HAIR DISEASES NEC			
Unknown Age			
7061 ACNE NEC			
Male			
Age 0-11 yrs			
7061 ACNE NEC			
0780 MOLLUSCUM CONTAGIOSUM			
Age 12-45 yrs			
7061 ACNE NEC			
7048 HAIR DISEASES NEC			
6953 ROSACEA			
Age 46+ yrs			
7061 ACNE NEC			
6953 ROSACEA			
7020 ACTINIC KERATOSIS			
Unknown Age			
Unknown sex			

Source: Encuity Research, LLC., TreatmentAnswers™ with Pain Panel, Dec 2010 - Nov 2015. Extracted December 2015. File: PDDA 2015-2278 Adapalene by gender AgeDx4 1-6-16.xls

**"Drug uses" - refer to the mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. "Drug uses" does not necessarily result in prescription being generated but are the projected number of times a given drug was mentioned during an office visit.*

NEC - Not Elsewhere Classified NOS - Not Otherwise Specified

7.2 APPENDIX B. DRUG UTILIZATION DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail

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

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

IMS, National Prescription Audit

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

IMS Health, Vector One®: Total Patient Tracker (TPT)

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

Encuity Research, LLC., TreatmentAnswers™

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

7.3 APPENDIX C. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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

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

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05

and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

7.4 APPENDIX D. TOPICAL RETINOIDS CURRENTLY MARKETED IN THE US

Generic Name	Trade Name	Formulation	Strength	FDA Application Type/Number/ Related ANDAs	NDA Sponsor	Indication for Use	FDA Approval Date
Adapalene	Differin	Gel	0.1%	NDA 20380 ANDA 90962, 91314	Galderma	acne vulgaris	May 31, 1996
Adapalene	Differin	Cream	0.1%	NDA 20748 ANDA 90824	Galderma	acne vulgaris	May 26, 2000
Adapalene	Differin	Gel	0.3%	NDA 21753 ANDA 200298	Galderma	acne vulgaris	June 19, 2007
Adapalene	Differin	Lotion	0.1%	NDA 22502	Galderma	acne vulgaris	March 17, 2010
Adapalene/ Benzoyl peroxide	Epiduo	Gel	0.1%/2.5%	NDA 22320	Galderma	acne vulgaris	December 8, 2008
Alitretinoin	Panretin	Gel	0.1%	NDA 20886	Eisai	cutaneous lesions in AIDS-related Kaposi's sarcoma	February 2, 1999
Bexarotene	Targretin	Gel	1%	NDA 21056	Eisai	cutaneous lesions in cutaneous T-cell lymphoma	June 28, 2000
Tazarotene	Tazorac	Gel	0.05%, 0.1%	NDA 20600	Allergan	plaque psoriasis, acne	June 13, 1997
Tazarotene	Tazorac	Cream	0.05%, 0.1%	NDA 21184	Allergan	plaque psoriasis	September 29, 2000
Tazarotene	Tazorac	Cream	0.1%	NDA 21184	Allergan	acne vulgaris	October 11, 2011
Tazarotene	Avage	Cream	0.1%	NDA 21184	Allergan	facial fine wrinkling, hypo- and hyper-pigmentation, benign facial	September 30, 2002

Generic Name	Trade Name	Formulation	Strength	FDA Application Type/Number/ Related ANDAs	NDA Sponsor	Indication for Use	FDA Approval Date
						lentigines	
Tazarotene	Fabior	Foam	0.1%	NDA 202428	Stiefel	acne vulgaris	May 11, 2012
Tretinoin	Atralin	Gel	0.05%	NDA 22070	Dow	acne vulgaris	July 26, 2007
Tretinoin	Avita	Cream	0.025%	NDA 20404	Mylan Bertek	acne vulgaris	January 14, 1997
Tretinoin	Avita	Gel	0.025%	NDA 20400	Mylan	acne vulgaris	January 29, 1998
Tretinoin	Renova	Cream	0.05%	NDA 19963 ANDA 76498	Valeant	mitigation of fine wrinkles, mottled hyperpigmentation, tactile roughness of facial skin	December 29, 1995
Tretinoin	Renova	Cream	0.02%	NDA 21108	Valeant	mitigation of fine facial wrinkles	August 31, 2000
Tretinoin	Retin-A	Solution	0.05%	NDA 16921 ANDA 75260	Valeant	acne vulgaris	October 20, 1971
Tretinoin	Retin-A	Cream	0.1%	NDA 17340 ANDA 75213	Valeant	acne vulgaris	January 26, 1973
Tretinoin	Retin-A	Cream	0.05%	NDA 17522 ANDA 75265	Valeant	acne vulgaris	July 19, 1974
Tretinoin	Retin-A	Gel	0.025%	NDA 17579 ANDA 75529	Valeant	acne vulgaris	April 18, 1975
Tretinoin	Retin-A	Gel	0.01%	NDA 17955 ANDA 75589	Valeant	acne vulgaris	October 17, 1978
Tretinoin	Retin-A	Cream	0.025%	NDA 19049 ANDA 75264	Valeant	acne vulgaris	September 16, 1988
Tretinoin	Tretin-X	Cream	0.0375%	ANDA 90098	N/A	acne vulgaris	March 22, 2010
Tretinoin	Retin-A Micro	Gel	0.04%, 0.1%	NDA 20475	Valeant	acne vulgaris	February 7, 1997
Tretinoin/ Clindamycin	Veltin	Gel	0.025%/1.2 %	NDA 50803	Stiefel GSK	acne vulgaris	July 16, 2010

Generic Name	Trade Name	Formulation	Strength	FDA Application Type/Number/ Related ANDAs	NDA Sponsor	Indication for Use	FDA Approval Date
Tretinoin/ Clindamycin	Ziana	Gel	0.025%/1.2 %	NDA 50802	Medicis	acne vulgaris	November 7, 2006
Tretinoin/ Fluocinolone acetonide/ Hydroquinone	Tri-Luma	Cream	0.05%/0.01 %/4%	NDA 21112	Galderma	moderate to severe melasma of the face	January 18, 2002
Tretinoin/ Mequinol	Solage	Solution	0.01%/2%	NDA 20922	Aqua	solar lentigines	December 10, 1999

7.5 APPENDIX E. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS FOR CONGENITAL ANOMALY CASES FROM PREVIOUS DPV REVIEWS

Table 7.5.1. Cases from two previous adapalene associated congenital anomaly reviews (Brinker 2004, Pitts, 2006)

Case #	Location	Congenital Anomaly	Product	When Exposed	Comments
FI20000001	Foreign	Functional anomaly Trampling of feet, swallowing absent, absent primitive reflex; clinical signs of serious brain damage	Adapalene 0.1%	1st trimester Between weeks 6 and 10 of mother's pregnancy	Case previously described by Brinker, 2004
FR19960020	Foreign	Structural malformation Extreme anophtalmia or microphtamia, absence of callus corpus without another malformation, agenesia of the optical chiasma and of the eyeball	Adapalene 0.1%	1st trimester One month before pregnancy, and continued through week 13 of pregnancy	Case previously described by Brinker, 2004 and published in the medical literature
FR199636045.2	Foreign	Structural malformation Living male at 9 months delivered with single kidney and single umbilical artery	Adapalene 0.1%	3rd trimester Applied twice during 9th month of pregnancy	Case previously described by Brinker, 2004.

Table 7.5.1. Cases from two previous adapalene associated congenital anomaly reviews (Brinker 2004, Pitts, 2006)					
Case #	Location	Congenital Anomaly	Product	When Exposed	Comments
FR19970008.2	Foreign	Structural malformation Live male delivered with hypotonia, facial dysmorphy. Aarskog's syndrome suspected (monogenic x-linked recessive disorder) because two oldest sons were born with same syndrome	Adapalene 0.1%	1st trimester Twice daily during 1st 3 months of pregnancy	Case previously described by Brinker, 2004.
USGD0310554	US	Structural malformation Cleft lip, cleft palate, brain,gastric, cardiovascular, intestinal anomalies	Adapalene 0.1% gel	1st, 2nd trimester exposure	Case previously described by Brinker, 2004.
CHGDP0511971	Foreign	Structural malformation Scimitar syndrome which included partial abnormal pulmonary vein drainage, right lung hypoplasia, cardiac arrhythmia, right lower lung sequestration; atrial septum defect, dysplasia of aortic valve, hypospadias glans penis, right inguinal hernia, Dandy walker malformation. Normal caryotype	Adalapene 0.1% gel + topical clindamycin	1st trimester Applied agents during first two weeks of pregnancy	New Case. Some cardiac and brain anomalies; however, total anomalies are inconsistent with retinoid exposure

7.6 APPENDIX F. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS

Table 7.6.2 Cases of adapalene associated abnormal pregnancy outcomes

Case# Version Manufacturer #	Country /Year	Type	Age	Past Medial History	Abnormal Pregnancy Outcome/Event	Drug/Indication	Concomitants	When exposed	Duration of adapalene use	Comments
1. 10084260 1 NL-GALDERMA-NL14001284	Netherlands/2014	15-day	Unknown	Patient had a history of hypertension, tobacco user; patient had one previous abortion and one healthy child	Bilateral club feet	Adapalene 0.1% gel acne	Folic acid Ferrous sulfate epidural	First 14 weeks (1st and 2nd trimester)	One month	
2. 6636807 1 FR-GDP-08403799	France/ 2008	15-day	Unknown	Unknown	VACTERL Syndrome; abortion	Adapalene	doxycycline, topical erythromycin, acetone, methanol, l-propanol, benzene, di chlorethylene, vinyl chloride	Unknown	Unknown	Lack of information
3. 7014857 1 CH-BAYER-200922158GPV	Switzerland/2009	15-day	Unknown	Unknown	anomaly on the left hand of the fetus with brachydactyly, oligodactyly, overlapping fingers was detected in ultrasonography	Adapalene acne	azelaic acid (topical), erythromycin (oral 50 mg)	For seven days during third week (1st trimester)	7 days	Minocycline suspected
4.	US/	15-	28	Pt has a	Genetic defect	Adapalene	Unknown	Used until 21	15 months	

Table 7.6.2 Cases of adapalene associated abnormal pregnancy outcomes										
Case# Version Manufacturer #	**Country /Year**	**Type**	**Age**	**Past Medial History**	**Abnormal Pregnancy Outcome/Event**	**Drug/Indication**	**Concomitants**	**When exposed**	**Duration of adapalene use**	**Comments**
7059072 2 US-GDP- 09406176	2009	day		history of PCN, amoxicillin allergies, gestational diabetes, 6th pregnancy	2q37 deletion abortion	gel 0.3%		weeks (1st and 2nd trimester)		
5. 7703133 2 AT-GDP- 10409245	AUT/201 0	15- day	35		Dandy Walker Syndrome (case in literature with oral isotretinoin) abortion	Adapalene 0.1% qod Mucinosis follicularis		Used until 7 weeks	Approximately 3 months	
6. 8308811 1 CH-GDP- 11412563	Switzerla nd 2011	15- day	35	Unknown	Premature at 36 weeks, no congenital anomalies	Adapalene acne	Unknown	1st trimester	Approximately 2 months	
7. 10280142 2 JP- GALDERMA- JP14002384	Japan/ 2014	15- day	30		miscarriage	Adapalene 0.1% gel QOD acne	Clindamycin heparinoid	Unknown		
8. 10551327 2 GB- GALDERMA- GB14000228	Great Britain/2 014	15- day	Unkn own	Unknown	miscarriage	Adapalene 0.1%	Unknown	4 days in 1st trimester	4 days	
9. 10751357 4 BR- GALDERMA-	Brazil 2015	15- day	35	abortion	miscarriage	Adapalene 0.3% acne	Folic acid Vitamin supplement	1st trimester	10 months	

Table 7.6.2 Cases of adapalene associated abnormal pregnancy outcomes										
Case# Version Manufacturer #	**Country /Year**	**Type**	**Age**	**Past Medial History**	**Abnormal Pregnancy Outcome/Event**	**Drug/Indication**	**Concomitants**	**When exposed**	**Duration of adapalene use**	**Comments**
BR15000241										
10. 61232871 CH-GLAXOSMITHKLINE-B0437080A	Switzerland 2006	15-day	28	Unknown	abortion	Adapalene gel	Salbutamol Citalopram Clindamycin triclosan	1st trimester		
11. 61460222 SE-GDP-0613650	Sweden 2006	15-day	30	Unknown	miscarriage	Adapalene	Unknown	3 days	Four years	
12. 65198962 US-GDP-07403339	US 2008	15-day	30	Penicillin allergy Yeast infection	miscarriage	Adapalene 0.3%	Minocycline Unspecified contraceptive	1st trimester	Four weeks	
13. 68329231 US-GDP-08403747	US 2008	15-day	28	Pregnancy acne	miscarriage	Adapalene 0.1% gel acne	Benzoyl peroxide/clindamycin	1st trimester	6 weeks	
14. 70162331 GR-GDP-09405983	GRC 2009	15-day	32	two prior pregnancies	Miscarriage	Adapalene 0.1%	Doxycycline Azelaic acid	1st trimester	32 days	
15. 85191681 GR-GDP-12413383	GRC 2012	15-day	28		abortion	Adapalene 0.1% gel acne		1st trimester	50 months	
16.	Switzerla	15-	Unkn	Unknown	Miscarriage	Adapalene	Unknown	Unknown	Unknown	Lack of

Table 7.6.2 Cases of adapalene associated abnormal pregnancy outcomes										
Case# Version Manufacturer #	**Country /Year**	**Type**	**Age**	**Past Medial History**	**Abnormal Pregnancy Outcome/Event**	**Drug/Indication**	**Concomitants**	**When exposed**	**Duration of adapalene use**	**Comments**
8572108 1 CH-GDP-12413655	nd 2012	day	own							information
17. 92579913 BR-GALDERMA-BR13001245	Brazil 2013	15-day	28	Hypertension Placenta localized in lower part of uterus	miscarriage	Adapalene 0.3%	Unknown	1st trimester	1 week	
18. 93704032 JP-GALDERMA-JP13001984	Japan 2013	15-day	29	Unknown	hemorrhage	Adapalene 0.1% gel	Unknown	1st trimester	Less than a month	

Table 7.6.3 Cases of tretinoin, tazorotene, bexarotene, and alitretinoin associated abnormal pregnancy outcomes

Case# Version# Manufacturer #	Country/Year	Type	Medical History	Age	Abdnormal Pregnancy Outcome/ Event	Drug/indication	Concomitants	When exposed	Duration of exposure	Comments
1. 102198332 IT-ALLERGAN-1404733US	Italy/ 2014	15-day	Miscarriage, normal pregnancy	33	miscarriage	Tazarotene gel 0.1% acne	None reported	1st trimester	First few weeks of pregnancy, few days/week	Had miscarriage in past
2. 104006941 AU-ALLERGAN-1417801US	Australia/ 2014	15-day	Unknown	23	miscarriage	Tazarotene 0.1% gel acne	venlafaxine	1st trimester	12 days	Lack of information
3. 107500981 US-ALLERGAN-1404651US	US/ 2015	15-day	Unknown	Unknown	miscarriage	Tazarotene cream 0.1%	Unknown	Unknown	Unknown	Lack of information
4. 30496841 961210107056225	USA/ 1997	15-day	Had isotretinoin in past but d/c'd 12 months prior to pregnancy	26	Spina bifida dx by ultrasound/ alpha fetoprotein testing	Retin A cream 0.05%	Unknown	1st and 2nd trimester	First 30-40 days	No other information
5. 30599961 970909107055279	USA/ 1997	15-day	Has 3 children; Denies any other relevant medical history	29	miscarriage	Retin A cream 0.05% Retin A Micro Gel 0.1% (applied to legs, abdomen, buttocks for stretch marks)	APAP with codeine, Multivitamin, mineral supplement	1st trimester	Approximately during first seven weeks of pregnancy	Use in large body surface area and 2 different retinoids
6.	UK/	15-	Unknown	32	miscarriage	Retin A 0.05%	Trimethoprim	Unknown	Unknown	Lack of information

Table 7.6.3 Cases of tretinoin, tazorotene, bexarotene, and alitretinoin associated abnormal pregnancy outcomes

Case# Version# Manufacturer #	Country/Year	Type	Medical History	Age	Abdnormal Pregnancy Outcome/ Event	Drug/indication	Concomitants	When exposed	Duration of exposure	Comments
3069516 1 970318005010 814	1997	day				(form unknown)	200 mg BID			
7. 3117781 1 199803163	US/ 1998	15-day	Plaque psoriasis	27	Trisomy 18	Tazarotene gel 0.1%		1st trimester	Over 2 months	Used over 30% of body surface; no genetic abnormality in either family
8. 3119991 1 980508-107053405	US 1998	15-day			Coarctation of the aorta, hypoplastic left hand, hypertelorism, small ear canals	Tretinoin 0.05%	Topical benzoyl peroxide 2.5% Doxycycline 100 mg BID	1st trimester (first 2 months)	First 2 months	Karyotype was normal; family revealed no evidence of congenital disease
9. 3238600 2 990226-107051423	US 1999	15-day	Miscarriage in 1st trimester x2 in past 10 months	43	miscarriage	Tretinoin 0.05% (Renova)	Vitamins (unspecified)	1st trimester (?)	67 days	Had miscarriages in past
10. 3254173 4 PRIUSA19990 00493	US 2000	15-day			Microtia, atresia, and possible retardation	Tretinoin cream 0.035% Father was on isotretinoin	Prenatal vitamins	1st trimester	Approx 10 months	She used over face and large surface area of back
11. 3329202 1 PRIUSA19990 04817	US 1999	15-day		32	miscarriage	Tretinoin cream 0.05%	Unknown	1st trimester	"for years"	No other information
12. 3931450 1 200302932	US 2003	15-day	Patient had 2 pregnancies in past	29	miscarriage	Tazarotene 0.05% cream BID psoriasis		1st trimester	Two weeks	Used on knees, legs, elbows, ankles, under breasts

Table 7.6.3 Cases of tretinoin, tazorotene, bexarotene, and alitretinoin associated abnormal pregnancy outcomes

Case# Version# Manufacturer #	Country/Year	Type	Medical History	Age	Abdnormal Pregnancy Outcome/ Event	Drug/indication	Concomitants	When exposed	Duration of exposure	Comments
13. 39726332 US-JNJFOC-20030701392	US 2003	15-day	Sickle cell trait, speech impediment; newborn brother died (unknown cause);maternal uncle and his child have cleft palate	30	Cleft lip and palate; elective abortion	Retin A microsphere 0.1% gel acne	APAP Prenatal vitamins	"early in pregnancy"	One month	
14. 41962572 200407162	US 2004	15-day	Infertility	39	miscarriage	Tazarotene 0.05% cream (frequency unknown) acne	Fluticasone nasal loratadine	1st trimester	Two weeks	Patient had a blighted ovum
15. 42132811 200407751	LBN 2004	15-day	Rhesus positive Immunization against rubella and toxoplasmosis, tobacco use (40 cigarettes/day)	19	miscarriage	Tazarotene 0.05% gel QD Psoriasis on elbows and knees	No concomitant medications	1st trimester	One month	
16. 44874231 RETA60	US 1986	15-day	Not reported	Not reported	Miscarriage, then D&C	Retin A cream 0.05%	Not reported	Not reported	Several months	Lack of information
17. 45725451 RETA100 Literature	US 1985	15-day	Virus during 1st trimester	31	Microcephaly, agenesis of corpus callosum,	Retin A gel 0.01%, 0.025%; acne	diphenhydramine triamcinolone 0.025% for acne		Four years	Litigation

Table 7.6.3 Cases of tretinoin, tazorotene, bexarotene, and alitretinoin associated abnormal pregnancy outcomes

Case# Version# Manufacturer #	Country/Year	Type	Medical History	Age	Abdnormal Pregnancy Outcome/ Event	Drug/indication	Concomitants	When exposed	Duration of exposure	Comments
							scopolamine			
18. 46268351 RETA307	US 1988	15-day			widely spaced horns of lateral ventricles, craniofacial dysmorphia, hypoastic supraorbital ridge, prominent eyes, hypoteloris m, beak nose, low ears, moderately high palate, bifid uvula, oxycephaly	Retin A gel as DW	Benzoyl peroxide, Prenatal vitamins, APAP, Dimetapp			Litigation; vitamin A and beta carotene levels normal for patient and mother
19. 46341241 RETA318	US 1989	15-day	Not reported	37	Partial cleft palate	Retin A cream 0.05%	Not reported	1st trimester	7 weeks	
20. 46369481	US 1989	direct	None	29	Anencephaly; elective abortion	Retin A cream	None	1st trimester	7 months	
21. 46408261 RETA333	US 1989	15-day	Denied drug, alcohol, tobacco use, denies illness	29	Myelomenin gocele; elective abortion	Retin A 0.5% cream	Clindamycin once per reporter, vitamins	1st trimester	4 months	Negative for history of neural tube defects
22. 4648970	US 1989	15-day	No history of birth defects	21	gastroschisis	Retin A cream 0.05%	None	1st trimester	1 month	

Table 7.6.3 Cases of tretinoin, tazorotene, bexarotene, and alitretinoin associated abnormal pregnancy outcomes

Case# Version# Manufacturer #	Country/Year	Type	Medical History	Age	Abdnormal Pregnancy Outcome/ Event	Drug/indication	Concomitants	When exposed	Duration of exposure	Comments
1 RETA362						acne				
23. 4658487 1 RETA392	US 1989	15-day	Denies history of alcohol use, viral disease	36	Encephalocele, single orbit, holoprosencephaly, minor amniotic bands, one finger missing	Retin A cream (strength unspecified) acne	psoralen	Unknown	unknown	
24. 4746619 1 90104746	US 1990	15-day	Unknown	unknown	Double aortic arch, Vocal cord paralysis	Retin A cream 0.05% acne	Unknown	Unknown	Unknown	
25. 4816354 1 91104944	US 1991	15-day	Unknown	unknown	Facial palsy, cleft palate, PDA, hearing loss, partial blindness, calcium deficiency	Retin A (strength unspecified)	Unknown	1st trimester	unknown	
26. 4834374 1 4834374	US 1991	15-day	Viral infection		No left forearm or hand	Retin A gel 0.025% acne	Macrodantin, benzoyl peroxide, erythromycin	1st trimester	Approx 3 months	Litigation; report states defect caused by amniotic band syndrome
27. 4917371 1	US 1992	15-day	None reported	16	Stillborn, holoprosencephaly with cebocephaly	Tretinoin 0.1% rash	TAC ointment Triamcinolone acetonide, carboxymethyl	Unknown	5 days	Negative family history of birth defects; autopsy normal

Table 7.6.3 Cases of tretinoin, tazorotene, bexarotene, and alitretinoin associated abnormal pregnancy outcomes

Case# Version# Manufacturer #	Country/Year	Type	Medical History	Age	Abdnormal Pregnancy Outcome/ Event	Drug/indication	Concomitants	When exposed	Duration of exposure	Comments
					cleft palate		lcellulose, polysorbate, sodium chloride, benzyl alcohol, hydroxychloride			chromosomes
28. 49179091	AUS 1992	direct	None reported	33	Central cleft palate, fused papebral fissures, shallow empty orbits, depressed nasal bridge, hypertelorism	Retin A cream 0.05% acne	None reported	Entire pregnancy	22 months	
29. 50374091 930914016011918	AUS 1993	15-day	Unknown	33	Cleft palate	Retin A lotion (unknown form, strength) acne	Folic acid multivitamins	1st trimester	5 months	
30. 50374261 930914016011919	AUS 1994	15-day	Normal pregnancy x 2	Unknown	Urogenital malformation (missing kidney),bronchospam, strabismus	Retin A cream (strength unspecified) acne	Ascorbic acid, APAP	1st trimester	2 months	
31. 50790871 940111016010067	AUS 1994	15-day	Unknown	33	Malformed fingers of the left hand, thumb small, other	Retin A ointment	Unknown	Unknown	Unknown	Lack of information

Table 7.6.3 Cases of tretinoin, tazorotene, bexarotene, and alitretinoin associated abnormal pregnancy outcomes

Case# Version# Manufacturer #	Country/Year	Type	Medical History	Age	Abdnormal Pregnancy Outcome/ Event	Drug/indication	Concomitants	When exposed	Duration of exposure	Comments
					fingers missing terminal phlanges					
32. 5079088 1 940111016010 066	AUS 1993	15-day	Unknown	33	Congenital cataract	Retin A cream	None reported	Entire pregnancy	Prior to and during pregnancy	Lack of information
33. 5079134 1 940111016010 064	AUS 1994	15-day	Unknown	Unknown	gastroschisis	Retin A cream (strength unspecified)	Unknown	1st trimester (exposed 2 weeks)	Four weeks	Lack of information
34. 5082365 1 940111016010 065	AUS 1994	15-day	Unknown	Unknown	Hypoplastic left heart syndrome, died	Tretinoin (dosage form/strength unspecified)	Unknown	1st trimester	Six weeks of pregnancy	Lack of information
35. 5103958 1	US 1994	15-day	Had previous miscarriage on RetinA	Unknown	Craniofacial deformity, absent corpus collosum, enlarged ventricles, right microphtalmus, deformed ear, short leg, deformed lip and palate,	Retin A 0.05% acne	Benzoyl peroxide, erythromycin, prenatal vitamins Calcium sulfate	1st trimester	More than a year	Lack of information

Table 7.6.3 Cases of tretinoin, tazorotene, bexarotene, and alitretinoin associated abnormal pregnancy outcomes										
Case# Version# Manufacturer #	**Country/Year**	**Type**	**Medical History**	**Age**	**Abdnormal Pregnancy Outcome/ Event**	**Drug/indication**	**Concomitants**	**When exposed**	**Duration of exposure**	**Comments**
					partial aplasia of optic nerves, imperforate anus, diagnosed goldenhar syndrome					
36. 51906751 941213107050582	US 1994	15-day	Unknown	Unknown	Missing 3 fingers, and shortened 4th finger	Retin A cream 0.025%	Topical clindamycin	1st trimester	8 months	Lack of information
37. 53390541 951129107052346	US 1995	15-day	Unknown	Unknown	Neuroblastoma of the mediastinum	Retin A cream 0.025% and Retin A 0.05% to abdomen 3x/week	Albuterol inhaler once or twice during pregnancy	3rd trimester	2-3 months	Lack of information
38. 53949811 0010945960174	US 1996	15-day	Partial complex seizures, stroke	27	Amniocentesis showed fetus had 69 chromosomes; triploidy; elective abortion	Retin A 0.01% gel	Gabapentin 400 mg QID, tetracycline 250 mg BID, Clindamycin solution	Unknown is ongoing	Short while before pregnancy	
39. 54391951 960807107053471	US 1996	15-day	Unknown	Unknown	Transpositif the great vessels	Retin A (strength, form, unknown)	Unknown	Unknown	6-7 weeks	Lack of information
40. 56592642	US 2004	15-day	Unknown	31	Miscarriage; fetus anencephalic	Tazarotene 0.05% cream once q 2-3 days	Unknown	1st trimester	3 months	Patients folate levels low; dermatologist stated that

Table 7.6.3 Cases of tretinoin, tazorotene, bexarotene, and alitretinoin associated abnormal pregnancy outcomes

Case# Version# Manufacturer #	Country/Year	Type	Medical History	Age	Abdnormal Pregnancy Outcome/ Event	Drug/indication	Concomitants	When exposed	Duration of exposure	Comments
200409149						acne				miscarriage not secondary to medication
41. 5716675 3 200409491	US 2005	15-day	toxemia of pregnancy 2 weeks prior delivery, 1 prior pregnancy without complications	33	Patient had single umbilical artery; tracheoesophageal fistula, esophageal atresia, tracheomalacia, laryngomalacia, GERD	Tazarotene 0.01% cream acne	Prenatal vitamins	1st trimester	1 month	
42. 5725200 2 200401255	US 2005	15-day	unknown	39	miscarriage	Tazarotene gel 0.05% acne	unknown	1st trimester	5 weeks	
43. 5725202 1 200218953	US 2005	15-day	unknown	30	Elective abortion	Tazarotene gel 0.01% acne	tetracycline	1st trimester	5 weeks	
44. 5726411 3 200310413	US 2005	15-day	unknown	32	anencephaly	Tazarotene cream 0.05% acne	Thyroid medication (unspecified)	1st and part of 2nd trimester	Four months	
45. 5726475 1 200500414	US 2005	15-day		30	Nail disorder	Tazarotene gel 0.01% Acne	Calcium citrate Prenatal vitamins	1st and part of 2nd trimester	Eight months	
45. 5726476	US 2000	15-day	Unknown	Unknown	Elective abortion	Tazarotene gel 0.01%	Unknown	Unknown	Unknown	Patient terminated pregnancy for many

Table 7.6.3 Cases of tretinoin, tazorotene, bexarotene, and alitretinoin associated abnormal pregnancy outcomes										
Case# Version# Manufacturer #	**Country/Year**	**Type**	**Medical History**	**Age**	**Abdnormal Pregnancy Outcome/ Event**	**Drug/indication**	**Concomitants**	**When exposed**	**Duration of exposure**	**Comments**
1 200210426										reasons; primarily due to tazarotene
47. 57270472 200500172	US 2005	15-day	Unknown	Unknown	Two right sided ureters, acute dysplasia (bald spot on top of head)	Tazarotene cream 0.05% Acne	Benzoyl peroxide	1st trimester	2 months	
48. 57279981 200500188	US 2005	15-day	Unknown	Unknown	Congenital pilonidal dimple at the spinal cord	Tazarotene cream 0.05% Acne	Unknown	Unknown	Unknown	Used only 2-3 times while pregnant
49. 57280011 200312575	US 2005	15-day	Unknown	Unknown	Miscarriage due to unspecified chromosomal abnormalities	Tazarotene cream 0.1% Acne	Unknown	1st trimester	Four weeks	
50. 57287641 200110749	France 2005	15-day	psoriasis	Unknown	Miscarriage, patient had a large uterus fibroma	Tazarotene 0.05% psoriasis	Unknown	1st trimester	Three weeks	
51. 57342881 200407100	US 2004	15-day			Miscarriage	Tazarotene				Lack of information
52. 60830152 0601756US	US 2006	15-day	Seven pregnancies, 4 miscarriages,	24	miscarriage	Tazarotene 1% cream clinical trial	None	1st trimester	Approx. 2 months	

Table 7.6.3 Cases of tretinoin, tazorotene, bexarotene, and alitretinoin associated abnormal pregnancy outcomes

Case# Version# Manufacturer #	Country/Year	Type	Medical History	Age	Abdnormal Pregnancy Outcome/ Event	Drug/indication	Concomitants	When exposed	Duration of exposure	Comments
			1 elective abortion, one molar pregnancy, one normal vaginal delivery							
53. 61103581 CH-JNJFOC-20060801898	Switzerland 2006	15-day	Social history not specified	40	2 miscarriages Approx. a year apart	Retin A cream daily, then 2-3x/week	Unknown	Unknown	At least 1 year	
54. 64784561 GB-JNJFOC-20071001255	Great Britain 2007	15-day	2 normal pregnancies in past; no history of substance abuse, no risk factors	Unknown	miscarriage	Retin A	unknown	1st trimester		
55. 65452961 DSA_31321_2008	US 2008	15-day	Unknown	Unknown	Congenital hernia, perforated bowel	Retin A	Lorazepam Venlafaxine, dexamethasone, erythromycin, hydrocodone, Ibuprofen, Retin A, estazolam, amitriptyline, sumatriptan, methadone, carisoprodol, hyoscyamine, IV gamma	1st and 2nd trimester	14 weeks	Multiple concomitant medications

Table 7.6.3 Cases of tretinoin, tazorotene, bexarotene, and alitretinoin associated abnormal pregnancy outcomes

Case# Version# Manufacturer #	Country/Year	Type	Medical History	Age	Abdnormal Pregnancy Outcome/ Event	Drug/indication	Concomitants	When exposed	Duration of exposure	Comments
							globulin, cefadroxil, azithromycin, beclomethasone, ipratropium			
56. 66950402 US-ALLERGAN-0807131US	US 2008	15-day	Unknown	23	miscarriage	Tazarotene cream 0.05% Acne	Escitalopram oxybutynin	1st and 2nd trimester		
57. 67447581 US-JNJFOC-20080805890	US 2008	15-day	Patient had one elective abortion in the past	29	miscarriage	Tretinoin gel 0.1% (Retin A Micro) acne	Unknown	1st trimester		
58. 68043951 US-ALLERGAN-0813843US	US 2008	15-day	Patient did not smoke, drink	34	Premature atrial contractions, ventricular septal effect, patent foramen ovale, and patent ductus arteriosis	Tazarotene 1% cream	No tocolytic agents were used	Entire pregnancy	Approx. 1 year	
59. 68304761	US 2008	Direct		40	Report from OB reporting fetal death in a term infant	Tazarotene	Unknown	"early in pregnancy"	Unknown	

Table 7.6.3 Cases of tretinoin, tazorotene, bexarotene, and alitretinoin associated abnormal pregnancy outcomes										
Case# Version# Manufacturer #	**Country/Year**	**Type**	**Medical History**	**Age**	**Abdnormal Pregnancy Outcome/ Event**	**Drug/indication**	**Concomitants**	**When exposed**	**Duration of exposure**	**Comments**
					delivered by cesarean complicated Severely impacted vertex requiring traction to release maternal head from pelvis; nothing used to cause head to stick; reduction to singleton					
60. 68663281 US-ALLERGAN-0701780US	US 2008	15-day	Unknown	Unknown	Elective abortion	tazarotene	Unknown	Unknown	Unknown	
61. 69290741 GB-VALEANT-2009VX000328	Great Britain 2009	15-day	2 normal pregnancies	Unknown	miscarriage	tretinoin	Unknown	1st trimester	68 days	
62. 70244191	Cyprus 2009	15-day	Unknown	Unknown	Elective abortion	Tretinoin gel Acne	Unknown	1st trimester	2 months	

Table 7.6.3 Cases of tretinoin, tazorotene, bexarotene, and alitretinoin associated abnormal pregnancy outcomes

Case# Version# Manufacturer #	Country/Year	Type	Medical History	Age	Abdnormal Pregnancy Outcome/ Event	Drug/indication	Concomitants	When exposed	Duration of exposure	Comments
CY-JNJFOC-20080104391										
63. 7368512 AU-JNJFOC-20100407103 Literature	Australia 2010	15-day	Unknown	Unknown	Supraumbilical exomphalos, anterior diaphragmatic hernia, inferior pericardial defect consisting of hypoplastic scapula and humerus, absence of radius and ulna, fused 4th and 5th metacarpals, mildly hypoplastic hand with a small thumb and 5th digit	Topical tretinoin alcohol based liquid preparation 0.05% acne	Unknown	1st trimester	First 5 weeks	Topical fluid preparation of 0.05% tretinoin with 45% alcohol available in Australia without a prescription
64. 73754491 US-ALLERGAN-1005617US	US 2010	15-day	Unknown	Unknown	miscarriage	Tazarotene cream	Unknown	1st trimester	6 weeks	Lack of information
65. 80469781	US 2011	15-day	Unknown	Unknown	Elective abortion due to	Tretinoin 0.02% cream	Unknown	Unknown	Unknown	Lack of information

Table 7.6.3 Cases of tretinoin, tazorotene, bexarotene, and alitretinoin associated abnormal pregnancy outcomes

Case# Version# Manufacturer #	Country/Year	Type	Medical History	Age	Abdnormal Pregnancy Outcome/ Event	Drug/indication	Concomitants	When exposed	Duration of exposure	Comments
US-JNJFOC-20110706189					developmental cyst					
66. 87505121	US 2011	direct	Unknown	Unknown	TAPVD	Tazarotene cream Acne	unknown	1st trimester	unknown	
67. 92619971 US-ALLERGAN-1306072US	US 2013	15-day	hypertension	Unknown	Skeletal dysplasia, died later	Tazarotene cream 0.05%	Unspecified antihypertensive	1st trimester	5 weeks	
68. 95174572 US-ALLERGAN-1313462US	US 2013	15-day	One full term birth	21	miscarriage	Tazarotene gel 0.01% Acne	Cephalexin 500 mg for acne	1st trimester	20 months	Patient declines any concurrent medical conditions, exposure to X –ray, teratogens, alcohol, or smoking, no known allergies

7.7 APPENDIX G. DEPI TABLES AND FIGURES

7.7.1 Table1. Summary of studies on the safety of topical retinoids in literature

Author (Year)	Study Design	Exposure	Outcome	Cohort Size	Result	Comment
				Pregnancy Outcomes		
Jick (1993)	retrospective cohort	topical tretinoin	major congenital disorders	exposed: 215, controls: 430	RR=0.7 (0.2-2.3)	1. Exposed to topical tretinoin in the first trimester of pregnancy. 2. Stillbirth and fetal death (3 in exposed and 3 in controls) were excluded in the analyses. 3. aged matched.
Shapiro (1997)	prospective cohort	topical tretinoin	pregnancy outcomes, major malformations in live births, mean	exposed: 94, controls: 133	1. No significance difference in the rates of live births, miscarriages, elective terminations of pregnancy, and major malformations. 2. Mean birthweight which was borderline modestly but statistically lower in cases exposed women (***P=0.05***).	1. Exposed to topical tretinoin in the first trimester of pregnancy.

			birthweight			2. matched with similar maternal age, patterns of smoking, and alcohol use.
Loureiro (2005)	prospective cohort	topical tretinoin	birth outcomes, minor malformations	exposed: 106, controls: 389	No difference	Exposed to topical tretinoin in the first trimester of pregnancy.
Kaplan (2015)	meta-analysis	topical tretinoin	pregnancy outcomes	exposed: 654, controls: 1,375	major congenital malformations: OR=1.22 (0.65-2.29) spontaneous abortions: OR=1.02 (0.64-1.63) stillbirth: OR=2.06 (0.43-9.86) elective termination: OR=1.89 (0.52-6.80) low birthweight: OR=1.01 (0.31-3.27) prematurity: OR=0.69 (0.39-1.23)	Exposed to topical tretinoin in the first trimester of pregnancy.
Panchaud (2012)	prospective cohort	topical retinoids	congenital malformations	exposed: 235 (tretinoin 143, isotretinoin 52, adapalene 24, retinoic acid 10, motretinide 1, combination 5),	spontaneous abortion: OR=1.5 (0.8-2.7) minor bith defects: OR=1.3 (0.4-2.7) major bith defects OR=1.8 (0.6-5.4) elective termination: ***OR=3.4 (1.5-7.8)***	Exposed to topical tretinoin in the first trimester of pregnancy.

				controls: 444		
Other Serious Adverse Effects						
Alhusaye n (2013)	retrospect ive cohort	1. oral isotretinoin 2. topical acne medication (benzoyl peroxide, erythromy cin, clindamyci n, retinoic acid, or adapalene)	inflammatory bowel disease (IBD)	oral isotretinoi n: 46,922 topical acne medicatio n: 184,824 control: 1,526,946	1. oral isotretinoin and IBD: all patients: RR=1.14 (0.99-1.24) patients aged 12-19: ***RR=1.39 (1.03-1.87)*** 2. topical acne medication and IBD RR=1.11 (0.99-1.24) 3. topical acne medication and Ulcerative Colitis ***RR=1.19 (1.00-1.42)***	
Weinstoc k (2009)	RCT	topical tretinoin	all-cause mortality	1,113	***OR=1.54 (1.10-2.15)***	1. Veterans Affairs Topical Tretinoin Chemopreven tion trial (VATTC). 2. Mean age: 71 years
Cutanous Adverse Effects						

Tirado-Sanchez (2013)	RCT	adapalene 0.1% and 0.3%, tretinoin 0.05%	efficacy and safety	171	adapalene 0.1% vs adapalene 0.3% and tretinoin 0.05%: Skin irritation (dermatitis): ***P<0.05*** scaling: ***P<0.05*** dry skin: ***P<0.05*** pruitus: ***P<0.05*** burning: ***P<0.05*** postinglammatory hyperpigmentation: ***P=0.001*** total adervse events: ***P<0.05*** patients reporting adverse events: ***P<0.05***
Feldman (2013)	RCT	Tazarotene 0.1%	efficacy and tolerability	first study: 744 second study: 742	Only application-site skin irritation and dryness were reported by >5% of participants in active treatment groups in both studies
Goh (2009)	RCT	adapalene 0.1% , tretinoin 0.025%	erythema, desquamation, dryness, stinging/burning, pruritus, irritation, pruritus, colorimetry, trans-epidermal water loss	73	The irritation potential of adapalene gel 0.1% was significantly lower than that of tretinoin gel 0.025% in all tolerability assessment
Kawashima (2008)	RCT	adapalene 0.1%	efficacy and safety	200	well tolerated. Adverse events were mostly mild-to-moderate and transient in nature compared with gel vehicle.

Ioannides (2002)	RCT	adapalene 0.1%, isotretinoin gel 0.05%	efficacy and tolerability	80	adapalene 0.1% vs isotretinoin gel 0.05% at week 12: erythema 27.8% vs 41.9%, ***P<0.05*** scaling 25.0% vs 41.9%, ***P<0.05*** pruitus-burning 30.6% vs 45.2%, ***P<0.05***
Dunlap (1998)	RCT	adapalene 0.1%	skin tolerance (erythema, skin dryness, desquamation and burning/stinging), patient perference	100	compared to tretinoin 0.025% cream: 1. 64-68% of patients found adapalene 0.1% gel more tolerable than tretinoin 0.025% cream, ***P<0.05*** 2. 65% of patients preferred adapalene 0.1% gel, ***P=0.003*** 3. adapalene 0.1% gel was significantly less irritating to the skin in terms of producing erythema, dryness, desquamation and burning/stinging, ***P<0.02***
Rao (2009)	RCT	microsphere adapalene 0.1%, conventional adapalene 0.1%	efficacy, safety, tolerability	175	microsphere adapalene vs conventional adapalene: 1. reported side effect: 50% vs 71.3%, ***P<0.05*** 2. dryness: 7.9% vs 32.2%, ***P<0.01*** 3. erythema: 7.9% vs 25.3%, ***P<0.01***
Ellis (1998)	RCT	adapalene 0.1%, tretinoin 0.025%	efficacy and safety	adapalene: 149 tretinoin: 148	1. no serious adverse events reported 2. skin reactions (burning, pruritus, scaling, dryness and erythema) were similar between adapalene and tretinoin treatment

Figure 1. Meta-analysis of major congenital malformation rates in topical-retinoid-exposed vs. control infants. (Kaplan et al 2015)

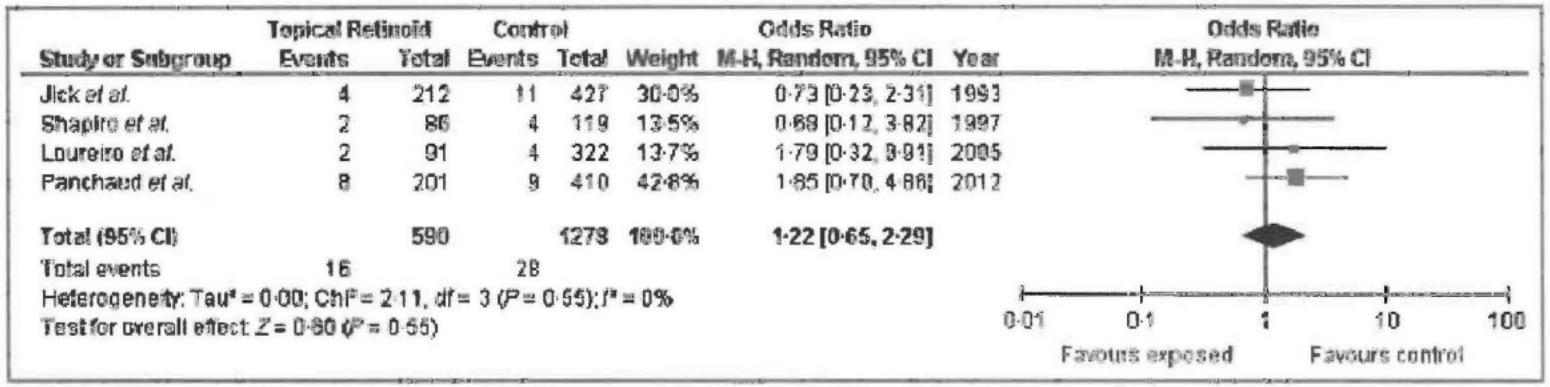
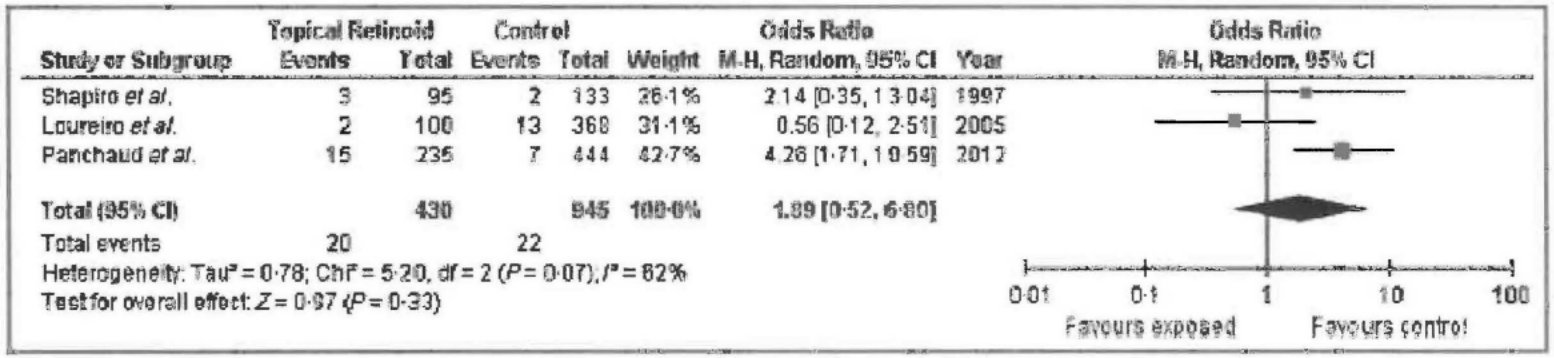


Figure 2. Meta-analysis of elective termination of pregnancy rates in topical-retinoid-exposed vs. control pregnancies. (Kaplan et al 2015)



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M E M O R A N D U M

From:	Mona Khurana, MD, Medical Officer Division of Pediatric and Maternal Health Office of Drug Evaluation IV
Through:	Hari Cheryl Sachs, MD, Medical Team Leader John Alexander, MD MPH Acting Deputy Director
To:	Division of Nonprescription Drug Products
Proprietary Name:	Differin Gel, 0.1%
Active Ingredient:	Adapalene
Drug Category:	Topical synthetic retinoid-like
Sponsor:	Galderma Laboratories, L.P.
Subject:	Prior approval efficacy supplement for Rx to OTC switch
PDUFA Goal Date:	July 10, 2016

Materials Reviewed

- Submission history for supplemental new drug application (sNDA) 020380/S-010 in DARRTS (accessed 1/5/16)

- Documents submitted under Investigational New Drug (IND) 116864 in DARRTS (accessed 1/5/16)
- Labeling information and approval dates for adapalene single-ingredient and combination drug products at Drugs@FDA (accessed 1/8/16)

Consult Request:

The Division of Nonprescription Drug Products (DNDP) consulted the Division of Pediatric and Maternal Health (DPMH) for advisory committee (AC) preparation for this prior approval efficacy supplement which proposes a full prescription (Rx) to over-the-counter (OTC) switch for 0.1% Differin Gel for topical treatment of acne in adults and pediatric patients 12 years of age and older. DNDP is requesting DPMH's expertise to help determine if adapalene may be used by OTC adolescent consumers safely and effectively without prescriber oversight.

I. Topical Adapalene Drug Products

Four topical dosage forms containing adapalene are approved for prescription treatment of acne vulgaris in the United States under the trade name Differin. Two fixed-dose combination gels containing adapalene and benzoyl peroxide have also been approved under the trade name Epiduo. Epiduo gel is the only drug product approved for use in pediatric patients down to age 9 years, while all other approved adapelene drug products are approved for use only in patients' age 12 years and older. See Table 1.

DPMH Comments: The lack of approval for use of single-ingredient topical adapalene drug products in younger pediatric patients is unlikely to be based on lack of demonstrated efficacy or on safety concerns. Since approval of most Differin drug products pre-dated PREA, early acne programs focused on 12 years and older and pediatric studies in younger patients were not mandated. Consequently, when the NDA for Differin lotion 0.1% was submitted in 2009, FDA waived PREA studies in patients less than 12 years of age but requested a pharmacokinetic study under maximum use conditions in adolescents 12 years to 17 years of age. For newer acne programs such as Epiduo, drugs are studied in pubertal patients down to 9 years of age since 12 years of age is no longer considered to be the lower end of range for the age of acne vulgaris onset.[1] *Epiduo was initially approved for use down to age 12 years, but FDA issued a PREA post-marketing requirement (PMR) for the sponsor to conduct pediatric studies in patients 9 years to 11 years of age. FDA waived the pediatric study requirement for patients less than 9 years of age. The sponsor fulfilled this PREA PMR, resulting in FDA approval to expand the*

[1] Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-Based Recommendations for the Diagnosis and Treatment of Pediatric Acne. Pediatrics 131 (Supplement 3), 2013.

pediatric indication down to age 9 years on February 1, 2013. When Epiduo Forte was approved in 2015, FDA waived the pediatric study requirement for patients less than 12 years of age on the basis that the product does not represent a meaningful benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients in this age group.

Table 1. Topical adapalene-containing drug products approved for U.S. marketing to date*

Differin Product	NDA#	Approval Date	Pediatric Use	Marketing Status	PREA PMR
Gel, 0.1%	020380	May 31, 1996	12 years and older	Rx	No
Solution, 0.1%	020338	May 31, 1996	12 years and older	D/C	No
Cream, 0.1%	020748	May 26, 2000	12 years and older	Rx	No
Gel, 0.3%	021753	June 19, 2007	12 years and older	Rx	No
Epiduo gel[2]	022320	December 8, 2008	9 years and older	Rx	Yes
Lotion, 0.1%	022502	March 17, 2010	12 years and older	Rx	No
Epiduo Forte gel[3]	207917	July 15, 2015	12 years and older	Rx	No

Source: Created by this reviewer from labeling information retrieved from Drugs@FDA; accessed 1/8/16 using search term "Differin"

Rx: prescription; D/C: discontinued

*Galderma is the sponsor for all drug products listed in this table

II. Regulatory History of this Application

The sponsor submitted a Prior Approval Efficacy Supplement for a full Rx to OTC switch for the 0.1% gel formulation of Differin on September 10, 2015. This application was submitted via the 505(b)(1) regulatory pathway and is undergoing a standard review. A Nonprescription Drugs AC meeting is planned for April 15, 2016 since this application proposes a first-in-class OTC switch for a topical retinoid-like drug product. Given the known teratogenicity risks of oral retinoids and retinoid-like drugs, the AC discussion will focus on whether or not female consumers with reproductive potential can safely use this topical retinoid-like drug product without prescriber oversight.

This application does not trigger a pediatric assessment under PREA because the proposed OTC drug product will be identical to the existing prescription drug product in terms of indication, strength, dosage, formulation, manufacturing process, and route and frequency of administration. All other approved Differin drug products will continue to be marketed by prescription (see Section III).

[2] This is a fixed-dose combination gel containing 0.1% adapalene with 2.5% benzoyl peroxide indicated for treatment of acne vulgaris

[3] This fixed-dose combination gel contains a higher adapelene concentration of 0.3% with the same benzoyl peroxide concentration of 2.5%

The studies included in this submission were conducted under IND 116864 and consist of the following:

1. Pharmacokinetic (PK) maximal usage trial (Study 18254)
2. Pivotal label comprehension study (Study 100544, Protocol 13048)
3. Pivotal targeted self-selection study (Study 103439, Protocol 14043)
4. Actual use study (Study 100931, Protocol 13049)
5. Rx standard of care study (Study 102234, Protocol 13050)

The sponsor did not conduct or submit new non-clinical studies with this application in support of the OTC switch. The sponsor is not proposing to make any changes in Chemistry, Manufacturing, and Control (CMC) processes.

DNDP also consulted the following Office of Surveillance and Epidemiology (OSE) divisions for assistance with AC meeting preparation:

- The Division of Pharmacovigilance to assess post-marketing data for any safety signals
- The Division of Epidemiology to conduct a literature search to identify and evaluate any safety signals
- Drug Utilization Analysis staff to describe adapalene use by age and sex

III. Pediatric-Focused Review of Submission Contents

A. PK Maximal Usage Trial (MUsT)

The MUsT was a multi-center, open-label PK study in 24 adults and adolescents 12 years of age or older with moderate to severe facial acne vulgaris. The primary objective of the study was to assess the systemic exposure to adapalene under maximal use conditions for 4 weeks. Adapalene gel 0.1% (Differin Gel 0.1%) was applied once daily for 29 days on the face, shoulders, upper chest and upper back. All 24 enrolled subjects (6 adults and 18 adolescents, ages 12 years to 17 years) completed the study. Per the sponsor, systemic concentrations of adapalene were low but quantifiable (lower limit of quantification 0.02 nanograms/milliliter [ng/mL]) in 63% of (15/24) subjects after the first topical application and in 100% of subjects after 4 weeks of daily application. The mean ± standard deviation (SD) maximal plasma concentration (Cmax) and area under the curve ($AUC_{0\text{-}24hours}$) on Day 29 were 0.049 ± 0.030 ng/mL and 0.83 ± 0.43 ng·hour/mL, respectively. The patient with the highest C_{max} and AUC was a 16 year old male who received 1.89 grams (g) of study drug on 1,899 squared centimeters

(cm^2) of body surface area (BSA) daily. Quantifiable plasma adapalene levels were observed in this patient as early as after the first application. The highest systemic exposure was observed at Day 29 with a Cmax value of 0.171 ng/mL and an $AUC_{0\text{-}24h}$ of 2.897 ng·hour/mL.

DPMH Comments: DPMH defers to Pharmacology/Toxicology to determine how the systemic exposures detected in the MUsT compare to the no observed adverse event level established in non-clinical studies.

B. Pivotal Label Comprehension Study (Protocol 13048)

This label comprehension Study (LCS) was a single-visit, interview-only study conducted at eight geographically-dispersed market research facilities in 586 consumers 12 years of age and older. Approximately 54.7% (321/586) of enrolled consumers were adolescents 12 years to 17 years of age. The primary communication objectives in the study tested consumer understanding of the following warning and directions on the proposed Drug Facts Label (DFL):

1) Do not use on damaged skin (cuts, abrasions, eczema, sunburned)

2) Directions: a) Use once daily

According to the sponsor, results showed that label comprehension scores for both primary communication objectives exceeded the pre-specified threshold (a two-sided lower bound 95% confidence interval [CI] of 85%). The sponsor found that sub-group analysis by age showed scores between adult and adolescent subjects closely paralleled each other. Comprehension rates for eight of the ten secondary communication objectives reportedly ranged from 87.6% to 100%. Notably, only 77.5% (399/515) of consumers understood that they should stop product use and ask a doctor if irritation becomes severe. An even lower percentage (62.7%; 323/515) of consumers understood that irritation is more likely to occur with product use if more than one topical acne drug is used concomitantly.

C. Pivotal Targeted Self-Selection Study in Pregnant and Breastfeeding Women (Protocol 14043)

This self-selection study was a single-visit, interview-only market research study performed at 26 geographically-dispersed U.S. research facilities in 293 female subjects 13 years of age and older with self-reported acne who were pregnant, breastfeeding, or both. The primary objective of the study was to determine if subjects could make a correct self-selection decision based on the labeled warning “if pregnant or breastfeeding, ask a health professional before use”. The secondary objective of this study was to assess reasons for incorrect self-selection.

Per the sponsor, 74.4% (95% CI 68.4, 79.8; n=180) of female subjects who were pregnant,

breastfeeding, or both stated they would ask a health care professional before product use, but this point estimate did not exceed the pre-specified threshold (a two-sided lower bound 95% confidence interval of 90%). Most subjects (59 of 62 subjects) who incorrectly self-selected indicated that it was okay to use the product, primarily because they focused on the product indication of acne (36 of 62).

DPMH Comments: Only two adolescent subjects were enrolled and therefore, sub-group analyses among the adolescent subjects were not possible. Both adolescents chose to use the product, stating, "Yes, okay for me". Confirming whether or not these two adolescents thought they were pregnant is an important consideration when interpreting the appropriateness of their self-selection decision."

D. Pivotal Actual Use Study (Protocol 13049)

This pivotal actual use study (AUS) was a six-week, open-label, single-arm, multi-center observational study in males and females with self-reported acne. The objective of the study was to understand how subjects would use adapalene gel 0.1% (Differin Gel 0.1%) in an unsupervised OTC setting. The primary objectives were:

1. To evaluate the correct frequency of use (i.e., no more than once daily in the same location)
2. To determine if the drug was used for acne only. These objectives were established to evaluate the potential for over-use or off-label use of the drug.

Secondary objectives included the following:

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

A total of 1,277 subjects were entered into the study, and 947 (74.2%) of the subjects who used the study drug at least once were included in the actual use and safety populations. Overall, 21.4% (203/947) of subjects were adolescents 12 years to 17 years of age of whom 10.8% (22/203) had low literacy. At Day 0, 6 subjects were pregnant and 10 subjects were breastfeeding, but none of these subjects were under age 18 years.

According to the sponsor, the results show the study met its primary endpoint objectives. The proportions of subjects in the normal literacy and low literacy groups who correctly used the drug were similar (89.1% and 89.6%, respectively). Since the lower limit of the 95% CI was greater than 85%, the sponsor considered the primary endpoint results to be successful. When

considered by age, 90.6% of the adolescent patients and 88.7% of adult subjects correctly used the drug. See Table 2.

Table 2. Analyses of primary and select secondary endpoints stratified by age group

Category	12-17 Years (n=203)	18 Years or Older (n=744)	All Subjects (N=947)
Proportion of subjects who used the drug no more than once daily in the same location			
n (%)	184 (90.6%)	660 (88.7%)	844 (89.1%)
95% CI	(85.8, 94.3)	(86.2, 90.9)	(87.0, 91.0)
Proportion of subjects who used the drug only for acne			
n (%)	202 (99.5%)	736 (99.2%)	938 (99.3%)
95% CI	(97.3, 100)	(98.2, 99.7)	(98.5, 99.7)
Proportion of subjects who used the drug on the correct body areas			
n (%)	194 (95.6%)	727 (98.0%)	921 (97.5%)
95% CI	(91.8, 98.0)	(96.7, 98.9)	(96.2, 98.4)

CI: confidence interval

Source: adapted by this reviewer from Tables 11 (page 21), 12 (page 22), and 13 (page 23) of the Abbreviated Clinical Study Report for the Pivotal Actual Use Study for Adapalene 0.1% Gel (Project "Juno") (Module 5.3.5.2)

Nearly all subjects (99.0%; 938/947) completed the study but there were 8 adverse dropouts including the following three adolescents:

- Subject 20054, a white, 15-year-old male, experienced 2 AEs, skin irritation and erythema, within 4 days of the first application of study product. The AEs were considered related to the study product, treatment was used (although the treatment administered was not specified), and the subject recovered within 4 days without sequelae.
- Subject 25012, an Asian/white or Latino, 14-year-old female, experienced an increase in acne within 36 days of the first application of study product. The AE was considered related to the study product, treatment (salicylic acid preparation) was required, and the subject recovered within 12 days without sequelae.
- Subject 26047, a white 13-year-old female, experienced dry skin within 30 days of the first application of study product. The AE was considered related to the study product, treatment (salicylic acid preparation) was required, and the event was ongoing at the time of discontinuation.

No serious AEs were reported by any subjects in the study. Four subjects of child-bearing potential had positive pregnancy tests at the end of the study, but all of these subjects were adults 18 years of age or older.

Mean (standard deviation [SD]) amount of drug product use was 23.30 (16.87) grams (g) which represents about half of the 45 g tube. Most subjects used less than 40 g but 13 subjects used more than 80 g. A higher percentage of adolescent patients compared to adult subjects used a total amount of 40 g or more during the 6-week study period (17.2% vs. 13.8%). See Table 3.

Table 3. Total dosage of study drug used during the 6-week study period by adolescent and adult subjects compared to the total study population.

Category	12-17 Years (n=203)	18 Years or Older (n=744)	All Subjects (N=947)
Proportion of subjects who used specified total dosages of study drug during actual use period			
< 40 g	167 (82.2%)	645 (86.7%)	812 (85.7%)
40 to < 50 g	13 (6.4%)	65 (8.7%)	78 (8.2%)
50 to < 60 g	12 (5.9%)	19 (2.6%)	31 (3.3%)
60 to < 70 g	5 (2.5%)	1 (0.1%)	6 (0.6%)
80 to < 90 g	2 (0.9%)	4 (0.5%)	6 (0.6%)
90 to < 100 g	1 (0.5%)	1 (0.1%)	2 (0.2%)
100 to < 110 g	0 (0.0%)	2 (0.3%)	2 (0.2%)
110 to < 120 g	1 (0.5%)	0 (0.0%)	1 (0.1%)
120 to < 130 g	1 (0.5%)	1 (0.1%)	2 (0.2%)

Source: adapted by this reviewer from Table 16 on page 28 of the Abbreviated Clinical Study Report for the Pivotal Actual Use Study for Adapalene 0.1% Gel (Project "Juno") (Module 5.3.5.2)

DPMH Comments: In both adults and adolescents, Differin Gel 0.1% is labeled to be applied as a thin film of gel once a day to affected areas after washing in the evening before retiring. Labeling directions do not contain any information about maximum dosage. Study investigators who applied adapalene gel 0.1%, based on these labeling directions, to enrolled patients in the MUsT used a mean of 2 g of drug daily. If each tube of adapelene gel 0.1% contains 45 g of drug and each daily application consumes 2 g of drug, then each tube has the potential to provide approximately 22 days of treatment if applied correctly.

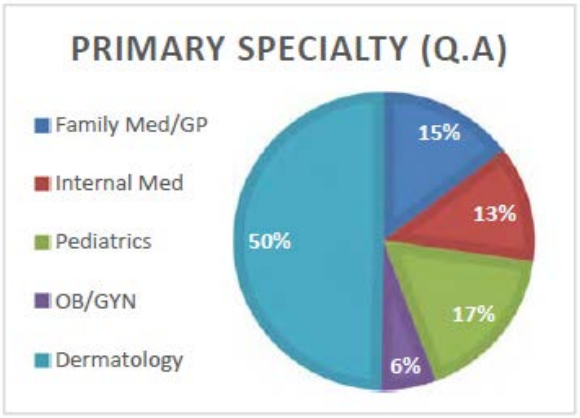
E. Rx Standard of Care Study

The purpose of this Rx Standard of Care (SOC) study was to gain insights into current physician prescribing patterns for adapalene and topical retinoids (tretinoin, tazarotene) and into the self-reported habits and practices by patients 13 years of age and older who use these drug products. The study used an online panel to recruit physicians and patients. A physician questionnaire was targeted to dermatologists and primary care physicians who had written a prescription for adapalene (Differin or EpiDuo) in the past 6 months (n=151). The physician questionnaire design incorporated questions relating to current prescribing, treating, monitoring, counseling and follow-up behaviors for patients on retinoid and retinoid-like topical Rx acne drugs. A patient questionnaire was targeted to patients who had used a topical retinoid or retinoid-like acne drug (adapalene and/or tretinoin and/or tazarotene) currently or in the past 12 months (n=233). The patient questionnaire design included current consumer patterns of behavior with acne medications, guidance received from physicians, awareness of and compliance with warnings and directions.

DPMH Comments: Based on information provided in the study report, physician respondents did not appear to be provided with any safety information about oral retinoids prior to or during the questionnaire.

Half of the physician respondents were dermatologists while the remainder was balanced across the primary specialties. See Figure 1.

Figure 1. Specialties of physician respondents



Source: Page 7 of Rx Standard of C Study Report 102234

While 95% of physicians surveyed believed that topical Rx acne drug products are "extremely or very safe", 35% do have concerns about female patients of childbearing age using topical retinoids for their acne. Physician survey results summarized by the sponsor in the study report also include the following:

- "When asked directly, approximately 60% of physicians reported that they provide *special instructions* to their patients of childbearing potential when prescribing a topical retinoid"…."to stop use/do not use if pregnant or planning to become pregnant or to use a contraceptive"
- "Only 21% require a pregnancy test for women of child-bearing potential *before* prescribing a topical retinoid"
- "Only 9% of physicians reported they routinely perform pregnancy tests at *follow-up visits* on female patients of childbearing potential who use Rx topical retinoids"
- "Most physicians (84%) would advise a patient who actually becomes pregnant while using a topical retinoid to stop taking it"

IV. Safety Considerations

A. Safety Labeling

Current product labeling for Rx topical Differin drug products identifies them as Pregnancy Category C but includes no specific human teratogenicity warning.

Approved Rx labeling for Differin Gel 0.1% states this product should not be administered to those who are hypersensitive to adapalene or to any of the product components. The Warnings section states the gel should be discontinued if hypersensitivity is noted and that patients with

sunburn should not use the product until fully recovered. The Precautions section emphasizes the importance of avoiding exposure to sunlight including sunlamps and to wear sunscreen and protective apparel when sun exposure cannot be avoided. The Precautions section also warns of the possibility for local cutaneous reactions to occur such as erythema, scaling, dryness, and stinging or burning.

Labeling Warnings and Precautions for Epiduo gel, which is labeled for use down to age 9 years, are identical to those for Differin Gel 0.1%. The Adverse Reactions section of Epiduo labeling summarizes the safety data from the pediatric study used to support product approval down to age 9 years. The vehicle-controlled study enrolled 286 pediatric patients, 9 years to 11 years of age, with acne vulgaris. Overall, the safety profile in patients 9 years to 11 years of age was comparable to that observed in older patients 12 years of age and above both in the nature and frequency of the observed events.

B. Relevant Prior FDA Post-Marketing Safety Reviews of Adapalene Drug Products

On August 30, 2010, the OSE recommended adding hypersensitivity-related AE information to the Contraindications and Post-Marketing sections of Epiduo labeling based on AE reports received in patients 16 years of age and younger. An Epiduo safety review, conducted and presented at the December 7, 2010 Pediatric AC (PAC) meeting, identified the Epiduo-related concerns of hypersensitivity reactions. The PAC advised FDA to revise Epiduo labeling to include the potential for patient hypersensitivity with product use. Labeling changes stating irritant and allergic contact dermatitis may occur were added to Subsection 5.2 (Cutaneous Reactions) and the adverse reactions of eyelid edema, pruritus, swelling face, conjunctivitis, skin discoloration, rash, eczema, throat tightness, and allergic contact dermatitis were added to Subsection 6.2 (Post-Marketing Experience).

As part of a pediatric-focused safety review of Differin lotion 0.1% presented at the May 7, 2012 PAC meeting, OSE identified 3 serious, non-fatal unlabeled AEs of idiopathic intracranial hypertension (IIH) in pediatric patients from the date of approval of the first Differin formulation (May 31, 1996) through January 3, 2012. While these three cases did not lead to modification of adapalene labeling at the time, they did prompt FDA to conduct a review of IIH associated with the use of topical retinoids in all ages. A follow-up OSE review identified ten cases reported to FDA's Adverse Events Reporting System (AERS) database and three literature cases of IIH reported in association with two of the topical retinoids, tretinoin and adapalene.[4] The AERS cases lacked information about height, weight, cerebrospinal fluid pressure, medical history, concomitant drug use, and age. The literature cases were confounded by concomitant tetracycline

[4] June 7, 2012 Pharmacovigilance Review under NDA 020380 (DARRTS Reference ID 3142108)

derivative use, possible excess dietary vitamin A intake, or patient weight greater than 20% above ideal body weight, all of which are associated with IIH. Based on the limited number of cases, most of which were poorly documented, OSE concluded at that time that there was insufficient evidence to suggest an association between the topical retinoids and IIH.

Discussion

The Rx SOC study suggests that, despite believing topical retinoid and retinoid-like drugs are safe, a majority of prescribing physicians counsel female patients with reproductive potential to stop product use if they become or plan to become pregnant. This patient counseling appears to be physician-driven and is likely based on prior knowledge or experience with oral retinoids since instructions about product use during pregnancy and human teratogenicity risks are not currently conveyed in approved labeling for Differin Gel 0.1% or other topical Rx adapalene drug products but are clearly listed in product labeling for oral retinoids.

OTC availability of the proposed drug will eliminate the requirement for a learned intermediary such as a prescribing physician to counsel patients on pregnancy during product use and will place the onus on the OTC consumer to use the product appropriately as labeled. Anticipating what potential risks, if any, could be encountered with product misuse in the OTC setting by pediatric patients who don't read or incorrectly follow the DFL requires an understanding of the extent to which topically applied Differin Gel 0.1% is systemically absorbed and if the resultant systemic exposure is associated with reproductive or non-reproductive risks. DPMH defers to Clinical Pharmacology to determine how the detected plasma levels and extent of exposure in the MUsT compare to systemic exposures for other approved topical adapalene drug products and whether such comparisons are feasible given the formulation- and vehicle-differences across products. DPMH defers to Pharmacology/Toxicology to determine the safety margin for reproductive and non-reproductive toxicity given the findings from the MUsT. Determining the clinical significance of the exposures detected in the MUsT will help determine how much emphasis DPMH should place on demonstration of correct adolescent behavior in the consumer use studies. Based on the sponsor's summary, the level of exposure appears to be low and may provide an adequate margin of safety.

Rx labeling for topical adapalene drug products identifies these products as Pregnancy Category C and includes no specific human teratogenicity warning. A determination that there are reproductive risks with the use of Differin Gel 0.1% for this Rx to OTC switch application would appear to be inconsistent with the Rx labeling for these topical adapalene products. If reproductive risks are identified with use of Differin Gel 0.1%, then the limitations identified in the LCS and self-selection studies are problematic from the pediatric perspective since neither

study adequately demonstrated that adolescents understand the pregnancy/breastfeeding warning and can correctly de-select from product use if the warning applies to them.

Although the LCS included an adequate number of adolescents and had favorable results, the study did not test consumer understanding of the two key primary communication objectives (pregnancy/breastfeeding and sun exposure warnings) recommended by FDA during OTC product development. Most importantly, the pregnancy/breastfeeding warning was not tested at all. Given questions about the teratogenicity potential of the proposed product, FDA had previously conveyed to the sponsor during the pre-IND phase that the "If pregnant or breast-feeding, ask a (b) (4) before use" warning would need further evaluation and is the most important primary communication objective to be tested in the LCS.[5] Results from the LCS also suggest that skin irritation warnings on product labeling should be strengthened.

The self-selection study enrolled only two adolescents 13 years to 17 years of age, so any conclusions regarding adolescent self-selection behavior in this study cannot be generalized to the U.S. adolescent population. In addition, the self-selection study's approach to identifying pregnant adults and adolescents was problematic. No pregnancy confirmation occurred for enrolled adolescent patients. Assuming all enrolled adolescents were pregnant without asking them directly is problematic and may have led to incorrect interpretation of the study results. Confirming whether or not the two adolescents thought they were pregnant is important consideration when interpreting the appropriateness of their self-selection decision.

Although the AUS showed that high percentages of adolescent patients correctly used the product as labeled in terms of application frequency, BSA, and indication for use, the number of low literate subjects both overall and among the adolescent cohort was much lower than the 20% to 25% targeted by the sponsor. Further sub-group analyses of the demographic characteristics of the adolescent patient may help determine if they were otherwise representative of the U.S. adolescent population. DPMH is unclear whether or not the sponsor's strategy for interpreting health literacy in the adolescent subjects is validated. A higher percentage of adolescent patients compared to adult subjects used a total amount of 40 g or more during the 6-week study period. DPMH recommends further discussions with Clinical Pharmacology to determine how estimates of the amount of drug product use during the actual use study compare to the amounts evaluated in the MuST. Understanding the demographic characteristics of the outlying adolescent patients who used more than 1 tube (45 g) of study drug during the 6-week study period and their reasons for using large amounts of the study drug may provide some insight into the type of adolescent consumer who may misuse the product in the OTC setting. This information may also help inform development of the DFL.

[5] March 12, 2013 Type B Meeting Minutes under Pre-IND 116864 (DARRTS Reference ID 3284838)

Results from both the LCS and AUS suggest that skin irritation warnings on the DFL should be strengthened. Less than 80% of tested consumers in the LCS understood that they should stop product use and ask a doctor if irritation becomes severe, and an even lower percentage (62.7%) understood that irritation (redness, itching, dryness, burning) is more likely to occur with product use if more than one topical acne drug is used concomitantly.[6] Failure for consumers to adhere to skin irritation warnings may not necessarily preclude this product from OTC approval since consumers who develop skin irritation are unlikely to continue using the product. This behavior was seen in the AUS. While no serious AEs were reported in the AUS, two of the three adolescents who dropped out of the study due to AEs reported application site reactions of irritation and dryness.

All single-ingredient topical Rx adapalene drug products are approved for use down to age 12 years, but topical retinoids could be widely used off-label in patients younger than 12 years of age. The actual use study captured five pediatric patients less than 12 years of age who were willing to purchase Differin Gel 0.1% if they had been allowed to do so. Drug Use Analysis of topical adapalene drug products may help determine the extent of off-label use. While PREA-mandated pediatric studies for acne drug products have traditionally been waived in patients less than 12 years of age, for newer acne programs DPMH is recommending drugs be studied in pubertal patients down to 9 years of age since 12 years of age is no longer considered to be the lower end of range for the age of acne vulgaris onset.

If DNDP confirms the safety margin for systemic toxicity is wide and that Differin Gel 0.1% is likely to be used off-label in younger pediatric patients, then expansion of use in the OTC setting down to 9 years of age should be considered. Since this sNDA does not trigger PREA, post-marketing requirements cannot be issued to obtain additional clinical data in pediatric patients 9 years to less than 12 years of age. However, existing data may be adequate to expand the pediatric indication based on extrapolation of efficacy from older adolescents to this age group. Therefore, DPMH recommends issuing an information request to the sponsor to obtain existing safety data from the pediatric studies used to support approval of Epiduo, a fixed-combination adapalene/benzoyl peroxide product approved for use down to 9 years of age for which Galderma is also the sponsor. Post-marketing safety data from the sponsor's pharmacovigilance database for all approved topical Rx adapalene drug products could also be used to help make a safety determination in patients 9 years to less than 12 years of age. Expansion of pediatric use down to age 9 years should be part of the PAC discussion at the April meeting.

DPMH Recommendations:

[6] These percentages are based on unmitigated responses provided by the sponsor on page 12 of the Final Study Report for the Pivotal LCS. After the sponsor applied their mitigation strategy, these percentages increased to 87.0% and 84.7%, respectively.

1. There appears to be no safety concerns in adolescents that are distinct from that in older patients of reproductive potential.

2. If DNDP concurs that the margin of safety for Differin Gel 0.1% is acceptable, then DPMH recommends approving the drug for OTC use and consideration should be given to expanding pediatric use down to age 9 years. Additionally, skin irritation warnings on the proposed DFL should be strengthened. Failure for consumers to adhere to these warnings should not preclude this product from OTC approval since consumers who develop skin irritation are unlikely to continue using the product.

3. If DNDP concludes there are reproductive risks with use of Differin Gel 0.1%, then the drug should remain Rx for pediatric patients.

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

/s/

MONA K KHURANA
02/18/2016

HARI C SACHS
02/19/2016
I agree with these recommendations.

JOHN J ALEXANDER
02/19/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 20380	NDA Supplement #: S-010	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☒ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Differin Gel Established/Proper Name: adapalene Dosage Form: Gel Strengths: 0.1%		
Applicant: Galderma Laboratories, L.P. Agent for Applicant (if applicable): N/A		
Date of Application: September 10, 2015 Date of Receipt: September 10, 2015 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: July 10, 2016 (Sunday)	Action Goal Date (if different): July 8, 2016	
Filing Date: November 9, 2015	Date of Filing Meeting: October 22, 2015	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): • For the treatment of acne • Clears up acne pimples and acne blemishes		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☒ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): Division of Dermatology and Dental Products (DDDP)	
List referenced IND Number(s): 116864	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				N/A
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		N/A
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☐ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☒		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it;*	☒	☐	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☒	☐	Sent request to sponsor by email on 11/6/15
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*	☐	☒		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☐	☒	
Prescription Labeling	☒ **Not applicable**			
Check all types of labeling submitted.	☐ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☐	☐		
Is the PI submitted in PLR format?[4]	☐	☐		N/A

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

[4]

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☐	☐	☐	
Has a review of the available pregnancy and lactation data been included?	☐	☐	☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☐	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☐	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☐	☐	☐	
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☒ Outer carton label ☒ Immediate container label ☐ Blister card ☐ Blister backing label ☒ Consumer Information Leaflet (CIL) ☐ Physician sample ☒ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☒	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)?	☒	☐	☐	

http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

If no, request in 74-day letter.				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☒	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☒	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	DPMH – 11/13/15 OSE – 10/14/15 OSI – 11/13/15
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** Pre-sNDA meeting - June 10, 2015 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 10/22/15

BACKGROUND: Differin (adapalene) Gel 0.1% was approved May 31, 1996 under NDA 20380 for the treatment of acne vulgaris. Differin (adapalene) is also available in 2 other dosage forms - Cream, 0.1% (approved under NDA 20748) and Lotion, 0.1% (approved under NDA 22502).

This efficacy supplement, submitted as supplement 10, proposes a complete Rx-to-OTC switch of Differin Gel, 0.1% only. No changes to the active ingredient, indication, dosage form, dosing regimen or route of administration are proposed.

In addition, no changes are being proposed to the drug substance/drug product, drug substance/product manufacturing process, suppliers, specifications, and primary packaging components, therefore Module 3 is not included in this supplement as no changes to the Quality aspects are proposed from those currently approved in NDA 20380.

New clinical studies relied on to support the sNDA submission include:

- RD.06.SPR.18254 – PK Study on systemic exposure under maximal use condition x 4 weeks in adults and adolescents with acne vulgaris
- Study 13049/SRE.100931: Pivotal Actual Use Study for Adapalene 0.1% Gel
  - Requesting 3 years' exclusivity for 'essential' clinical trial

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lara Akinsanya	Y
	CPMS/TL:	Dan Brum	Y
Cross-Discipline Team Leader (CDTL)	Jane Filie		Y
Division Director/Deputy	Terri Michele		Y
Office Director/Deputy	Charles Ganley		N
Clinical	Reviewer:	Ryan Raffaelli	Y
	TL:	Jane Filie	Y
Social Scientist Review (*for OTC products*)	Reviewer:	Barbara Cohen	Y
	TL:		
OTC Labeling Review (*for OTC*	Reviewer:	Yoon Kong	Y

products)			
	TL:	Steve Adah	Y
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Chinmay Shukla	N
	TL:	Doanh Tran	N
• Genomics	Reviewer:	N/A	
• Pharmacometrics	Reviewer:	N/A	
Biostatistics	Reviewer:	Scott Komo	Y
	TL:	Daphne Lin	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Cindy Li	Y
	TL:	Paul Brown	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC) Review Team:	ATL:	N/A	
	RBPM:	N/A	
• Drug Substance	Reviewer:	N/A	
• Drug Product	Reviewer:	N/A	
• Process	Reviewer:	N/A	
• Microbiology	Reviewer:	N/A	
• Facility	Reviewer:	N/A	
• Biopharmaceutics	Reviewer:	N/A	
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)	Donald Klein – EA reviewer		Y
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	N/A	
	TL:	N/A	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	N/A	
	TL:	N/A	
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Grace Jones	N

	TL:	Alice Tu	N
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	
Bioresearch Monitoring (OSI)	Reviewer:	To be assigned	N
	TL:	To be assigned	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers/disciplines			
• DDDP *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:	Amy Woitach	Y
	TL:	David Kettl	Y
Other attendees	Valerie Pratt, Betsy Scroggs, Lydia Springs, Amy Egan, Abiola Olagundoye		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation?	☒ YES ☐ NO

If no, explain:	
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☒ YES Date if known: 03/03/2016 ☐ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☐ Not Applicable ☐ YES ☒ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY	☒ Not Applicable

Comments:	☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: The Sponsor submitted data from a new maximal use PK trial	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
SOCIAL SCIENCE **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested?	☒ YES ☐ NO

If no, was a complete EA submitted? **Comments**:	☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**: N/A	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Charles Ganley, MD, Office Director for ODE IV
Julie Beitz, MD, Office Director for ODE III

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): N/A

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review

ACTION ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☒	Send review issues/no review issues by day 74

Annual review of template by OND ADRAs completed: September 2014

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

/s/

MONSURAT O AKINSANYA
11/09/2015