

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 21-789/S004**

***Trade Name:*** METROGEL

***Generic Name:*** metronidazole

***Sponsor:*** Galderma Labs LP

***Approval Date:*** October 19, 2011

***Indications:*** for the topical treatment of inflammatory lesions of rosacea.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**NDA 21-789/S004**

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 21-789/S004**

**APPROVAL LETTER**



NDA 021789/S-004

**SUPPLEMENT APPROVAL**

Galderma Laboratories, L.P.  
Attention: Richard Almond  
Manager, Regulatory Affairs  
14501 North Freeway  
Fort Worth, TX 76177

Dear Mr. Almond:

Please refer to your Supplemental New Drug Application (sNDA) dated August 11, 2010, received August 13, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Metrogel<sup>®</sup> (metronidazole) Gel, 1%.

We acknowledge receipt of your amendments dated September 30 and October 21, 2010; January 11 and 18, June 23, September 30, October 5 and 11, 2011.

The June 23, 2011, submission constituted a complete response to our February 7, 2011, action letter.

This "Prior Approval" supplemental new drug application proposes an alternate container/closure system consisting of a 55 gram pump.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effectuated" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on January 11, 2011, as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 021789/S-004.**” Approval of this submission by FDA is not required before the labeling is used.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

*{See appended electronic signature page}*

Stanka Kukich, M.D.  
Deputy Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

### ENCLOSURES:

Content of Labeling  
Carton and Container Labeling

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/s/  
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STANKA KUKICH  
10/19/2011

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-789/S004**

**OTHER ACTION LETTERS**



NDA 021789/S-004

**COMPLETE RESPONSE**

Galderma Laboratories, L.P.  
Attention: Shylah D. Merrick  
Manager, Regulatory Affairs  
14501 North Freeway  
Fort Worth, TX 76177

Dear Ms. Merrick:

Please refer to your Supplemental New Drug Application (sNDA) dated August 11, 2010, received August 13, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Metrogel<sup>®</sup> (metronidazole) Gel, 1%.

We acknowledge receipt of your amendments dated September 30 and October 21, 2010, and January 11, 2011.

This "Prior Approval" labeling supplemental new drug application proposes a new container/closure system adding a pump top dispenser.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

**PRODUCT QUALITY**

**Deficiencies:**

1. Lack of adequate identification testing for the components of the proposed container/closure system
2. Specification for 0.26 mL pump is unclear
3. Extractable testing results for the 2 oz. High Density Polyethylene (HDPE) bottles could not be found
4. Inadequate stability information
5. Insufficient stability protocol
6. Inadequate test procedures for the drug product specification
7. Inadequate response (dated September 14, 2010) to the Agency's Information Request (#1, dated September 14, 2010) in that raw data of the dispensed amount were not included
8. Inadequate information to support the proposed expiration dating period

**Items Needed for Resolution:**

1. Identification test (b) (4) should be performed on each part of the proposed container/closure system that is in contact with Metrogel Gel, 1%. Add identification tests to the specifications for each lot of incoming bottles and dispersing pumps.
2. Provide specification for the 0.26ml dispensing pump [in the same format as that for 2 oz. bottle (Table 3.2.P.7.2.1)].
3. Provide extractable testing for the bottle according to United States Pharmacopeia (USP) <661> or provide the specific location (e.g. date of submission, section, and pages) to the data in Drug Master File (DMF) (b) (4)
4. Provide a minimum of three months of stability data under both accelerated and long-term stability conditions from a minimum of three drug product batches.
5. Revise the stability protocol to include water loss testing, packaging integrity testing to evaluate changes of physical properties that may adversely affect the suitability of the container/closure system and appropriate pumping performance testing (e.g. number of priming, amount of actuation and actuation force).
6. Revise test procedures of the product specification by stating that all tests should be performed on the samples pumped out from the proposed container/closure system.
7. Provide the raw data of the dispensed amount (in grams) per actuation for the first 20 actuations and the last ten before exhaustion for all ten bottles included in 3.2.P.2.4 *Container Closure System Testing* submitted on September 30, 2010.
8. Provide an explanation as to (b) (4)

Provide information to demonstrate that Metrogel 1% stored in the proposed HDPE bottle with dispersing pump will remain within the specification through the proposed expiration date (24 months).

**LABELING**

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

**OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have

such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

*{See appended electronic signature page}*

Stanka Kukich, M.D.  
Deputy Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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STANKA KUKICH  
02/07/2011



NDA 021789/S-004

**INFORMATION REQUEST**

Galderma Laboratories, L.P.  
Attention: Shylah D. Merrick  
Manager, Regulatory Affairs  
14501 North Freeway  
Fort Worth, TX 76177

Dear Ms. Merrick:

Please refer to your August 11, 2010 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metrogel (metronidazole) Gel, 1%.

We are reviewing your submission and have the following information requests.

1. For the proposed 55 gram pump configuration, provided the following:
  - a. The number of full doses which can be delivered
  - b. The amount of product (in grams) dispensed per actuation for the first 20 actuations and the last ten before exhaustion
  - c. Total deliverable amount
  - d. Targeted fill weight

Be sure to provide raw data (not average) from at least 10 randomly selected pump units.

2. Update the manufacturing section (3.2.P.3) of the NDA for any changes caused by the proposed new container/closure system (bottle with dispensing pump). Provide the updated Master Batch Record.
3. Provide the photostability study protocol (b) (4) and the test results at each time point.
4. Provide stability data (preferably one year under long-term storage condition and 6 month under accelerated storage condition) from a minimum of three drug product stability batches to support the proposed specification and expiration dating period.
5. Provide mock-up labels for the bottle and the carton of the newly proposed container/closure system (bottle with dispensing pump).

Please submit your responses to the above items by close of business on September 30, 2010.

If you have questions, call me, at (301) 796-3935.

Sincerely,

*{See appended electronic signature page}*

J. Paul Phillips, M.S.  
Regulatory Health Project Manager  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-21789

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SUPPL-4

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GALDERMA  
LABORATORIES  
LP

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METRONIDAZOLE GEL 1%

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/s/  
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J P PHILLIPS

09/14/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-789/S004**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use METROGEL (metronidazole) Gel, 1% safely and effectively. See full prescribing information for METROGEL (metronidazole) Gel, 1%

**METROGEL® (metronidazole) gel, 1%**

**For topical use**

**Initial U.S. Approval: 1963**

### INDICATIONS AND USAGE

METROGEL® (metronidazole) Gel, 1% is a nitroimidazole indicated for the topical treatment of inflammatory lesions of rosacea. (1)

### DOSAGE AND ADMINISTRATION

- Not for oral, ophthalmic or intravaginal use.
- Apply and rub in a thin film of METROGEL once daily to affected area(s). (2)
- Treated areas should be cleansed before the application of METROGEL. (2)
- Cosmetics may be applied after the application of METROGEL. (2)

### DOSAGE FORMS AND STRENGTHS

Gel, 1%.

### CONTRAINDICATIONS

METROGEL is contraindicated in those patients with a history of hypersensitivity to metronidazole or to any other ingredient in this formulation. (4)

### WARNINGS AND PRECAUTIONS

- Peripheral neuropathy, characterized by numbness or paresthesia of an extremity has been reported in patients treated with systemic metronidazole. Although not evident in clinical trials for topical metronidazole, peripheral neuropathy has been reported with the post approval use. The appearance of abnormal neurologic signs should prompt immediate reevaluation of METROGEL therapy. (5.1)
- Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or history of, blood dyscrasia. (5.2)
- If dermatitis occurs, patients may need to discontinue use. (5.3)
- Topical metronidazole has been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided. (5.4)

### ADVERSE REACTIONS

Most common adverse reactions (incidence > 2%) are nasopharyngitis, upper respiratory tract infection, and headache. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Galderma Laboratories, L.P. at 1-866-735-4137 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### DRUG INTERACTIONS

Oral metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin, resulting in a prolongation of prothrombin time. Drug interactions should be kept in mind when METROGEL is prescribed for patients who are receiving anticoagulant treatment, although they are less likely to occur with topical metronidazole administration because of low absorption. (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2011

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\*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

METROGEL<sup>®</sup> is indicated for the topical treatment of inflammatory lesions of rosacea.

### 2 DOSAGE AND ADMINISTRATION

Apply and rub in a thin film of METROGEL once daily to affected area(s).

A gentle cleanser should be used before the application of METROGEL.

Cosmetics may be applied after the application of METROGEL.

Not for oral, ophthalmic or intravaginal use.

### 3 DOSAGE FORMS AND STRENGTHS

Gel, 1%. METROGEL is a clear, colorless to pale yellow gel. Each gram of METROGEL contains 10 mg (1%) of metronidazole.

### 4 CONTRAINDICATIONS

METROGEL is contraindicated in patients with a history of hypersensitivity to metronidazole or to any other ingredient in the formulation.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Neurologic Disease

Peripheral neuropathy, characterized by numbness or paresthesia of an extremity has been reported in patients treated with systemic metronidazole. Although not evident in clinical trials for topical metronidazole, peripheral neuropathy has been reported with the post approval use. The appearance of abnormal neurologic signs should prompt immediate reevaluation of METROGEL therapy. Metronidazole should be administered with caution to patients with central nervous system diseases.

#### 5.2 Blood Dyscrasias

Metronidazole is a nitroimidazole; use with care in patients with evidence of, or history of, blood dyscrasia.

#### 5.3 Contact Dermatitis

Irritant and allergic contact dermatitis have been reported. If dermatitis occurs, patients may need to discontinue use.

#### 5.4 Eye Irritation

Topical metronidazole has been reported to cause tearing of the eyes. Avoid contact with the eyes.

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a controlled clinical trial, 557 patients used metronidazole gel, 1% and 189 patients used the gel vehicle once daily for up to 10 weeks. The following table summarizes selected adverse reactions that occurred at a rate of  $\geq 1\%$ :

**Table 1: Adverse Reactions That Occurred at a Rate of  $\geq 1\%$**

System Organ Class/Preferred Term	Metronidazole Gel, 1%	Gel Vehicle
	N= 557	N= 189
<b>Patients with at least one AE</b> Number (%) of Patients	<b>186 (33.4)</b>	<b>51 (27.0)</b>
<b>Infections and infestations</b>	<b>76 (13.6)</b>	<b>28 (14.8)</b>
Bronchitis	6 (1.1)	3 (1.6)
Influenza	8 (1.4)	1 (0.5)
Nasopharyngitis	17 (3.1)	8 (4.2)
Sinusitis	8 (1.4)	3 (1.6)
Upper respiratory tract infection	14 (2.5)	4 (2.1)

Urinary tract infection	6 (1.1)	1 (0.5)
Vaginal mycosis	1 (0.2)	2 (1.1)
<b>Musculoskeletal and connective tissue disorders</b>	<b>19 (3.4)</b>	<b>5 (2.6)</b>
Back pain	3 (0.5)	2 (1.1)
<b>Neoplasms</b>	<b>4 (0.7)</b>	<b>2 (1.1)</b>
Basal cell carcinoma	1 (0.2)	2 (1.1)
<b>Nervous system disorders</b>	<b>18 (3.2)</b>	<b>3 (1.6)</b>
Headache	12 (2.2)	1 (0.5)
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>22 (3.9)</b>	<b>5 (2.6)</b>
Nasal congestion	6 (1.1)	3 (1.6)
<b>Skin and subcutaneous tissue disorders</b>	<b>36 (6.5)</b>	<b>12 (6.3)</b>
Contact dermatitis	7 (1.3)	1 (0.5)
Dry skin	6 (1.1)	3 (1.6)
<b>Vascular disorders</b>	<b>8 (1.4)</b>	<b>1 (0.5)</b>
Hypertension	6 (1.1)	1 (0.5)

**Table 2: Local Cutaneous Signs and Symptoms of Irritation That Were Worse Than Baseline**

	<b>Metronidazole Gel, 1%</b>	<b>Gel Vehicle</b>
<b>Sign/Symptom</b>	<b>N= 544</b>	<b>N= 184</b>
<b>Dryness</b>	<b>138 (25.4)</b>	<b>63 (34.2)</b>
Mild	93 (17.1)	41 (22.3)
Moderate	42 (7.7)	20 (10.9)
Severe	3 (0.6)	2 (1.1)
<b>Scaling</b>	<b>134 (24.6)</b>	<b>60 (32.6)</b>
Mild	88 (16.2)	32 (17.4)
Moderate	43 (7.9)	27 (14.7)
Severe	3 (0.6)	1 (0.5)
<b>Pruritus</b>	<b>86 (15.8)</b>	<b>35 (19.0)</b>
Mild	53 (9.7)	21 (11.4)
Moderate	27 (5.0)	13 (7.1)
Severe	6 (1.1)	1 (0.5)
<b>Stinging/burning</b>	<b>56 (10.3)</b>	<b>28 (15.2)</b>
Mild	39 (7.2)	18 (9.8)
Moderate	7 (1.3)	9 (4.9)
Severe	10 (1.8)	1 (0.5)

The following additional adverse experiences have been reported with the topical use of metronidazole: skin irritation, transient redness, metallic taste, tingling or numbness of extremities, and nausea.

## 6.2 Post Marketing Experience

The following adverse reaction has been identified during post approval use of topical metronidazole: peripheral neuropathy. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

## 7 DRUG INTERACTIONS

Oral metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin, resulting in a prolongation of prothrombin time. Drug interactions should be kept in mind when METROGEL is prescribed for patients who are receiving anticoagulant treatment, although they are less likely to occur with topical metronidazole administration because of low absorption.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

*Teratogenic Effects:* Pregnancy Category B.

There are no adequate and well-controlled studies with the use of METROGEL in pregnant women.

Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed after oral administration of metronidazole in rats or mice at 200 and 20 times, respectively, the expected clinical dose. However, oral metronidazole has shown carcinogenic activity in rodents. Because animal reproduction studies are not always predictive of human response, METROGEL should be used during pregnancy only if clearly needed.

### 8.3 Nursing Mothers

After oral administration, metronidazole is secreted in breast milk in concentrations similar to those found in the plasma. Even though blood levels taken after topical metronidazole application are significantly lower than those achieved after oral metronidazole a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the risk to the infant.

### 8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

### 8.5 Geriatric Use

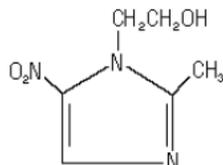
Sixty-six subjects aged 65 years and older were treated with metronidazole gel, 1% in the clinical study. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

## 10 OVERDOSAGE

There are no reported human experiences with overdosage of METROGEL. Topically applied metronidazole can be absorbed in sufficient amount to produce systemic effects.

## 11 DESCRIPTION

METROGEL (metronidazole) Gel, 1% contains metronidazole, USP. Chemically, metronidazole is 2-methyl-5-nitro-1 *H*-imidazole-1-ethanol. The molecular formula for metronidazole is C<sub>6</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>. It has the following structural formula:



Metronidazole has a molecular weight of 171.16. It is a white to pale yellow crystalline powder. It is slightly soluble in alcohol and has solubility in water of 10 mg/mL at 20°C. Metronidazole belongs to the nitroimidazole class of compounds.

METROGEL is a clear, colorless to pale yellow, aqueous gel; each gram contains 10 mg of metronidazole in a base of betadex, edetate disodium, hydroxyethyl cellulose, methylparaben, niacinamide, phenoxyethanol, propylene glycol, propylparaben and purified water.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of metronidazole in the treatment of rosacea is unknown.

### 12.2 Pharmacodynamics

The pharmacodynamics of metronidazole in association with the treatment of rosacea are unknown.

### 12.3 Pharmacokinetics

Topical administration of a one gram dose of METROGEL to the face of 13 patients with moderate to severe rosacea once daily for 7 days resulted in a mean  $\pm$  SD C<sub>max</sub> of metronidazole of 32  $\pm$  9 ng/mL. The mean  $\pm$  SD AUC<sub>(0-24)</sub> was 595  $\pm$  154 ng\*hr/mL. The mean C<sub>max</sub> and AUC<sub>(0-24)</sub> are less than 1% of the value reported for a single 250 mg oral dose of metronidazole. The time to maximum plasma concentration (T<sub>max</sub>) was 6-10 hours after topical application.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats, but not in studies involving hamsters.

In several long-term studies in mice, oral doses of approximately 225 mg/m<sup>2</sup>/day or greater (approximately 37 times the human topical dose on a mg/m<sup>2</sup> basis) were associated with an increase in pulmonary tumors and lymphomas. Several long-term oral studies in the rat have shown statistically significant increases in mammary and hepatic tumors at doses >885 mg/m<sup>2</sup>/day (144 times the human dose).

Metronidazole has shown evidence of mutagenic activity in several *in vitro* bacterial assay systems. In addition, a dose-related increase in the frequency of micronuclei was observed in mice after intraperitoneal injections. An increase in chromosomal aberrations in peripheral blood lymphocytes was reported in patients with Crohn's disease who were treated with 200 to 1200 mg/day of metronidazole for 1 to 24 months. However, in another study, no increase in chromosomal aberrations in circulating lymphocytes was observed in patients with Crohn's disease treated with the drug for 8 months.

In one published study, using albino hairless mice, intraperitoneal administration of metronidazole at a dose of 45 mg/m<sup>2</sup>/day (approximately 7 times the human topical dose on a mg/m<sup>2</sup> basis) was associated with an increase in ultraviolet radiation-induced skin carcinogenesis. Neither dermal carcinogenicity nor photocarcinogenicity studies have been performed with METROGEL or any marketed metronidazole formulations.

## 14 CLINICAL STUDIES

In a randomized, vehicle-controlled trial, 746 subjects with rosacea were treated with metronidazole gel, 1% or gel vehicle once daily for 10 weeks. Most subjects had "moderate" rosacea at baseline. Efficacy was determined by recording reduction in inflammatory lesion counts and success rate in the Investigator Global Assessment (percentage of subjects "clear" and "almost clear" of rosacea at the end of the study). The scale is based on the following definitions:

**Table 3: Investigator Global Assessment Scale**

Score	Grade	Definition
0	Clear	No signs or symptoms present; at most, mild erythema
1	Almost Clear	Very mild erythema present. Very few small papules/pustules
2	Mild	Mild erythema. Several small papules/pustules
3	Moderate	Moderate erythema. Several small or large papules/pustules, and up to 2 nodules
4	Severe	Severe erythema. Numerous small and/or large papules/pustules, up to several nodules

The results are shown in the following table:

**Table 4: Inflammatory Lesion Counts and Global Scores in a Clinical Trial of Rosacea**

	Metronidazole Gel, 1%		Vehicle	
	N	Results N (%)	N	Results N (%)
<b>Inflammatory lesions</b>	557		189	
Baseline, mean count		18.3		18.4
Week-10, mean count		8.9		12.8
Reduction		9.4 (50.7)		5.6 (32.6)
<b>Investigator Global Assessment</b>	557		189	
Subject clear or almost clear		214 (38.42)		52 (27.51)
Subject with no change		159 (28.5)		77 (40.7)

Subjects treated with metronidazole gel, 1% experienced a mean reduction of 9.4 inflammatory lesions in the Week-10 LOCF group, compared to a reduction of 5.6 for those treated with vehicle, or a difference in means of 3.8 lesions.

The contribution to efficacy of individual components of the vehicle has not been established.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

METROGEL<sup>®</sup> is clear, colorless to pale yellow in color, and supplied as follows:

60 gram tube – NDC 0299-3820-60

55 gram pump – NDC 0299-3820-01

**Storage Conditions:** Store at controlled room temperature: 20° to 25°C (68° to 77°F), excursions permitted between 15° and 30°C (59° and 86°F).

## 17 PATIENT COUNSELING INFORMATION

Patients using METROGEL should receive the following information and instructions:

1. This medication is to be used as directed.
2. It is for external use only.
3. Avoid contact with the eyes.
4. Cleanse affected area(s) before applying METROGEL.
5. This medication should not be used for any condition other than that for which it is prescribed.
6. Keep out of reach of children.
7. Patients should report any adverse reaction to their physicians.

### **Rx Only**

US Patent No. 6,881,726 and 7,348,317

### **Manufactured by:**

G Production Inc.  
Baie d'Urfé, QC, H9X 3S4 Canada  
Made in Canada.

### **Marketed by:**

Galderma Laboratories, L.P.  
Fort Worth, Texas 76177 USA  
P50742-1 0207

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-789/S004**

**MEDICAL REVIEW(S)**

## Medical Officer's Review of NDA 021789

Prior Approval Labeling Supplement: addition of HDPE bottle with dispensing pump  
**Resubmission after Complete Response**

**Document ID Number:** SD-69

**Correspondence date:** 2011-06-23

**CDER Stamp date:** 2011-06-23

**Type of Submission:**

- Resubmission after CR {Prior Approval Supplement (**S-004**): an alternative container/closure system-HDPE bottle with dispensing pump.}

**Sponsor:**

Galderma Laboratories, LP

14501 N. Freeway

Fort worth, TX 76177

**Drug:** METROGEL<sup>®</sup> (metronidazole) Gel, 1%

**Route of Administration:** topical

**Dosage Form:** gel

**Active Ingredient(s):** metronidazole

**Pharmacologic Category:** nitroimidazole

**Indication:** topical treatment of inflammatory lesions of rosacea

**Review completion date:** 2011-10-12

**Project Manager:** Paul Phillips

**Team Leader:** Gordana Diglisic, M.D.

**Reviewer:** Melinda McCord, M.D.

METROGEL<sup>®</sup> (metronidazole) Gel, 1% (NDA 021789) was approved on June 30, 2005 for the topical treatment of inflammatory lesions of rosacea.

Currently, METROGEL<sup>®</sup> (metronidazole) Gel, 1% is marketed in (b) (4) 60g aluminum tubes.

### **CURRENT SUBMISSION**

- The sponsor has **resubmitted** a labeling supplement after receiving a Complete Response (letter dated February 7, 2011) proposing an alternate container/closure system (2oz high density polyethylene (HDPE) white bottle fitted with a 0.26mL dispensing pump with 22/410 tread). The bottle with dispensing pump will contain 55g of METROGEL Gel, 1%.

### **Regulatory Background**

On **August 11, 2010** the sponsor submitted Prior Approval Supplement (S-004): an alternative container/ closure system-HDPE bottle with dispensing pump (SD-60).

On **February 7, 2011** the sponsor was notified that after reviewing their application that the Agency determined “that we cannot approve this application in its present form.”

The deficiencies in product quality were the following:

1. Lack of adequate identification testing for the components of the proposed container/closure system
2. Specification for 0.26 mL pump is unclear

3. Extractable testing results for the 2 oz. High Density Polyethylene (HDPE) bottles could not be found
4. Inadequate stability information
5. Insufficient stability protocol
6. Inadequate test procedures for the drug product specification
7. Inadequate response (dated September 14, 2010) to the Agency's Information Request (#1, dated September 14, 2010) in that raw data of the dispensed amount were not included
8. Inadequate information to support the proposed expiration dating period

Items Needed for Resolution were the following:

1. Identification test (e.g. by (b) (4) ) should be performed on each part of the proposed container/closure system that is in contact with Metrogel Gel, 1%. Add identification tests to the specifications for each lot of incoming bottles and dispersing pumps.
2. Provide specification for the 0.26ml dispensing pump [in the same format as that for 2 oz. bottle (Table 3.2.P.7.2.1)].
3. Provide extractable testing for the bottle according to United States Pharmacopeia (USP) <661> or provide the specific location (e.g. date of submission, section, and pages) to the data in Drug Master File (DMF) (b) (4) .
4. Provide a minimum of three months of stability data under both accelerated and long term stability conditions from a minimum of three drug product batches.
5. Revise the stability protocol to include water loss testing, packaging integrity testing to evaluate changes of physical properties that may adversely affect the suitability of the container/closure system and appropriate pumping performance testing (e.g. number of priming, amount of actuation and actuation force).
6. Revise test procedures of the product specification by stating that all tests should be performed on the samples pumped out from the proposed container/closure system.
7. Provide the raw data of the dispensed amount (in grams) per actuation for the first 20 actuations and the last ten before exhaustion for all ten bottles included in 3.2.P.2.4 *Container Closure System Testing* submitted on September 30, 2010.
8. Provide an explanation as to (b) (4)

Provide information to demonstrate that Metrogel 1% stored in the proposed HDPE bottle with dispersing pump will remain within the specification through the proposed expiration date (24 months).

The sponsor was also notified that further comments regarding the proposed labeling would be provided after the application was considered adequate.

On **March 30, 2011** a teleconference was conducted between the sponsor and the FDA to clarify questions regarding the Agency's Complete Response letter dated February 7, 2011. The following is a summary of the meeting discussion which focused on deficiencies #4, 5, 6 and 8:

**#4: "Provide a minimum of three months of stability data under both accelerated and long term stability conditions from a minimum of three drug product batches."**

**Response:**

Batch 755 is not considered to be a registration stability batch because it is not packaged in the proposed to-be-marketed container/closure system.

**Meeting Discussion:**

The applicant agreed to provide the requested stability data in the resubmission.

**# 5:** *“Revise the stability protocol to include water loss testing, packaging integrity testing to evaluate changes of physical properties that may adversely affect the suitability of the container/closure system and appropriate pumping performance testing (e.g. number of priming, amount of actuation and actuation force).”*

**Response:**

The proposed stability protocol is inadequate to support the proposed container/closure system because the examination of the pumping performance is not included and there is no acceptance criterion for Weight Loss testing in the protocol. To evaluate the performance of the pumping system upon storage, the test procedure for pump performance should include assessment of the following: number of priming, amount dispensed per actuation, actuation force, and total deliverable by weight per container. The Agency acknowledges that the proposed container/closure system is not a metered dose system. Therefore, we will not require you to conform to the standards that are strictly specific to metered dose products.

**Meeting Discussion:**

The applicant agreed to develop a specification limit for the weight loss test and to revise the packaging integrity test. The applicant inquired whether pump performance will become a routine test.

**#6:** *“Revise test procedures of the product specification by stating that all tests should be performed on the samples pumped out from the proposed container/closure system.”*

**Response:**

All test data should be indicative of the chemo-physical properties, quality and performance of the drug product immediately prior to applying to the patient.

**Meeting Discussion:**

The Agency recommended that the applicant acquire samples through the pump for analytical testing.

**Post-Meeting Addendum:**

The applicant can provide data (from “fresh” and “aged” product) demonstrating that test results for pumped out material are similar to data generated from non-pumped out material.

**#8:** *“Provide an explanation as to why* (b) (4)*”*

*Provide information to demonstrate that Metrogel 1% stored in the proposed HDPE bottle with dispersing pump will remain within the specification through the proposed expiration date (24 months).”*

**Response:**

(b) (4)

**Meeting Discussion:**

(b) (4)

**CURRENT SUBMISSION**

On **June 23, 2011** the sponsor **resubmitted** a labeling supplement after receiving a Complete Response proposing an alternate container/closure system (2oz high density polyethylene (HDPE) white bottle fitted with a 0.26mL dispensing pump with 22/410 tread). The current submission contains complementary data to address the deficiencies and to document pump functionality as requested by FDA in the February 7, 2011 Complete Response Letter and the March 30, 2011 Type A Meeting.

The following data was submitted in support of the suitability of the proposed package system:

- Pump Performance Specifications
- Batch data of the 4 stability batches in the proposed package system including specifications
- Description of the alternate container closure system
- Results of an identification test which was added to all product contact parts of the package system
- Pump Functionality Testing including results of pump performance studies and Pump Performance in long term Stability
- (b) (4) performed on the HDPE bottle of proposed package system
- Stability data from 4 lots updated to include (b) (4) conditions with comparative analysis of drug product stability in the approved tube versus the proposed bottle/pump.
- Literature references that supports the explanation that (b) (4)

**A Teleconference** was conducted on **September 16, 2011** regarding the acceptance criteria for the pump priming test. Prior to the teleconference, the sponsor submitted the document “Priming Specification Justification.pdf” by email.

Galderma agreed to submit the following by Monday, September 19, 2011:

1. The “Priming Specification Justification.pdf” document that was provided by email.
2. The reference reports that support the “Priming Specification Justification.pdf”, if not already submitted.
3. Galderma will confirm what numbers of bottles were used to generate the data tables.
4. The reference and derivation used to generate the last table in “Priming Specification Justification.pdf”.
5. An estimation of the number of bottles in each batch.
6. Any available pump priming testing data for batch release and batch stability

An **Information Request** dated September 20, 2011 (email) stated that:

Your proposal to provide responses this week is acceptable.

“In addition, we would like you to respond to the following post-meeting issues:

1. Provide the batch size for each of the lots listed in the Tables contained in the "Priming Specification Justification. pdf" document.
2. Provide the sampling plan for the commercial scale batch.
3. Provide the justification for the AQL values (b) (4) and their function in determining batch acceptability or rejection (as described in the method

(b) (4) .”

**Amendment #2** to the CMC Prior Approval Supplement (dated September 30, 2011; SN 0050, SD 251) provided additional information in response to the information requested during the teleconference (September 16, 2011) and email dated September 20, 2011. Refer to Appendix 2 for the full content of the document.

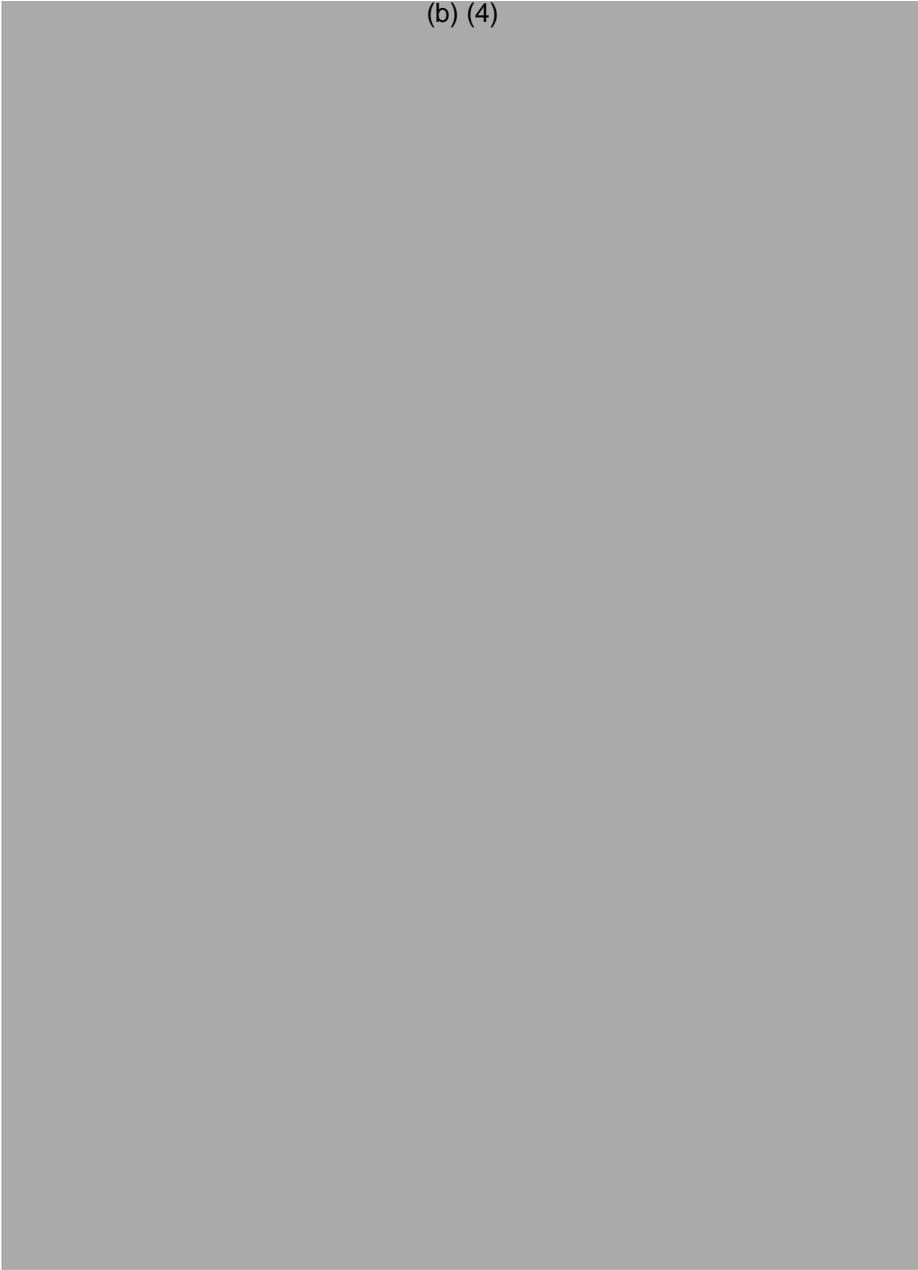
**A Teleconference** was conducted on **October 3, 2011** regarding the unspecified acceptance criteria, (e.g. report results in the specification). The sponsor agreed to modify the pump performance testing data provided in the specification table.

The **amendment dated October 3, 2011** (Amendment #3) contained a specification table in which **all** the pump performance testing was removed. The sponsor was notified that the Agency recommended removal of testing results for "amount dispensed (first 20/last 10)" and retention of data on acceptance criteria for additional pump functions (e.g., “number of pumps to prime” and “total amount of product dispensed”.)

Draft labeling was also submitted.

Galderma agreed to modify the table. (SN 0051, SD 253 submitted October 5, 2011). Refer to the Table 1 below for Pump function performance testing specifications..

(b) (4)



**A Teleconference** was conducted on **October 7, 2011** regarding the expiry of the drug product.

**(b) (4)** In order to maintain an expiry of 24 months for drug product dispensed in the alternate container/closure system (bottle with dispensing pump), the sponsor was asked to submit additional 6 month stability data under accelerated conditions and at room temperature.

Galderma agreed and provided an amendment by email (Amendment #4) to be followed by an official submission (dated October 7, 2011; SN 0053, SD 255).

The Quality reviewer provided the following comments regarding the adequacy of the submission in a review dated October 11, 2011:

“This resubmission is a complete response to the Agency’s not-approval decision made on February 07, 2011 at the end of the first review cycle. Supplement 004 to NDA 21-789

provided for an alternate container/closure system to Metrogel Gel, 1%: 2oz. high density polyethylene (HDPE) white bottle fitted with a 0.26mL dispensing pump with 22/410 tread and containing 55g of Metrogel Gel, 1% drug product. Total of eight (8) deficiencies were identified in the first review cycle. The supplement also provides for the labeling change corresponding to the proposed container/closure system change.”

“The main concerns found in the first review cycle include: (1) inadequate stability study to support the capability of the proposed container/closure system, (2) inadequate identification testing for the incoming packaging materials, and (3) inadequate pump performance testing for the proposed container/closure system. In this complete response and its amendments, the applicant addressed all the deficiencies adequately and provided sufficient justifications.”

“The revised labels and packaging insert were reviewed and found acceptable from the CMC perspective.”

“Therefore, the supplement is recommended for “Approval”.

**Reviewer’s comment:**

*I concur with the CMC reviewer regarding the adequacy of the submission to address the deficiencies and to document pump functionality as requested by FDA in the February 7, 2011 Complete Response Letter.*

**LABELING**

**Consults to evaluate the labeling submitted in S-4:**

**A. DDMAC:**

The reviewer provides the following comments in a review dated 2010-12-06:

**HIGHLIGHTS OF PRESCRIBING INFORMATION/ FULL PRESCRIBING INFORMATION INDICATIONS AND USAGE**

1. We note that safety and effectiveness in pediatric patients have not been established. Would it be appropriate to revise the Indications and Usage section of the label to say that METROGEL® is indicated for the topical treatment of inflammatory lesions of rosacea in adults? Otherwise, promotional materials may not communicate that the product is not for pediatric patients.

**Reviewer’s comment:**

*The disease population is adults. Since rosacea does not occur in the pediatric population, the use in children is off label and does not need to be communicated in labeling.*

**FULL PRESCRIBING INFORMATION DOSAGE AND ADMINISTRATION**

2. Claims regarding application may appear in promotional materials. (b) (4)  
(b) (4) HIGHLIGHTS section of the label states that treated areas should be cleansed before application. (b) (4)

(b) (4)

**Reviewer's comment:**

(b) (4)

*During the phase 3 trials, all subjects were instructed to use a gentle cleanser although compliance was not documented.*

**B. DMEPA (Division of Medication Error Prevention and Analysis):**

The reviewer provides the following comments in a review dated 2010-12-09:

- **CLARIFICATION OF LABELING:** Applies to labeling for both delivery systems, the pump and the tube

**COMMENTS TO THE APPLICANT**

DMEPA proposes the following recommendations for the proposed Metrogel pump container label and carton labeling.

**A. Principal display panels (container label and carton labeling)**

1. Ensure the size of the established name is at least ½ size the letters comprising the proprietary name and has prominence consistent with the proprietary name (type, size, color, and font) in accordance with 21 CFR 201.10 (g)(2).
2. The route of administration should be presented on the principal display panel as follows; 'For Topical Use Only'.

(b) (4)

**B. Proposed back panel (container label) and side panels (carton labeling)**

1. (b) (4)
2. Remove the following unnecessary statements so that there is less clutter on the back panel: "Excursions permitted between 59 and 86 F<sup>(b) (4)</sup>-30C", (b) (4) "US Patents Nos: 6,881,726 and 7,348,317" and "Galderma is a registered trademark".

3. (b) (4)

4. (b) (4)

C. (b) (4)

D. (b) (4)

**Reviewer's comment:**

- (b) (4)
- *This reviewer concurs with the recommendations from DMEPA for the 55 gram pump and 60 gram tube.*

In a review dated January 19, 2011 the CMC Reviewer, Yubing Tang, Ph. D., provided the following assessment of labeling:

**Evaluation: Inadequate**

**(Note: The following deficiencies have been communicated to the applicant via clinical PM, Paul Phillips, on December 21, 2010).**

(b) (4)

4. Add a bar code to the container label of pump configuration.

**On January 11, 2011, the sponsor submitted revised labels** for the carton and container in response to the email from the Agency dated January 3, 2011. In the cover letter, the sponsor addresses each recommendation and provides a justification for each decision not to incorporate Agency recommendations.

The following recommendations addressed in the letter dated January 11, 2011 were not fully implemented:

**55 g Pump**

- **Add a bar code to the container label of the pump configuration**
  - **Galderma response:** Based on 21 CFR 201.25(b)(1)ii this product is exempt from bar code requirement. It is sold through a distribution system directly to patients.
- **Remove the following unnecessary statements so that there is less clutter on the back panel: “US Patents Nos.: 6,881,726 and 7,348,317 and “Galderma is a registered trademark”.**
  - (b) (4)

(b) (4)

**60 g Tube**

- (b) (4)
  - (b) (4)
- **Remove the following unnecessary statements so that there is less clutter on the back panel: “US Patents Nos.: 6,881,726 and 7,348,317 and “Galderma is a registered trademark”.**
  - **Galderma response:** As space was not an issue for the tube,...the verbiage for the patent numbers and the trademark information remains. Please see the enclosed tube label.

***Reviewer’s comment:***

*In emails dated September 1, 2011 reviewers from DMEPA and CMC agreed that these responses from the sponsor were acceptable.*

**Revised Labeling submitted January 11, 2011 (Refer to Appendix 1 for proposed labels for 55 g pump submitted October 21, 2010.)**

**1) Proposed Metrogel (metronidazole) Gel, 1% 55 g Pump Labels**

**a) Container**

3 Pages Immediately Following Withheld - Draft Labeling b(4)

The **Quality Reviewer** provided the following comments regarding the adequacy of the amended labeling in a review dated October 11, 2011:

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

[Redacted]

[Redacted]

(b) (4)

**Reviewer comments regarding labeling:**

- *I concur with the reviewers from DMEPA and CMC (emails dated September 1, 2011) that the rationale provided by the sponsor for not implementing the changes below is acceptable.*
  - *US Patents Nos.: 6,881,726 and 7,348,317 were not removed from the back panel of the 55 g pump or 60 g tube “as space was not an issue”.*
  - (b) (4)
  - *According to the sponsor this product (55 g pump and 60 g tube) is exempt from the bar code requirement based on 21 CFR 201.25(b)(1)ii as it is sold through a distribution system directly to patients.*
- (b) (4)

• (b) (4)

**Conclusion:**

I concur with the CMC reviewer that the response to the Complete Response letter dated February 7, 2011 is adequate and the amended labeling is acceptable. Final Package Insert labeling is attached to this document.

**Recommended regulatory action:**

I recommend approval of the resubmission of the Prior Approval Labeling Supplement for the addition of container/ closure system (HDPE bottle with dispensing pump).

Melinda McCord, M.D.  
Medical Officer/Dermatology

11 Pages Immediately Following Withheld - b(4)

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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.**  
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/s/  
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MELINDA L MCCORD

01/17/2012

Letter signed, supplement approved  
Submission of this review delayed

GORDANA DIGLISIC

01/18/2012

## Medical Officer's Review of NDA 021789

Prior Approval Labeling Supplement: addition of HDPE bottle with dispensing pump.

**Document ID Number:** SD-60 (SN 0041); SD62 (SN 0043) (Amendment to supplement 4 with draft labeling for container and carton); SD 63 (SN 0044) (draft labeling for container and carton)

**Correspondence date:** 2010-08-11, 2010-09-30; 2010-10-21

**CDER Stamp date:** 2010-08-11; 2010-10-12; 2010-11-4

**Type of Submission:**

- Prior Approval Supplement (S-004): an alternative container/ closure system- HDPE bottle with dispensing pump.

**Sponsor:**

Galderma Laboratories, LP  
14501 N. Freeway  
Fort worth, TX 76177

**Drug:** METROGEL® (metronidazole) Gel, 1%

**Route of Administration:** topical

**Dosage Form:** gel

**Active Ingredient(s):** metronidazole

**Pharmacologic Category:** nitroimidazole

**Indication:** topical treatment of inflammatory lesions of rosacea

**Received for Review:** 2010-08-11

**Review completion date:** 2011-01-28

**Project Manager:** Paul Phillips

**Team Leader:** Gordana Diglisic, M.D.

**Reviewer:** Melinda McCord, M.D.

**Consultants:**

- Division of Drug Marketing, Advertising, and Communications (**DDMAC**)
- Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (**DMEPA**)

METROGEL® (metronidazole) Gel, 1% (NDA 021789) was approved on June 30, 2005 for the topical treatment of inflammatory lesions of rosacea.

Currently, METROGEL® (metronidazole) Gel, 1% is marketed in (b) (4) 60g aluminum tubes.

**Current submission:**

The sponsor has submitted a labeling supplement proposing an alternate container/closure system (2oz high density polyethylene (HDPE) white bottle fitted with a 0.26mL dispensing pump with 22/410 tread). The bottle with dispensing pump will contain 55g of METROGEL Gel, 1%.

This submission also provides the labeling change in response to the proposed container/closure system change.

In support of this supplement, the sponsor provided:

- Three month stability data from a single batch
- Photostability Study
- Proposed changes to Package Insert:
- Proposed Labeling

**Justification:**

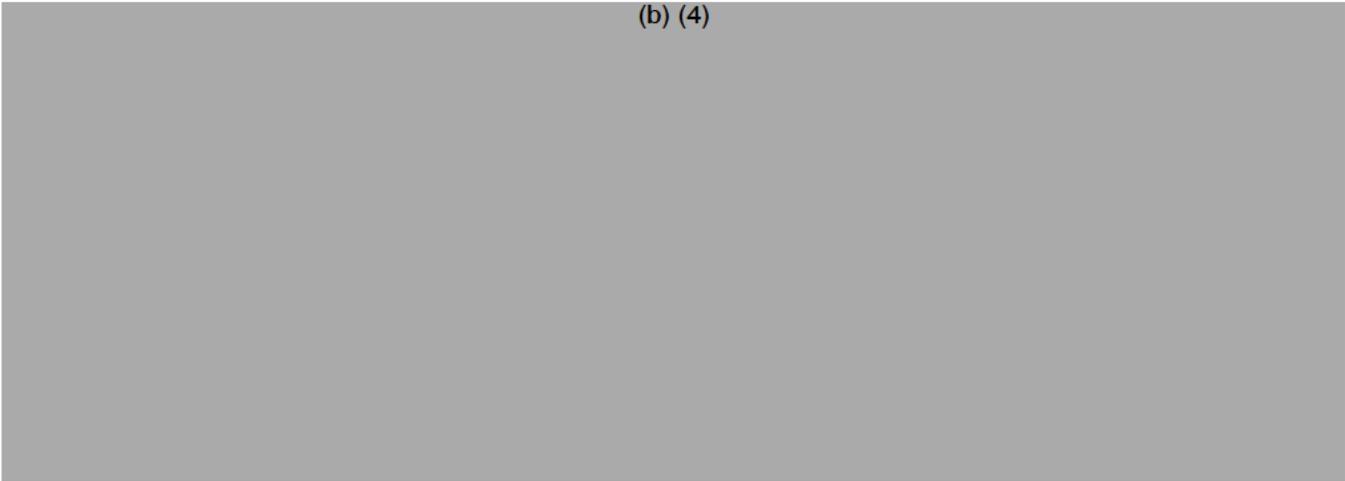
The sponsor maintains that the safety and efficacy of the product are unchanged due to the following:

- The drug product, Metronidazole Gel 1%, remains unchanged from the currently marketed product including the dosage form, excipients and formulation.
- All the materials used for the manufacturing of the container closure system comply with USP and 21 CFR regulations
- The suitability of the primary packaging for the protection of Metronidazole Gel, 1% from exposure to light was demonstrated by specific stability studies performed on the finished drug product
- Data obtained from accelerated and long-term stability studies demonstrate that the container closure system is well suited for the long-term storage of the drug product.

**Stability Studies:**

The applicant conducted the following studies in the stability program:  
Drug product release, photostability studies and accelerated and long-term stability studies from one industrial size batch.

(b) (4)



**Stability Data**

Metronidazole Gel, 1% remains within specifications (b) (4) for batch 070809 in the approved 60g aluminum tube and batch 071021 in the proposed 2oz bottle with dispensing pump. The values of all parameters remain within

specifications. The sponsor provides a commitment to conduct a long-term stability study on the first production batch to be reported in subsequent annual reports.

(b) (4)

(b) (4)

All values

remain with specifications.

**Photostability Study:** the Protocol is contained in SD 42 following Guidance for Industry: Q1B Photostability Testing of New Drug Substances and Products, November 1996

(b) (4)

- The proposed container closure system and the secondary packaging are adequate to protect the drug product. The metronidazole is stable when the drug product is directly exposed to light in the proposed container closure system.

According to ICH Q1B guideline, Metronidazole Gel, 1% in its proposed package is adequately protected from exposure to light.

**Proposed changes to Package Insert:**

**a) HIGHLIGHTS OF PRESCRIBING INFORMATION**

Revised: XX/2010

**b) HOW SUPPLIED/STORAGE AND HANDLING**

METROGEL® is supplied as follows:

60 gram tube – NDC 0299-3820-60

55 gram pump – NDC 0299-3820-01

**c) Rx Only**

US Patent No. 6,881,726 and 7,348,317

**Proposed Label for Metrogel pump: Carton/Container**

**A. Container:**

3 Pages Immediately Following Withheld - Draft Labeling b(4)

(b) (4)

**CMC:**

In a review dated January 19, 2011 the CMC Reviewer recommended a **COMPLETE RESPONSE** since “the **stability data indicated that the proposed container/closure system is less protective than the currently approved one (aluminum tube)**. In addition, the specifications for the incoming bottle and pump are not adequate in identification testing. The testing procedures for release and stability are not updated to include the package integrate testing for the proposed container/closure system.”

The following deficiencies were communicated to the applicant on December 21, 2010.

(b) (4)

4. Add a bar code to the container label of pump configuration.

**Summary of Deficiencies:**

**Deficiency 1.** Lack of adequate identification testing for the components of the proposed container/closure system

**Deficiency 2.** Specification for 0.26 mL pump is unclear.

**Deficiency 3.** Extractable testing results for the 2 oz. HDPE bottles could not be found.

**Deficiency 4.** Inadequate stability information

**Deficiency 5.** Insufficient stability protocol

**Deficiency 6.** Inadequate test procedures for the drug product specification

**Deficiency 7.** Inadequate response to the Agency’s IR letter (dated September 14, 2010)

**Deficiency 8.** Inadequate information to support the proposed expiration dating period

**Data necessary to resolve deficiencies:**

**Deficiency 1.**

**Item needed:** Identification test (b) (4) should be performed on each part of the proposed container/closure system that is in contact with Metrogel Gel, 1%. Add ID tests to the specifications for each lot of incoming bottles and dispersing pumps.

**Deficiency 2.**

**Item Needed:** Provide specification for the 0.26ml dispensing pump [in the same format as that for 2 oz. bottle (Table 3.2.P.7.2.1)].

**Deficiency 3.**

**Item Needed:** Provide extractable testing for the bottle according to USP <661> or provide the specific location (e.g. date of submission, section, and pages) to the data in DMF (b) (4)

**Deficiency 4.**

**Item Needed:** Provide a minimum of three months of stability data under both accelerated and long-term stability conditions from a minimum of three drug product batches.

**Deficiency 5**

**Item Needed:** Revise the stability protocol to include water loss testing, packaging integrity testing to evaluate changes of physical properties that may adversely affect the suitability of the container/closure system and appropriate pumping performance testing (e.g. number of priming, amount of actuation and actuation force).

**Deficiency 6.**

**Item Needed:** Revise test procedures of the product specification by stating that all tests should be performed on the samples pumped out from the proposed container/closure system.

**Deficiency 7.**

**Item Needed:** Provide the raw data of the dispensed amount (in grams) per actuation for the first 20 actuations and the last ten before exhaustion for all ten bottles included in 3.2.P.2.4 *Container Closure System Testing* submitted on September 30, 2010.

**Deficiency 8**

**Item Needed:** Provide an explanation as to (b) (4)  
Provide information to demonstrate that Metrogel 1% stored in the proposed HDPE bottle with dispersing pump will remain within the specification through the proposed expiration date (24 months).

**Complete Response (to be communicated to the applicant):**

1. Identification test (b) (4) should be performed on each part of the proposed container/closure system that is in contact with Metrogel Gel, 1%. Add ID tests to the specifications for each lot of incoming bottles and dispersing pumps.
2. Provide specification in the same format as that for 2 oz. bottle (Table 3.2.P.7.2.1) for 0.26ml dispensing pump.
3. We were unable to locate the extractable testing results for the 2 oz. HDPE bottles. Provide extractable testing for the bottle according to USP -:661.; or provide the specific location (e.g. date of submission, section, and pages) to the data in DMF (b) (4)
4. Provide minimum three month stability data under both accelerated and long-term stability conditions from a minimum of three batches.
5. Revise the stability protocol to include water loss testing, packaging integrity testing to evaluate changes of physical properties that may adversely affect the suitability of the container/closure system and an appropriate pumping performance testing (e.g. number of priming, amount of actuation and actuation force).
6. Revise test procedures of the product specification by stating that all tests should be performed on the samples pumped out from the proposed container/closure system.
7. As requested in the Agency's IR letter dated September 14, 2010, provide the raw data of the dispensed amount (in grams) per actuation for the first 20 actuations and the last ten before exhaustion for all ten bottles included in 32.P.2.4 Container Closure System Testing submitted on September 30, 2010.
8. Provide an explanation as to (b) (4)  
  
Provide information to demonstrate that Metrogel 1% stored in the proposed HDPE bottle with dispersing pump will remain within the specification through the proposed expiration date (24 months).

The recommendations regarding labeling and the carton/container label from the CMC reviewer were not fully implemented, and negotiations with the sponsor concerning labeling are in progress.

**Consults:**

**A. DDMAC:**

The reviewer provides the following comments in a review dated 2010-12-06:

**HIGHLIGHTS OF PRESCRIBING INFORMATION/ FULL PRESCRIBING INFORMATION INDICATIONS AND USAGE**

1. We note that safety and effectiveness in pediatric patients have not been established. Would it be appropriate to revise the Indications and Usage section of the label to say that METROGEL® is indicated for the topical treatment of inflammatory lesions of rosacea in adults? Otherwise, promotional materials may not communicate that the product is not for pediatric patients.

**Reviewer's comment:**

*The disease population is adults. Since rosacea does not occur in the pediatric population, the use in children is off label and does not need to be communicated in labeling.*

**FULL PRESCRIBING INFORMATION DOSAGE AND ADMINISTRATION**

2. Claims regarding application may appear in promotional materials. (b) (4)  
HIGHLIGHTS section of the label states that treated areas should be cleansed before application (b) (4)

**Reviewer's comment:**

(b) (4)

**B. DMEPA (Division of Medication Error Prevention and Analysis):**

The reviewer provides the following comments in a review dated 2010-12-09:

- We consider the pump system appropriate because it is consistent with the recommended dose of a “thin film” to the affected area and it looks like a topical product.
- **AERS RESULTS:** The AERS search retrieved a total of 35 reports. The majority of the reported cases involved adverse events such as peripheral neuropathy complaints and were not relevant to the medication error search, however one case did report a dispensing error that occurred with Metrogel and Metrogel-Vaginal.
- **CLARIFICATION OF LABELING:** Applies to labeling for both delivery systems, the pump and the tube

**COMMENTS TO THE APPLICANT**

DMEPA proposes the following recommendations for the proposed Metrogel pump container label and carton labeling.

**A. Principal display panels (container label and carton labeling)**

1. Ensure the size of the established name is at least ½ size the letters comprising the proprietary name and has prominence consistent with the proprietary name (type, size, color, and font) in accordance with 21 CFR 201.10 (g)(2).
2. The route of administration should be presented on the principal display panel as follows; ‘For Topical Use Only’.

(b) (4)

**B. Proposed back panel (container label) and side panels (carton labeling)**

1. (b) (4)
2. Remove the following unnecessary statements so that there is less clutter on the back panel: “Excursions permitted between 59 and 86 F<sup>(b) (4)</sup>-30C”, (b) (4) “US Patents Nos: 6,881,726 and 7,348,317” and “Galderma is a registered trademark”.

3. (b) (4)

4 (b) (4)

**C. (b) (4)**

(b) (4)

**D. (b) (4)**

(b) (4)

***Reviewer’s comment:***

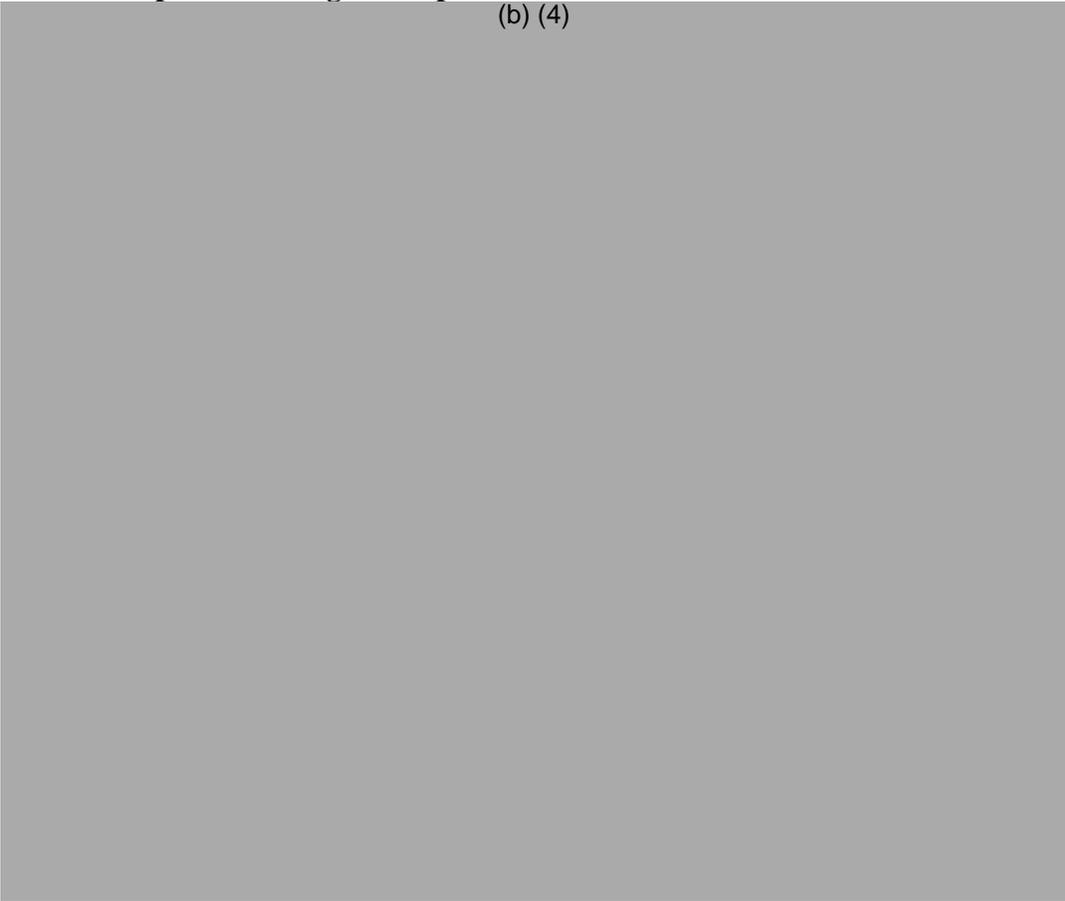
(b) (4)

*This reviewer concurs with the recommendations from DMEPA for the 55 gram pump and 60 gram tube.*

**On January 18, 2011, the sponsor submitted revised labels** for the carton and container and addressed each recommended revision of the label. In a letter dated January 11, 2011, the sponsor provides a justification for each decision not to incorporate Agency recommendations.

**Proposed Metrogel Pump labels**

(b) (4)



2 Pages Immediately Following Withheld - Draft Labeling b(4)



**Proposed Metrogel tube labels**

(b) (4)



The recommendations from the DMEPA reviewer were not fully implemented, and negotiations with the sponsor concerning labeling are in progress.

**Reviewer Conclusions:**

- I concur with the CMC reviewer that the stability data are inadequate to support the conclusion that the product remains safe and effective in the 2 oz bottle with dispensing pump.
- I concur with the CMC reviewer that the data from the study does not demonstrate that the 2 oz bottle with dispensing pump container/closure system preserves the claimed identity, strength, quality and purity of the drug product.
- I concur with recommendations by CMC and DMEPA for revisions of labeling. Negotiations with the sponsor are ongoing.
- Patient counseling information in Section 17 does not need to be amended for the proposed closure/ container system.

**Regulatory recommendation:**

Recommend: *Not approvable.*

This reviewer concurs with the CMC recommendation of COMPLETE RESPONSE to the Prior Approval Supplement for HDPE bottle with dispensing pump.

The above listed deficiencies and information needed for resolution should be communicated to the sponsor in the regulatory letter.

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/s/  
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MELINDA L MCCORD  
02/10/2011

GORDANA DIGLISIC  
02/10/2011

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-789/S004**

**CHEMISTRY REVIEW(S)**

<b>CHEMISTS REVIEW #2</b>		<b>1. ORGANIZATION</b>	<b>2. NDA NUMBER</b>
		ONDQA Div II, Branch VI and HFD-540	21-789
<b>3. NAME AND ADDRESS OF APPLICANT</b>		<b>4. COMMUNICATION, DATE</b>	
GALDEMA LABORATORIES, L.P. 14501 North Freeway Fort Worth, TX 76177		Supplement: S-004, Labeling Submission (PA) Letter Date ( <b>First Cycle</b> ): August 11, 2010 Complete Response Date ( <b>First Cycle</b> ): February 07, 2011 Letter Date ( <b>Resubmission</b> ): June 23, 2011 PDUFA Date ( <b>Resubmission</b> ): October 23, 2011	
<b>5. PROPRIETARY NAME</b>	<b>6. NAME OF THE DRUG</b>	<b>7. AMENDMENTS, REPORT, DATE</b>	
Metronidazole Gel 1%	METROGEL 1%	Amendment on September 30, 2011, October 05, 2011 and October 11, 2011	
<b>8. COMMUNICATION PROVIDES FOR:</b>			
The supplement provides alternate container/closure system – HDPE bottle with dispensing pump.			
<b>9. PHARMACOLOGICAL CATEGORY</b>	<b>10. HOW DISPENSED</b>	<b>11. RELATED IND, NDA, DMF</b>	
Treatment of the inflammatory lesions of rosacea	Rx	None	
<b>12. DOSAGE FORM</b>	<b>13. POTENCY</b>		
Gel	1%		
<b>14. CHEMICAL NAME AND STRUCTURE</b>			
Official Compendia: Metronidazole (USP) IUPAC name (b) (4) 2-methyl-5-nitro-(b) (4) 2-Methyl-5-nitroimidazole-1-ethanol. Empirical formula: C <sub>6</sub> H <sub>9</sub> N <sub>3</sub> O <sub>3</sub> Formula weight: 171.15 CAS registry number: CAS-443-48-1 Chemical structure:  <div style="text-align: center;">(b) (4)</div>			
<b>15. COMMENTS</b>			
This resubmission is a complete response to the Agency's not-approval decision made on February 07, 2011 at the end of the first review cycle. Supplement 004 to NDA 21-789 provided for an alternate container/closure system to Metrogel Gel, 1%: 2oz. high density polyethylene (HDPE) white bottle fitted with a 0.26mL dispensing pump with 22/410 tread and containing 55g of Metrogel Gel, 1% drug product. Total of eight (8) deficiencies were identified in the first review cycle. The supplement also provides for the labeling change corresponding to the proposed container/closure system change.  The main concerns found in the first review cycle include: (1) inadequate stability study to support the			

capability of the proposed container/closure system, (2) inadequate identification testing for the incoming packaging materials, and (3) inadequate pump performance testing for the proposed container/closure system. In this complete response and its amendments, the applicant addressed all the deficiencies adequately and provided sufficient justifications.

The revised labels and packaging insert were reviewed and found acceptable from the CMC perspective.

Therefore, the supplement is recommended for "Approval".

**16. CONCLUSION AND RECOMMENDATION**

Recommend Approval from CMC perspective.

<b>17. NAME</b>	<b>18. REVIEWERS SIGNATURE</b>	<b>19. DATE COMPLETED</b>
Yubing Tang	See appended electronic signature sheet	October 11, 2011

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/s/  
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YUBING TANG  
10/12/2011

THOMAS F OLIVER  
10/12/2011

# MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** January 24, 2010

**TO:** NDA 21-789/S004, CMC Review #1

**FROM:** Yubing Tang, Ph.D., Chemist  
(ONDQA Division II, Branch VI)

**THROUGH:** Tom Oliver, Ph.D., Chief, Branch VI  
(ONDQA Division II, Branch VI)

**CC:** Shulin Ding, Ph.D., Pharmaceutical Assessment Lead  
(ONDQA Division II, Branch IV)

**SUBJECT: CMC Review for the Amendment dated January 18, 2011**

The labeling deficiencies from CMC perspective were communicated to the applicant via clinical RPM, Paul Phillips, on December 21, 2010. These deficiencies are also documented in CMC review #1 dated January 18, 2011.

The applicant submitted the amendment on January 18, 2011 in response to the Agency's proposed labeling edits.

Evaluation on the amendment has found that all CMC labeling related issues identified in the communication on December 21, 2010 have been satisfactorily addressed.

Therefore, from a CMC perspective, this labeling in NDA 21-789/S004 is adequate.

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/s/  
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YUBING TANG  
01/24/2011

THOMAS F OLIVER  
01/24/2011

<b>CHEMISTS REVIEW #1</b>		<b>1. ORGANIZATION</b>	<b>2. NDA NUMBER</b>
		ONDQA Div II, Branch VI and HFD-540	21-789
<b>3. NAME AND ADDRESS OF APPLICANT</b>		<b>4. COMMUNICATION, DATE</b>	
GALDEMA LABORATORIES, L.P. 14501 North Freeway Fort Worth, TX 76177		Supplement #: S-004 Letter Date: August 11, 2010 Received Date: August 13, 2010 Type: Labeling Submission PDUFA DATE: February 13, 2011	
<b>5. PROPRIETARY NAME</b>	<b>6. NAME OF THE DRUG</b>		<b>7. AMENDMENTS, REPORT, DATE</b>
Metronidazole Gel 1%	METROGEL 1%		Amendments dated 09/30/2010 and 10/21/2010
<b>8. COMMUNICATION PROVIDES FOR:</b>			
The supplement provides alternate container/closure system – HDPE bottle with dispensing pump.			
<b>9. PHARMACOLOGICAL CATEGORY</b>	<b>10. HOW DISPENSED</b>		<b>11. RELATED IND, NDA, DMF</b>
Treatment of the inflammatory lesions of rosacea	Rx		DMF# (b) (4) and (b) (4) • Review of DMF (b) (4) is documented on DARRTS (b) (4) • Information is provided in the supplement application. Therefore, no separate review of DMF (b) (4) is necessary.
<b>12. DOSAGE FORM</b>	<b>13. POTENCY</b>		
Gel	1%		
<b>14. CHEMICAL NAME AND STRUCTURE</b>			
Official Compendia: Metronidazole (USP) IUPAC name: (b) (4), 2-methyl-5-nitro-; (b) (4) 2-Methyl-5-nitroimidazole-1-ethanol. Empirical formula: C <sub>6</sub> H <sub>9</sub> N <sub>3</sub> O <sub>3</sub> Formula weight: 171.15 CAS registry number: CAS-443-48-1 Chemical structure:  <div style="text-align: center;">(b) (4)</div>			
<b>15. COMMENTS</b>			
This supplement S-004 to NDA 21-789 provided changes to the approved container/closure system to Metrogel Gel, 1%. Alternate container/closure system – 2oz. high density polyethylene (HDPE) white bottle fitted with a 0.26mL dispensing pump with 22/410 tread is proposed. The bottle with dispensing pump will contain 55g of Metrogel Gel, 1%.			
This submission also provides the labeling change in response to the proposed container/closure system change.			

The construction materials of the c/c system comply with 21 CFR regulations for safe food contact. The functionality information was submitted at the request of the Agency. Photostability study was conducted per ICH 1QB and found acceptable. Three month stability data from a single batch (commercial size) are provided, under accelerated and long-term storage conditions. A post-approval stability commitment was included and found acceptable. Expiration dating period of is proposed to be 24 months at room temperature.

However, the **stability data indicated that the proposed container/closure system is less protective than the currently approved one (aluminum tube)**. In addition, the specifications for the incoming bottle and pump are not adequate in identification testing. The testing procedures for release and stability are not updated to include the package integrate testing for the proposed container/closure system.

This review also covers the labeling from CMC perspective. The deficiencies found have been communicated to the applicant by clinical PM, Paul Phillips, on December 21, 2010.

As the results of deficiencies and inadequacies, this supplement is recommended as “not approval”.

**16. CONCLUSION AND RECOMMENDATION**

Recommend COMPLETE RESPONSE from CMC perspective. Project manager is to draft the letter shown at the end of this review.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Yubing Tang	See appended electronic signature sheet	07-Jan.-2011

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/s/  
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YUBING TANG  
01/19/2011

THOMAS F OLIVER  
01/19/2011

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-789/S004**

**OTHER REVIEW(S)**



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

Date: December 9, 2010

Application Type/Number: NDA 021789

To: Susan Walker, MD, Director  
Division of Dermatology and Dental Products

Through: Melina Griffis, RPh, Team Leader  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Anne Crandall, PharmD  
Division of Medication Error Prevention and Analysis

Subject: Labeling Review

Drug Name(s): Metrogel (Metronidazole) Gel, 1%

Applicant: Galderma

OSE RCM #: 2010-2058

## **1 INTRODUCTION**

This review responds to a request from the Division of Dermatology and Dental Products (DDDP) for a medication error assessment of the proposed pump delivery system for Metrogel 1%. Metrogel is currently available in two strengths, 0.75% and 1% and is packaged in a tube. The proposed pump would be marketed only for the 1% strength. Both containers (pump and tube) will co-exist on the market and have the same directions for use. The proposed label and labeling were submitted as a CMC supplement on August 11, 2010.

## **2 METHODS AND MATERIALS**

For this review, DMEPA searched the FDA Adverse Event Reporting System (AERS) database for medication errors associated with the use of the currently marketed Metrogel. The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the labels or labeling of the product, the case was considered pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review (e.g. errors related to accidental exposures, intentional overdoses, etc.) were excluded from further analysis.

Additionally, the submitted labels and labeling were reviewed for medication error potential.

### **2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH CRITERIA**

The Adverse Events Reporting System (AERS) database search was limited to November 1, 2005 (the year the 1% gel was approved) to the date of the search, November 1, 2010 to capture relevant errors that reflect current clinical practice.

The following criteria were used for the AERS search: the trade name “Metrogel” was used exclusively to limit the cases to the topical formulation of Metronidazole and the MedRA reaction terms used for the search included “Medication Errors” and “Product Quality Issues”.

### **2.2 LABELS AND LABELING**

The Division of Medication Error Prevention and Analysis (DMEPA) uses Failure Mode and Effects Analysis<sup>1</sup> (FMEA) and lessons learned from post-marketing experience to evaluate the container and carton labeling and the prescribing information that was submitted on August 11, 2010 (no image). Additionally, DMEPA compared the proposed prescribing information to the currently approved package insert labeling (no image).

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

### **3 RESULTS**

The following summarizes our findings from the AERS search and review of the proposed container label and carton labeling.

#### **3.1 AERS RESULTS**

The AERS search retrieved a total of 35 reports. The majority of the reported cases involved adverse events such as peripheral neuropathy complaints and were not relevant to the medication error search, however one case did report a dispensing error that occurred with Metrogel and Metrogel-Vaginal. This report states that the topical formulation was dispensed rather than the prescribed vaginal formulation. The patient administered the topical formulation vaginally and experienced abdominal pain, however long term outcomes were not reported. The case provided no further details concerning the event.

#### **3.2 LABELS AND LABELING EVALUATION**

Our evaluation of the proposed label and labeling found that revisions could be made to the labels and labeling which remove unnecessary information in order to de-clutter the label and labeling and ensure pertinent statements are communicated and more visible.

### **4 DISCUSSION**

The pump delivery system and the labels and labeling for the new delivery system were evaluated for their medication error risk (b) (4)

#### **4.1 PUMP DELIVERY SYSTEM**

The introduction of the proposed pump delivery system is reasonable based on the dosage and administration of this product. Similar to the currently marketed (b) (4) 60 g tubes, the pump does not deliver metered doses. The pump delivery system may provide the additional advantage in limiting the amount that the pump releases as opposed to the tube which does not limit the amount released. Further we note that metered dose pumps typically are utilized with control substances which require an exact amount of drug to be delivered. Additionally, the pump resembles a topical container closure. Therefore, we consider the pump system appropriate because it is consistent with the recommended dose of a “thin film” to the affected area and it looks like a topical product.

#### **4.2 PRINCIPAL DISPLAY PANELS (CONTAINER LABEL AND CARTON LABELING)**

Analysis of the proposed label and labeling noted that there is no route of administration on the principal display panels. Metrogel is available in two different gel forms (vaginal and topical) which based on the formulation are delivered to distinct areas of the body. The AERS search indicates that errors can occur between these two different gel forms and may have negative outcomes. The currently marketed Metrogel Vaginal label and labeling states “For vaginal use only”. However, the proposed label and labeling does not include a route of administration. The proposed pump label and labeling should also

include the route of administration ‘topical’ or include the statement ‘for topical use only’ to avoid patient and prescriber confusion between the two formulations.

(b) (4)

#### **4.3 BACK PANEL (CONTAINER LABEL) AND SIDE PANELS (CARTON LABELING)**

The back panel of the container label and side panels of the carton labeling contain unnecessary statements which clutter the label and labeling thereby making important statements less visible. Removing unnecessary or repetitive statements and separating topics by space will increase the readability of important statements regarding application, storage and instructions for use.

### **5 CONCLUSION AND COMMENTS**

The Applicant submitted the labels and labeling for two different delivery systems (the pump and the tube) for Metrogel. The (b) (4) 60 g tube configuration (b) (4) currently marketed, however the proposed pump system is new for this product. Because the labels and labeling are virtually identical for these different delivery systems the recommendations provided below pertain to both Metrogel products.

Section 5.1 Comments to the Division contains our recommendations regarding the pump closure system. Section 5.2 Comments to the Applicant contains our recommendations for the container labels and the carton labeling. We request the recommendations in Section 5.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Janet Anderson, OSE project manager, at 301-796-0675.

#### **5.1 COMMENTS TO THE DIVISION**

The introduction of the proposed pump delivery system is reasonable based on the dosage and administration of this product as a “thin film” to the affected area. Additionally, the pump’s appearance is similar to other topically applied products.

#### **5.2 COMMENTS TO THE APPLICANT**

DMEPA proposes the following recommendations for the proposed Metrogel pump container label and carton labeling.

##### **A. Principal display panels (container label and carton labeling)**

1. Ensure the size of the established name is at least ½ size the letters comprising the proprietary name and has prominence consistent with the proprietary name (type, size, color, and font) in accordance with 21 CFR 201.10 (g)(2).

2. The route of administration should be presented on the principal display panel as follows; 'For Topical Use Only'.
3. Remove the small 1% statement next to the established name as there is a large 1% statement next to the Metrogel statement.

B. Proposed back panel (container label) and side panels (carton labeling)

1. [REDACTED] (b) (4)
2. Remove the following unnecessary statements so that there is less clutter on the back panel: "Excursions permitted between 59 and 86 F(°) (b) (4) -30C)", [REDACTED] (b) (4) "US Patents Nos: 6,881,726 and 7,348,317" and "Galderma is a registered trademark" .

3. [REDACTED] (b) (4)

4. [REDACTED] (b) (4)

[REDACTED] (b) (4)

- C. [REDACTED] (b) (4)

- D. [REDACTED] (b) (4)

## **6 REFERENCES**

### **1. Adverse Events Reporting System (AERS)**

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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/s/  
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ANNE CRANDALL  
12/09/2010

MELINA N GRIFFIS  
12/09/2010

DENISE P TOYER on behalf of CAROL A HOLQUIST  
12/09/2010

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

**\*\*PRE-DECISIONAL AGENCY MEMO\*\***

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**Date:** December 3, 2010

**To:** J. Paul Phillips, DDDP

**From:** Lynn Panholzer, PharmD, DDMAC

**Re:** NDA# 021789/S-004  
Metrogel® (metronidazole) Gel, 1%

As requested in your consult dated September 16, 2010, DDMAC has reviewed the draft labeling for Metrogel® (metronidazole) Gel, 1%. DDMAC's comments are based on the proposed labeling (PI, attached, and package labels for 60gm tube and 55gm pump) found in the electronic document room under the link <\\CDSESUB1\EVSPROD\NDA021789\021789.ENX>, submission date August 11, 2010.

DDMAC's comments on the PI are provided directly on the attached labeling. DDMAC has no comments on the package labels.

If you have any questions about DDMAC's comments on the PI please contact Lynn Panholzer at 6-0616 or at [Lynn.Panholzer@fda.hhs.gov](mailto:Lynn.Panholzer@fda.hhs.gov).

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/s/  
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LYNN M PANHOLZER  
12/06/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-789/S004**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No. 0910-0338  
Expiration Date: September 30, 2008  
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE  
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Galderma Laboratories, L.P.

DATE OF SUBMISSION

06/23/2011

TELEPHONE NO. (include Area Code)

817 961 5000

FACSIMILE (FAX) Number (include Area Code)

817 961 0020

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

14501 North Freeway  
Fort Worth, Texas 76177

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 021789

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Metrohidazole Gel

PROPRIETARY NAME (trade name) IF ANY

MetroGel

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

CGDE NAME (if any)

DOSAGE FORM:

gel

STRENGTHS:

1% w/w

ROUTE OF ADMINISTRATION:

Topical to the skin

(PROPOSED) INDICATION(S) FOR USE:

For the topical treatment of rosacea

APPLICATION DESCRIPTION

APPLICATION TYPE

(check one)

- NEW DRUG APPLICATION (CDA, 21 CFR 314.50)  ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)  
 BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE  505 (b)(1)  505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug

Holder of Approved Application

TYPE OF SUBMISSION (check one)

- ORIGINAL APPLICATION  AMENDMENT TO PENDING APPLICATION  RESUBMISSION  
 PRESUBMISSION  ANNUAL REPORT  ESTABLISHMENT DESCRIPTION SUPPLEMENT  EFFICACY SUPPLEMENT  
 LABELING SUPPLEMENT  CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT  OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

- CBE  CBE-30  Prior Approval (PA)

REASON FOR SUBMISSION

Amendment to S004

PROPOSED MARKETING STATUS (check one)

- PRESCRIPTION PRODUCT (Rx)  OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

1

THIS APPLICATION IS

- PAPER  PAPER AND ELECTRONIC  ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

<input checked="" type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input checked="" type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input checked="" type="checkbox"/>	4. Chemistry section
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input checked="" type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input checked="" type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify) _____

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <b>Paul Clark</b>		TYPED NAME AND TITLE Paul Clark, Director, Regulatory Affairs	DATE: 06/23/2011
ADDRESS (Street, City, State, and ZIP Code) 14501 North Freeway, Fort Worth TX 76177		Telephone Number 817 961 5336	

**Public reporting burden for this collection of information** is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
5901-B Ammendale Road  
Beltville, MD 20705-1266

Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research (HFM-99)  
1401 Rockville Pike  
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

## INSTRUCTIONS FOR FILLING OUT FORM FDA 356h

**APPLICANT INFORMATION** This section should include the name, street address, telephone and facsimile numbers of the legal person or entity submitting the application in the appropriate areas. Note that, in the case of biological products, this is the name of the legal entity or person to whom the license will be issued. The name, street address and telephone number of the legal person or entity authorized to represent a non-U.S. applicant should be entered in the indicated area. Only one person should sign the form.

**PRODUCT DESCRIPTION** This section should include all of the information necessary to identify the product that is the subject of this submission. For new applications, the proposed indication should be given. For supplements to an approved application, please give the approved indications for use.

**APPLICATION INFORMATION** If this submission is an ANDA or 505(b)(2), this section should include the name of the approved drug that is the basis of the application and identify the holder of the approved application in the indicated areas.

**TYPE OF SUBMISSION** should be indicated by checking the appropriate box:

**Original Application** = a complete new application that has never before been submitted;

**Amendment to a Pending Application** = all submissions to pending original applications, or pending supplements to approved applications, including responses to Information Request Letters;

**Resubmission** = a complete response to an action letter, or submission of an application that has been the subject of a withdrawal or a refusal to file action;

**Presubmission** = information submitted prior to the submission of a complete new application;

**Annual Report** = periodic reports for licensed biological products (for NDAs Form FDA-2252 should be used as required in 21 CFR 314.81 (b)(2));

**Establishment Description Supplement** = supplements to the information contained in the Establishment Description section (#15) for biological products;

**Efficacy Supplement** = submissions for such changes as a new indication or dosage regimen for an approved product, a comparative efficacy claim naming another product, or a significant alteration in the patient population; e.g., prescription to Over-The-Counter switch;

**Labeling Supplement** = all label change supplements required under 21 CFR 314.70 and 21 CFR 601.12 that do not qualify as efficacy supplements;

**Chemistry, Manufacturing, and Controls Supplement** = manufacturing change supplement submissions as provided in 21 CFR 314.70, 21 CFR 314.71, 21 CFR 314.72 and 21 CFR 601.12;

**Other** = any submission that does not fit in one of the other categories (e.g., Phase IV response). If this box is checked the type of submission can be explained in the **REASON FOR SUBMISSION** block.

**Submission of Partial Application** Letter date of agreement to partial submission should be provided. Also, provide copy of scheduled plan.

**CBE "Supplement-Changes Being Effected"** supplement submission for certain moderate changes for which distribution can occur when FDA receives the supplement as provided in 21 CFR 314.70 and 21 CFR 601.12.

**CBE-30** "Supplement-Changes Being Effectuated in 30 Days" supplement submission for certain moderate changes for which FDA receives at least 30 days before the distribution of the product made using the change as provided in 21 CFR 314.70 and 21 CFR 601.12.

**Prior Approval (PA)** "Prior Approval Supplements" supplement submission for a major change for which distribution of the product made using the change cannot occur prior to FDA approval as provided in 21 CFR 314.70 and 21 CFR 601.12.

**REASON FOR SUBMISSION** This section should contain a brief explanation of the submission, e.g., "manufacturing change from roller bottle to cell factory" or "response to Information Request Letter of 1/9/97" or "Pediatric exclusivity determination request" or "to satisfy a subpart H postmarketing commitment".

**NUMBER OF VOLUMES SUBMITTED** Please enter the number of volumes, including and identifying electronic media, contained in the archival copy of this submission.

**This application is**

Paper  Paper and Electronic  Electronic

Please check the appropriate box to indicate whether this submission contains only paper, both paper and electronic media, or only electronic media.

**ESTABLISHMENT INFORMATION** This section should include information on the locations of all manufacturing, packaging and control sites for both drug substance and drug product. If continuation sheets are used, please indicate where in the submission they may be found. For each site please include the name, address, telephone number, registration number (Central File Number), Drug Master File (DMF) number, and the name of a contact at the site. The manufacturing steps and/or type of testing (e.g. final dosage form, stability testing) conducted at the site should also be included. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Please note that, when applicable, the complete establishment description is requested under item 15.

**CROSS REFERENCES** This section should contain a list of all License Applications, Investigational New Drug Applications (INDs), NDAs, Premarket Approval Applications (PMAs), Premarket Notifications (510(k)s), Investigational Device Exemptions (IDEs), Biological Master Files (BMFs) and DMFs that are referenced in the current application.

**Items 1 through 20 on the reverse side of the form** constitute a check list that should be used to indicate the types of information contained within a particular submission. Please check all that apply. The numbering of the items on the checklist is not intended to specify a particular order for the inclusion of those sections into the submission. The applicant may include sections in any order, but the location of those sections within the submission should be clearly indicated in the Index. It is therefore recommended that, particularly for large submissions, the Index immediately follows the Form FDA 356h and, if applicable, the User Fee Cover Sheet (Form FDA 3397).

The CFR references are provided for most items in order to indicate what type of information should be submitted in each section. For further information, the applicant may consult the guidance documents that are available from the Agency.

**Signature** The form must be signed and dated. Ordinarily only one person should sign the form, i.e., the applicant, or the applicant's attorney, agent, or other authorized official. However, if the person signing the application does not reside or have a place of business within the United States, the application should be countersigned by an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

## David, Jeannie C

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**From:** David, Jeannie C  
**Sent:** Tuesday, September 20, 2011 3:35 PM  
**To:** 'ALMOND Richard'  
**Cc:** Phillips, J. Paul  
**Subject:** RE: Metrogel, 1% NDA 21-789 amendment

Dear Mr. Almond,

After discussion with the chemistry review team, your proposal to provide responses this week sounds fine.

In addition, we would like you to respond to the following post-meeting issues:

- 1. Provide the batch size for each of the lots listed in the Tables contained in the "Priming Specification Justification.pdf" document.*
- 2. Provide the sampling plan for the commercial scale batch.*
- 3. Provide the justification for the AQL values (b) (4) and their function in determining batch acceptability or rejection (as described in the method (b) (4))*

Please include your response to these additional issues in your upcoming amendment this week.

Regards,

Jeannie

Jeannie David, M.S.  
Regulatory Health Project Manager  
CDER/OPS/ONDQA  
Food and Drug Administration  
10903 New Hampshire Avenue  
Building 22, Room 1475  
Silver Spring, MD 20993  
Phone: (301) 796-4247  
Fax: (301) 796-9877  
jeannie.david@fda.hhs.gov

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**From:** ALMOND Richard [mailto:Richard.Almond@galderma.com]  
**Sent:** Monday, September 19, 2011 4:52 PM  
**To:** David, Jeannie C; Phillips, J. Paul  
**Subject:** Metrogel, 1% NDA 21-789 amendment

Ms. David and Mr. Phillips,

This email is a follow up to the September 16, 2011 telecon between FDA and Galderma Laboratories, L.P. (GLLP) regarding specifications for pump performance testing submitted in the June 23, 2011 amendment to Supplement 004. I had stated that I would submit an amendment to NDA 21-789 today 9/19/2011 that provides data and statistical analysis of the proposed pump performance testing specifications. FDA also requested updated stability data that shows pump performance testing data. I cannot provide the amendment today (9/19/2011) because the updated stability data tables have not been completed and summarized. I will provide the information (including an emailed courtesy copy) this week. Thanks for your understanding.

Best Regards,  
Rich Almond  
Galderma Laboratories, L.P.

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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.**  
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/s/  
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JEANNIE C DAVID  
09/20/2011



## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** September 16, 2011  
**TIME:** 2:00 – 2:30 PM EST  
**APPLICATION:** NDA 21-789/S-004  
**DRUG NAME:** Metrogel® (metronidazole) Gel, 1%  
**SPONSOR:** Galderma Laboratories, L.P.  
**TYPE OF MEETING:** Teleconference  
**PHONE NUMBER CALLED:** Call-in numbers provided by Galderma  
**MEETING CHAIR:** Yubing Tang, Ph.D.  
**MEETING RECORDER:** Jeannie David, M.S.

### FDA PARTICIPANTS:

Yubing Tang, Ph.D., Review Chemist, Office of New Drug Quality Assessment (ONDQA)  
Jeannie David, M.S., Regulatory Project Manager, ONDQA  
Melinda McCord, M.D., Medical Officer, Division of Dermatology and Dental Products (DDDP)  
Gordana Diglisic, M.D., Clinical Team Leader, DDDP  
Barbara J. Gould, Chief Project Management Staff, DDDP

### EXTERNAL PARTICIPANTS:

Richard Almond, MBA, RAC, Galderma Laboratories, L.P.  
Oliver Watts, Ph.D., Galderma Laboratories, L.P.

### BACKGROUND:

The Sponsor submitted NDA 21-789/S-004 dated August 11, 2010, to the Division of Dermatology and Dental Products (DDDP) for Metrogel® (metronidazole) Gel, 1%. This supplement, classified as a labeling supplement and managed by DDDP, proposes a new container/closure system, adding a pump top dispenser. The Agency issued a Complete Response (CR) letter dated February 7, 2011. The applicant submitted a resubmission on June 23, 2011, which was determined to be a complete response to the CR letter. The action date for this supplement is December 23, 2011.

In reviewing the chemistry, manufacturing and controls (CMC) sections for the resubmission, the chemistry review team determined that clarification and requests for information were needed regarding the acceptance criteria for the pump priming test.

Just prior to the teleconference, Galderma provided an informal copy of a document titled, “Priming Specification Justification.pdf” by email to Jeannie David, ONDQA. This document is attached to these minutes.

### POINTS DISCUSSED:

1. Galderma briefly gave an overview of the document, “Priming Specification Justification.pdf”.
  - a. The data given in the first 3 tables are measurements from 3 batches at different times.

(b) (4)

- i. FDA requested what numbers of bottles were used to generate the data tables. Galderma stated at least 10 bottles.
  - b. The last table is from ANSI standard, using the data from the first 3 tables.
    - i. FDA requested that Galderma provide the reference and derivation used to generate this table.
2. FDA asked about the prime specification.
  - a. FDA requested how many bottles Galderma plans to test for each stability testing station and for each batch?
    - i. After some discussion and referral to documents, Galderma stated 10 bottles minimum depending on batch size, and referenced the pump priming method and the last table in “Priming Specification Justification.pdf”.
  - b. FDA asked the definition of “AQL” (e.g., percent or bottle number)
    - i. Galderma stated the definition is located in the pump priming method (3.2.P.5, page 5 of 5), whose acceptance criteria is based on the ANSI standard.
  - c. FDA requested clarification on the definition of the second and third levels of acceptance criteria (e.g., 11 – 15, and >15), and what constitutes a “minor” or “major” defect.
    - i. Galderma stated that the classifications of “minor” and “major” are not predetermined, but will trigger different scopes of investigation.
  - d. FDA asked how many bottles are in each batch, and how the sample size links to batch size.
    - i. Galderma stated that they haven’t decided on how any given batch would be split into bottles and tubes, but that (b) (4) batch size.
    - ii. Galderma clarified that the sample size will depend on the batch size.
  - e. FDA asked if Galderma had generated any pump priming testing data for batch release and batch stability.
    - i. Galderma stated that they can submit this information to the NDA.

**ACTION ITEMS FOR SPONSOR:**

Galderma agreed to officially submit the following by Monday, September 19, 2011:

1. The “Priming Specification Justification.pdf” document that was provided by email.
2. The reference reports that support the “Priming Specification Justification.pdf”, if not already submitted.
3. Galderma will confirm what numbers of bottles were used to generate the data tables.
4. The reference and derivation used to generate the last table in “Priming Specification Justification.pdf”.
5. An estimation of the number of bottles in each batch.
6. Any available pump priming testing data for batch release and batch stability.

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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.**  
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/s/  
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JEANNIE C DAVID  
09/28/2011

YUBING TANG  
09/28/2011



NDA 021789

**MEETING MINUTES**

Galderma Laboratories, L.P.  
Attention: Paul Clark  
Director, Regulatory Affairs and Quality Assurance  
14501 North Freeway  
Fort Worth, TX 76177

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metrogel (metronidazole) Gel, 1%.

We also refer to the teleconference between representatives of your firm and the FDA on March 30, 2011. The purpose of the meeting was to clarify questions related to the Agency's Complete Response letter dated February 7, 2011.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Paul Phillips, Regulatory Project Manager at (301) 796-3935.

Sincerely,

*{See appended electronic signature page}*

Stanka Kukich, M.D.  
Deputy Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type A  
**Meeting Category:** Guidance Meeting

**Meeting Date and Time:** March 30, 2011; 12:30 p.m.  
**Meeting Location:** Teleconference

**Application Number:** NDA 021789/S-004  
**Product Name:** Metrogel (metronidazole) Gel, 1%  
**Indication:** Rosacea  
**Sponsor/Applicant Name:** Galderma Laboratories, L.P.

**Meeting Chair:** Stanka Kukich, M.D.  
**Meeting Recorder:** Paul Phillips

**FDA ATTENDEES**

Stanka Kukich, M.D., Deputy Director, DDDP  
Gordana Diglisic, M.D., Clinical Team Leader, DDDP  
Melinda McCord, M.D., Clinical Reviewer, DDDP  
Tom Oliver, Ph.D., Branch Chief, DNDQA II, Branch V  
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DNDQA II  
Yubing Tang, Ph.D., Product Quality Reviewer, DNDQA II, Branch V  
J. Paul Phillips, M.S., Regulatory Health Project Manager, DDDP

**SPONSOR ATTENDEES**

Oliver Watts, V.P., Regulatory & Technical Affairs  
Paul Clark, Director, Regulatory Affairs & Quality Assurance  
Phillip Brown, M.D., J.D., Sr. V.P., Medical and Regulatory Affairs

## 1.0 BACKGROUND

NDA 021789/S-004 for Metrogel (metronidazole) Gel, 1% was submitted to the Agency on August 11, 2010 and received on August 13, 2010. The Agency issued a Complete Response letter dated February 7, 2011. The applicant requested a Type A meeting to clarify some of the deficiencies listed in the Complete Response letter.

## 2.0 DISCUSSION

### Chemistry, Manufacturing and Controls (CMC)

#### **Question 4:**

*“Provide a minimum of three months of stability data under both accelerated and longterm stability conditions from a minimum of three drug product batches.”*

Galderma would like to propose alternative approaches to provide evidence of product stability in the proposed container closure system. The initial submission provided stability data for batch 755 packaged in a similar 2 oz. HDPE bottle fitted with a dispensing closure. Specifications for this container closure system were not included in the submission as this package was not initially planned to be marketed. For reference, drawings for this container closure system can be found beginning on page 7.

The stability data for this study may be found in the original submission (0000) in section 3.2.P.8. (b) (4)

(b) (4). For ease of reference, tables presenting all this data can be found beginning on page 9. The results of this study indicate adequate physical, chemical, and microbiological stability for all test materials with essentially no variation for all parameters tested from the values obtained at study initiation under all storage conditions tested (b) (4)

(b) (4) Overall, this study supports that an HDPE container provides adequate protection for the drug product throughout its proposed shelf life of 24 months.

Stability data submitted from one lot (071021) packaged in the proposed container closure system (b) (4) was submitted to support S004 in sequence 0041 section 3.2.P.8.3. Additional data has been collected since the submission of sequence 0041. There is now (b) (4)

(b) (4) Data tables can be found beginning on page 28. A comparison of the 6 month accelerated stability data from batch 755 and lot 071021 shows similar values (b) (4)

(b) (4) This comparison supports that the proposed container closure system provides adequate protection for the drug product. In addition, 3 commercial batches have been placed on stability under long term (b) (4) and accelerated (b) (4) The results of these studies will be reported in future annual reports.

The sponsor suggests that the combined body of stability data presented above is sufficient to evaluate the adequacy of the proposed packaging components for their intended use. As indicated, the appropriate quality of this unit will be confirmed by results from the ongoing stability study on 3 commercial batches.

**Response:**

Batch 755 is not considered to be a registration stability batch because it is not packaged in the proposed to-be-marketed container/closure system. Therefore, its stability data are supporting only in the specification setting and shelf-life projection for the proposed to-be-marketed product.

Because the proposed HDPE bottle with dispersing pump is a new container closure system for Metrogel, as we indicated previously, stability data of three months from three registration stability batches in both long-term and accelerated storage conditions were requested for specification setting and shelf-life projection.

You indicated on Page 4 of the briefing package that you have placed three commercial batches on stability in addition to Lot 71021, and proposed to report the stability data of the three commercial batches in annual reports. The proposal is unacceptable. You need to include, in the re-submission, three months of stability data of these three commercial batches and up-to-date stability data of Lot 71021.

**Meeting Discussion:**

**The applicant agreed to provide the requested stability data in the resubmission.**

**Question 5:**

*“Revise the stability protocol to include water loss testing, packaging integrity testing to evaluate changes of physical properties that may adversely affect the suitability of the container/closure system and appropriate pumping performance testing (e.g. number of priming, amount of actuation and actuation force).”*

The stability protocol submitted contains weight loss and package integrity. Please see Sequence 0041 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitments.

The objective and utility of pump performance testing as a part of the stability program is unclear. This is not a metered dose system. The label instructs the patient to dispense a quantity required to cover the affected area with a thin film. Prior to priming, the product is in contact only with the dip tube and the reservoir.

If the Agency’s concern is that pump performance will be affected over time when the pump mechanism is in contact with the product, Galderma proposes a postapproval commitment to conduct a simulated in-use test to evaluate this interaction. The pump performance (priming, amount delivered) would be evaluated over a period of time simulating patient use. Residual product will be assayed for metronidazole content and degradation products to confirm that the stability of the product is not affected under simulated use conditions. Finally, we would also

propose to add a pump performance test to the stability protocol of three commercial batches consisting of the determination of the number of pumps to prime and the quantity delivered for the first 10 actuations.

**Response:**

The proposed stability protocol is inadequate to support the proposed container/closure system because the examination of the pumping performance is not included and there is no acceptance criterion for Weight Loss testing in the protocol. In addition, it is unclear whether you have revised Packaging Integrity test method for the proposed container/closure system, including examination of the dispensing pump.

To evaluate the performance of the pumping system upon storage, the test procedure for pump performance should include assessment of the following: number of priming, amount dispensed per actuation, actuation force, and total deliverable by weight per container.

The simulated in-use testing for the commercial batches under the stability program can be conducted as proposed. However, the simulated in-use testing cannot substitute the pump performance evaluation over time in stability studies described in the paragraph above.

The Agency acknowledges that the proposed container/closure system is not a metered dose system. Therefore, we will not require you to conform to the standards that are strictly specific to metered dose products. However, demonstration of an adequate pump performance throughout the shelf-life of a pump product is necessary in order for the Agency to assure the quality of a pump product.

**Meeting Discussion:**

**The applicant agreed to develop a specification limit for the weight loss test and to revise the packaging integrity test.**

**The applicant stated that the drug product and pump do not come in contact with each other as part of the stability program. The Agency indicated that the drug product/pump would need to be evaluated over time to determine any potential effects that the aged product has on pump performance and any potential effects of drug product/pump contact. The applicant proposed that this could be evaluated as part of their ongoing stability study. The applicant inquired whether pump performance will become a routine test. The Agency stated that from the data generated the applicant could make an argument as to why routine testing would not be needed. The Agency also responded that the determination on whether the test would become routine or not would be a review issue.**

**Question 6:**

*“Revise test procedures of the product specification by stating that all tests should be performed on the samples pumped out from the proposed container/closure system.”*

The objective and utility of this request is unclear. Prior to priming, the product is in contact only with the dip tube and exterior surface of the pump reservoir. Therefore it is unlikely that the

majority of the product quality characteristics described in the stability protocol would be affected by the product passing transiently through the pump. An interaction between the product and the pump materials that could affect product quality would likely be detected through standard stability testing.

To address the possibility that the product's physical characteristics would be affected by passing through the pump, Galderma has recently compared the viscosity of 3 stability lots at T<sub>3mo</sub> of product pumped from the proposed container/closure system to product poured from the bottle. The results are presented in Table 1. This comparison shows that the physical characteristics of the product are not affected by passing the product through the pump.

Table 1 Viscosity\* Comparison of MetroGel 1% pumped from proposed container/closure system and poured from bottle at T<sub>3mo</sub>

(b) (4)

**Response:**

All test data should be indicative of the chemo-physical properties, quality and performance of the drug product immediately prior to applying to the patient. Even though the viscosity data provided demonstrate that viscosity is comparable between bulk product and the pumped out gel, other tests (e.g. pH, impurities, preservative concentration, etc.) may not show the comparability.

(b) (4)

**Meeting Discussion:**

**The Agency recommended that the applicant acquire samples through the pump for analytical testing. Refer to responses to Q6 & Q8.**

**Post-Meeting Addendum:**

**The applicant can provide data (from "fresh" and "aged" product) demonstrating that test results for pumped out material are similar to data generated from non-pumped out material. Based on the similarity of the data, the applicant could provide a justification for their choice in acquiring samples.**

**Question 8:**

(b) (4)

(b) (4)

**Response:**

(b) (4)

**Meeting Discussion:**

(b) (4)

(b) (4)

(b) (4)

**Additional Comment:**

To provide relevant and useful data, we would like to reiterate that all tests for batch release and stability studies should be performed on the pumped-out samples from the proposed container/closure system.

**Additional Administrative Comments**

Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the IND might identify additional comments or information requests.

**Meeting Discussion:**

**The applicant questioned differences in review requirements between this supplement and an earlier supplement for a pump for another dermatological product. The previous product uses the same pump as proposed in this supplement. The Agency acknowledged that the different review requirements exist between the two submissions, but stated the requirements for this supplement are deemed necessary to assure the strength and quality**

**of the proposed pump product according to the Agency's current thinking in reviewing pump submissions.**

**Post-Meeting Addendum:**

**The applicant can contact Dr. Terrance Ocheltree (Director, Division of New Drug Quality Assessment II; at 301-796-0315) for questions regarding review standards.**

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/s/  
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STANKA KUKICH  
04/15/2011

## Crandall, Anne

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**From:** Crandall, Anne  
**Sent:** Wednesday, January 19, 2011 12:55 PM  
**To:** Phillips, J. Paul  
**Cc:** Griffis, Melina  
**Subject:** RE: NDA 021789/S-004 (Metrogel, 1%)

Hi Paul,

The proposed label and labeling revisions for Metrogel (tube and pump) are acceptable to DMEPA. I will enter this email into DARRTS.

Thank you.

Anne

~~~~~  
Anne Crandall Tobenkin, PharmD.  
Safety Evaluator  
FDA/CDER/OSE/Division of Medication Error Prevention and Analysis  
10903 New Hampshire Ave. Mail Stop 4447  
Silver Spring, MD 20993  
Building #22, Rm 4465  
Phone number: 301-796-2282

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**From:** Phillips, J. Paul  
**Sent:** Wednesday, January 19, 2011 12:40 PM  
**To:** McCord, Melinda; Tang, Yubing (ONDQA Chemist); Panholzer, Lynn; Crandall, Anne  
**Cc:** Diglisic, Gordana; Ding, Shulin; Gould, Barbara  
**Subject:** NDA 021789/S-004 (Metrogel, 1%)

Hello all,

The sponsor of NDA 021789/S-004 (Metrogel, 1%) has sent in their response to our proposed labeling edits (SDN-65 in DARRTS).

You may access the submission in the EDR at the following link, please choose the submission dated 1/11/11:  
<\\CDSESUB1\EVSPROD\NDA021789\021789.enx>

The submission contains the revised carton/container (55g and 60g) and package insert. I have also pulled the labeling and placed it into the eRoom: [http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofDematologyandDentalProducts/0\\_cdbb](http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofDematologyandDentalProducts/0_cdbb)

Please review and if the sponsor's proposed changes are acceptable, please enter a very brief memo/addendum into DARRTS to indicate your acceptance of their edits, so we can take an action. If the changes are not acceptable, please inform me of what still needs to be changed and wait to enter a memo/addendum until the correct changes are made.

**Please respond by noon this Friday, 1/21/11.**

Thank you very much everyone for your review of this information.

*J. Paul Phillips, M.S.  
Regulatory Health Project Manager*

*Division of Dermatology and Dental Products  
Center for Drug Evaluation and Research*

Reference ID: 2893326

*Food & Drug Administration  
Bldg. 22, Room 5189  
10903 New Hampshire Ave.  
Silver Spring, MD 20993*

*Telephone: (301) 796-3935  
Fax: (301) 796-9895  
e-mail: Paul.Phillips@fda.hhs.gov*

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/s/  
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ANNE CRANDALL  
01/19/2011



Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-21789

-----  
SUPPL-4

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GALDERMA  
LABORATORIES  
LP

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METRONIDAZOLE GEL 1%

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/s/  
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J P PHILLIPS

09/16/2010

# REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO:  
**CDER-DDMAC-RPM**

FROM: (Name/Title, Office/Division/Phone number of requestor)  
**J. Paul Phillips/RPM, ODE III/DDDP/x6-3935**

REQUEST DATE  
**9-16-10**

IND NO.

NDA/BLA NO.  
**021789/S-004**

TYPE OF DOCUMENTS  
(PLEASE CHECK OFF BELOW)

NAME OF DRUG  
**Metrogel (metronidazole) Gel,  
0.1%**

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
(Generally 1 week before the wrap-up meeting)  
**12-7-10**

NAME OF FIRM:  
**Galderma Labs**

PDUFA Date: 2-11-11

## TYPE OF LABEL TO REVIEW

### TYPE OF LABELING:

(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE(IFU)

### TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

### REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
- LABELING REVISION

### EDR link to submission:

<\\CDSESUB1\EVSPROD\NDA021789\021789.ENX>

Submission date: 8/11/10

**Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.**

### COMMENTS/SPECIAL INSTRUCTIONS:

Labeling Meetings: TBD

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

- DARTS
- eMAIL
- HAND

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-21789

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SUPPL-4

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GALDERMA  
LABORATORIES  
LP

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METRONIDAZOLE GEL 1%

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/s/  
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J P PHILLIPS

09/16/2010