

**JERUSSI CONSULTING, INC.**

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February 5, 2004

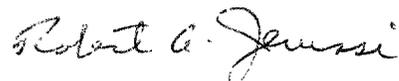
Dockets Management Branch  
Food and Drug Administration  
Department of Health and Human Services  
Room 1061  
5630 Fishers Lane  
Rockville, MD 20857

**Docket No. 2003P-0279**

Dear Madame or Sir:

Attached are our comments in response to a September 30, 2003 letter to this docket submitted by GrayCary on behalf of Hill Dermaceuticals, Inc. in which GrayCary commented negatively on our suitability petition requesting a change in the dosage form from a cream to a topical solution for the combination drug product containing Fluocinolone Acetonide, Hydroquinone and Tretinoin, 0.01%, 4% and 0.05% respectively.

Sincerely,



Robert A. Jerussi

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2003P-0279

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February 5, 2004

**RE: Suitability Petition 2003P-0279 Response from GrayCary on behalf of Hill Dermaceuticals, Inc./Galderma Laboratories USA.**

A letter of "Opposition" to the suitability petition filed by Jerussi Consultants, "Request for a Change in Dosage Form from a Cream to a Topical Solution for Fluocinolone Acetonide, Hydroquinone and Tretinoin", Petition #2003P-0279, was filed by GrayCary on or about 9/30/03.

This letter contains erratum and misrepresentations that are misleading in the interpretation of the petition now pending. A summary of the concerns of Jerussi Consulting to this letter are listed below:

1. Page 2, GrayCary letter Background: "As you know, Melasma is a skin condition that is manifested by dark (hyper pigmented) spots on the facial skin, especially on the cheeks and forehead. This condition usually happens with hormone changes."

Quoting from Robbins, Pathologic Basis of Disease, Cotran, R.S., Kumar, V., Collins, T. W. B. Saunders Co. 1999, page 1174, "The pathogenesis of melasma appears to relate to functional alterations in melanocytes resulting in enhanced pigmentation transfer to basal keratinocytes or to dermal macrophages. Apart from its association with pregnancy, melasma may occur during the administration of oral contraceptives or hydantoins, or it may be idiopathic." Please note Hydantoins and idiopathogenous has nothing to do with hormones. Nor can a reference be made to elevation of plasma progesterone.

2. Page 2, GrayCary letter, Labeling Precautions... Here the author claims the current approved package insert and patient medication guide for TRI-LUMA<sup>®</sup> Cream states the **PRECAUTIONS** section contains the text, "Application of TRI-LUMA<sup>®</sup> Cream should be kept away from the eyes, nose or angles of the mouth because the mucosa is much more sensitive than the skin to the irritant effect..." The Current package insert goes on to say, "if the irritation persists, to contact the health care provider and discontinue the medication". This is specific for the combination of the three active pharmaceutical ingredients, Tretinoin, Fluocinolone Acetonide, and Hydroquinone, not the dosage form.
3. Page 3, GrayCary letter. There are no additional safety concerns raised by the changes in dosage forms since the formulation contains the same levels of active pharmaceutical ingredients and may not contain sodium metabisulfite. This is an error of placing topical solutions in a different category than topical creams. The agency has had a long policy and many examples of approving topical solutions over creams and gels, especially when considering solubility aspects of the active pharmaceutical ingredients. Creams may not present the optimum distribution of ingredients. Therefore patients may over-apply the cream to gain efficacy.

4. Page 3, GrayCary letter: “The **PRECAUTIONS** section of the labeling... Here the author is over-reaching the data and applications. The statement of “dosing frequency with a topical solution with known irritants will greatly affect adverse reactions” is without warrant for topical solutions. Other products containing equivalent active ingredients in topical solutions are not significantly different in adverse reactions.
5. Page 4, GrayCary letter: The author’s statement about the formula is without creditably. The ingredients, excipients, have a long history of use in prescription and over-the-counter products. They represent no meaningful threat to the patient or the prescribing physician.

6. Page 4, GrayCary letter: **“The change in Dosage Form to a Topical Solution Has the Potential to Impact the Pharm/Tox Profile of the Triple Combination”**

Since the Reference Listed Drug manufacturer has not conducted preclinical studies to examine long-term potential risks of the combination of the actives, it is recommended that this statement is completely baseless. (See package insert)

7. Page 4, GrayCary letter: **“The Change in Dosage Form to a Topical Solution Has the Potential to Impact the Safe and Effective Dose of Each Ingredient of the Triple Combination”**.

Topical solutions are bio-available by definition, please refer to 21CFR§ 320.22(b)(3).

8. Page 5 GrayCary letter: **“The Petitioner Has Not Addressed How to Establish the Bioequivalence of the Topical Solution Dosage Form to the Currently Approved Reference Listed Drug, TRI-LUMA® Cream.**

Answered in #7.

9. Page 6, GrayCary letter: **“The Petitioner Has Not Addressed Monitoring the Unintended Usage in Pregnancy and Provide Measure on How This Can be Reduced.”**

Please refer to the RLD’s Package Insert and Patient information statements.