CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 200936

Name: Diclofenac Sodium Gel, 3%

Sponsor: Tolmar Inc.

Approval Date: October 28, 2013

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APPLICATION NUMBER:

ANDA 200936Orig1s000

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Other Action Letter(s)	
Labeling	**X**
Labeling Review(s)	**X**
Medical Review(s)	
Chemistry Review(s)	**X**
Pharm/Tox Review	
Statistical Review(s)	**X**
Bioequivalence Review(s)	**X**
Other Review(s)	**X**
Administrative & Correspondence Documents	**X**

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APPLICATION NUMBER:

ANDA 200936

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 200936

Tolmar Inc.
Attention: Michelle R. Ryder
Senior Director, Regulatory Affairs
701 Centre Ave.
Fort Collins, CO 80526

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 14, 2009, and submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Diclofenac Sodium Gel, 3%.

Reference is also made to your amendments dated March 10, July 8, and December 21, 2010; April 19 and September 27, 2011; March 23, May 11, July 12, September 28, October 31, and December 12, 2012; and January 24, August 8, August 14, and October 8, 2013. We also acknowledge receipt of your correspondences dated April 12 and November 8, 2010; April 27 and August 19, 2011; and September 14, 2012, addressing the patent issues noted below.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Diclofenac Sodium Gel, 3%, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Solaraze® Gel, 3%, of Fougera Pharmaceuticals Inc. (Fougera).

The RLD upon which you have based your ANDA, Fougera's Solaraze Gel, is subject to periods of patent protection. The following patents and their expiration dates are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

U.S. Patent Number	Expiration Date
5,639,738 (the '738 patent)	June 17, 2014
5,852,002 (the '002 patent)	June 17, 2014
5,929,048 (the '048 patent)	June 17, 2014
5,792,753 (the '753 patent)	August 11, 2015
5,914,322 (the '322 patent)	August 11, 2015
5,985,850 (the '850 patent)	August 11, 2015

Your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of these parents is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Diclofenac Sodium Gel, 3%, under this ANDA. You have notified the agency that Tolmar Inc. (Tolmar) complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation was initiated against Tolmar for infringement of these patents within the statutory 45-day period in the United States District Court for the District Court of New Jersey [Fougera Pharmaceuticals Inc. and Jagotec AG V. Tolmar Inc., Civil Action No. 10-02635 (KSH)(PS)]. You have also notified the agency that the litigation was dismissed.

With respect to 180-day generic drug exclusivity, we note that Tolmar was the first ANDA applicant for Diclofenac Sodium Gel, 3%, to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, Tolmar may be eligible for 180 days of generic drug exclusivity for Diclofenac Sodium Gel, 3%. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, would begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). The agency notes that Tolmar failed to obtain tentative approval of this ANDA within 30 months after the date on which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) (forfeiture of exclusivity for failed to obtain tentative approval). The agency is not, however, making a formal determination at this time of Tolmar’s eligibility for 180-day generic drug exclusivity. It will do so only if a subsequent paragraph IV applicant becomes eligible for full approval (a) within 180 days after Tolmar begins commercial marketing of Diclofenac Sodium Gel, 3%, or (b) at any time prior to the expiration of the last listed patent if Tolmar has not begun commercial marketing. Please submit correspondence to this ANDA informing the agency of the date commercial marketing begins.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA)(Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to

self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). 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 via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

ROBERT L WEST

10/28/2013

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200936

LABELING

CAP END (SHOULDER)

181 mm TUBE LENGTH

OPEN END

3.927" (1 1/4" diameter tube)

GLOBAL®

NDC 0115-1483-61

Diclofenac Sodium Gel

3%

FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.

℞ only

NET WT. 100 g

Diclofenac Sodium Gel, 3% contains Diclofenac Sodium (30 mg/g).

INACTIVE INGREDIENTS: Benzyl alcohol, hydroxyethyl cellulose, methoxypolyethylene glycol 350, PEG-60 hydrogenated castor oil, and purified water.

INDICATIONS: For the topical treatment of actinic keratosis.

WARNING: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

USUAL ADULT DOSAGE: 0.5 g of gel (size of a pea) applied to the affected skin and smoothed into the skin gently, or as directed by your physician. The usual duration of therapy is from 60 to 90 days. Please see package insert for full prescribing information.

Store at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature]. Protect from heat. Avoid freezing. See crimp of tube and/or carton for lot number and expiration date.

Manufactured by: TOLMAR Inc., Fort Collins, CO 80526

Distributed by: Global Pharmaceuticals, Division of IMPAX Laboratories, Inc., Philadelphia, PA 19124 02250 Rev. 1 06/13

TOLMAR Inc.
701 Centre Avenue
Fort Collins, CO 80526

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Fonts: (All type converted to outlines)
Helvetica condensed medium, Helvetica condensed bold, Helvetica
Futura EF medium; bold; book

Shown at 100%

Reference ID: 3392644

TOLMAR Inc.
701 Centre Avenue
Fort Collins, CO 80526

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Fonts: (converted to outline)
FuturaEF Book, Bold, Medium,
Helvetica LT Std Roman, Bold

Shown at 100%

GLOBAL®

NDC 0115-1483-61

Diclofenac Sodium Gel

3%

For external use only. Not for ophthalmic use.

℞ only **NET WT. 100 g**

GLOBAL®

NDC 0115-1483-61

Diclofenac Sodium Gel

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For external use only. Not for ophthalmic use.

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NDC 0115-1483-61
Diclofenac Sodium Gel
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For external use only. Not for ophthalmic use.
℞ only NET WT. 100 g

Manufactured by:
TOLMAR Inc., Fort Collins, CO 80526
Distributed by:
Global Pharmaceuticals, Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124

LOT and EXP on bottom flap

03441 Rev. 1 06/13

N
3 0115-1483-61 3

Non Varnish Area

Diclofenac Sodium Gel, 3% contains Diclofenac Sodium (30 mg/g).
INACTIVE INGREDIENTS: Benzyl alcohol, hydroxyethyl cellulose, methoxypolyethylene glycol 350, PEG-60 hydrogenated castor oil, and purified water.
INDICATIONS: For the topical treatment of actinic keratosis.
WARNING: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
USUAL ADULT DOSAGE: 0.5 g of gel (size of a pea) applied to the affected skin and smoothed into the skin gently, or as directed by your physician. The usual duration of therapy is from 60 to 90 days. Please see package insert for full prescribing information.
Store at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature].
Protect from heat. Avoid freezing.
Caution: For external use only. Not for ophthalmic use. Sun avoidance is indicated during therapy.

GLOBAL®

NDC 0115-1483-56

Diclofenac Sodium Gel

3%

For external use only. Not for ophthalmic use.

℞ only NET WT. 50 g

GLOBAL®

NDC 0115-1483-56

Diclofenac Sodium Gel

3%

For external use only. Not for ophthalmic use.

℞ only NET WT. 50 g

GLOBAL®

NDC 0115-1483-56

Diclofenac Sodium Gel

3%

For external use only. Not for ophthalmic use.

℞ only NET WT. 50 g

Manufactured by:
TOLMAR Inc., Fort Collins, CO 80526
Distributed by:
Global Pharmaceuticals, Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124

LOT and EXP on bottom flap

03440 Rev. 0 06/13

N 3 0115-1483-56 9

Non Varnish Area

Diclofenac Sodium Gel, 3% contains Diclofenac Sodium (30 mg/g).

INACTIVE INGREDIENTS: Benzyl alcohol, hydroxyethyl cellulose, methoxypolyethylene glycol 350, PEG-60 hydrogenated castor oil, and purified water.

INDICATIONS: For the topical treatment of actinic keratosis.

WARNING: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Store at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature]. Protect from heat. Avoid freezing.

USUAL ADULT DOSAGE: 0.5 g of gel (size of a pea) applied to the affected skin and smoothed into the skin gently, or as directed by your physician. The usual duration of therapy is from 60 to 90 days.

Caution: For external use only. Not for ophthalmic use. Sun avoidance is indicated during therapy. Please see package insert for full prescribing information.

TOLMAR Inc.
701 Centre Avenue
Fort Collins, CO 80526

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TOLMAR Inc.
701 Centre Avenue
Fort Collins, CO 80526

(b) (4)

Fonts:
Helvetica (bold, bold condensed, bold condensed oblique, bold narrow, light condensed, light condensed oblique, narrow

Shown at 100%

(b) (4)

GLOBAL®

Diclofenac Sodium Gel, 3%

℞ only

FOR DERMATOLOGIC USE ONLY. NOT FOR OPHTHALMIC USE.

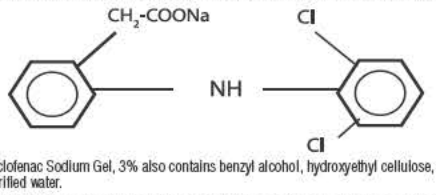
DESCRIPTION

Diclofenac Sodium Gel, 3%, contains the active ingredient, diclofenac sodium, in a clear, transparent, colorless to slightly yellow gel base. Diclofenac sodium is a white to slightly yellow crystalline powder. It is freely soluble in methanol, soluble in ethanol, sparingly soluble in water, slightly soluble in acetone, and partially insoluble in ether. The chemical name for diclofenac sodium is:

Sodium [o-(2,6-dichloranilino) phenyl] acetate

Diclofenac sodium has a molecular weight of 318.13.

The CAS number is CAS-15307-79-6. The structural formula is represented below:



Diclofenac Sodium Gel, 3% also contains benzyl alcohol, hydroxyethyl cellulose, methoxypolyethylene glycol 350, PEG-60 hydrogenated castor oil, and purified water.

1 g of Diclofenac Sodium Gel, 3% contains 30 mg of the active substance, diclofenac sodium.

CLINICAL PHARMACOLOGY

The mechanism of action of diclofenac sodium in the treatment of actinic keratoses (AK) is unknown. The contribution to efficacy of individual components of the vehicle has not been established.

Pharmacokinetics

Absorption

When diclofenac sodium gel, 3% is applied topically, diclofenac is absorbed into the epidermis. In a study in patients with compromised skin (mainly atopic dermatitis and other dermatitic conditions) of the hands, arms or face, approximately 10% of the applied dose (2 grams of 3% gel over 100 cm^2) of diclofenac was absorbed systemically in both normal and compromised epidermis after seven days, with four times daily applications.

After topical application of 2 g diclofenac sodium gel, 3% three times daily for six days to the calf of the leg in healthy subjects, diclofenac could be detected in plasma. Mean bioavailability parameters were $AUC_{0\,t}$ 9±19 ng/hr/mL (mean±SD) with a C_{max} of 4±5 ng/mL and a T_{max} of 4.5±8 hours. In comparison, a single oral 75 mg dose of diclofenac (Voltaren®)† produced an AUC of 1600 ng/hr/mL. Therefore, the systemic bioavailability after topical application of diclofenac sodium gel, 3% is lower than after oral dosing.

Comparative bioavailability studies have not been conducted between available diclofenac topical products (gels containing 1 - 3% diclofenac) which have different dosing regimens. A cross-study evaluation of the data indicates that diclofenac is more bioavailable when applied to diseased skin and less bioavailable when applied to intact skin.

Blood drawn at the end of treatment from 60 patients with AK lesions treated with diclofenac sodium gel, 3% in three adequate and well-controlled clinical trials was assayed for diclofenac levels. Each patient was administered 0.5 g of diclofenac sodium gel, 3% twice a day for up to 105 days. There were up to three 5 cm X 5 cm treatment sites per patient on the face, forehead, hands, forearm, and scalp. Serum concentrations of diclofenac were, on average, at or below 20 ng/mL. These data indicate that systemic absorption of diclofenac in patients treated topically with diclofenac sodium gel, 3% is much lower than that occurring after oral daily dosing of diclofenac sodium.

No information is available on the absorption of diclofenac when diclofenac sodium gel, 3% is used under occlusion.

Distribution

Diclofenac binds tightly to serum albumin. The volume of distribution of diclofenac following oral administration is approximately 550 mL/kg.

Metabolism

Biotransformation of diclofenac following oral administration involves conjugation at the carboxyl group of the side chain or single or multiple hydroxylations resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, however to a much smaller extent than diclofenac. Metabolism of diclofenac following topical administration is thought to be similar to that after oral administration. The small amounts of diclofenac and its metabolites appearing in the plasma following topical administration makes the quantification of specific metabolites imprecise.

Elimination

Diclofenac and its metabolites are excreted mainly in the urine after oral dosing. Systemic clearance of diclofenac from plasma is 263±56 mL/min (mean±SD). The terminal plasma half-life is 1-2 hours. Four of the metabolites also have short terminal half-lives of 1-3 hours.

INDICATIONS AND USAGE

Diclofenac Sodium Gel, 3% is indicated for the topical treatment of actinic keratoses (AK). Sun avoidance is indicated during therapy.

CLINICAL STUDIES

Clinical trials were conducted involving a total of 427 patients (213 treated with diclofenac sodium gel, 3% and 214 with a gel vehicle). Each patient had no fewer than five AK lesions in a major body area, which was defined as one of five 5 cm X 5 cm regions: scalp, forehead, face, forearm and hand. Up to three major body areas were studied in any patient. All patients were 18 years of age or older (male and female) with no clinically significant medical problems outside of the AK lesions and had undergone a 60-day washout period from disallowed medications (masoprocol, 5-fluorouracil, cyclosporine, retinoids, trichloroacetic acid/lactic acid/peel, 50% glycolic acid peel) and hyaluronan-containing cosmetics. Patients were excluded from participation for reasons of known or suspected hypersensitivity to any diclofenac sodium gel, 3% ingredient, pregnancy, allergies to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), or other dermatological conditions which might affect the absorption of the study medication. Application of dermatologic products such as sunscreens, cosmetics, and other drug products was not permitted. Patients were instructed to apply a small amount of diclofenac sodium gel, 3% (approximately 0.5 g) onto the affected skin, using their fingers, and gently smoothing the gel over the lesion. In addition, all patients were instructed to avoid sun exposure. Complete clearing of the AK lesions 30 days after completion of treatment was the primary efficacy variable. No long-term patient follow-ups, after the 30-day assessments, were performed for the detection of recurrence.

Complete Clearance of Actinic Keratosis Lesions 30 Days Post-Treatment (all locations)

	Diclofenac Sodium Gel, 3%	Vehicle	p-value
Study 1 90 days treatment	27/58 (47%)	11/59 (19%)	<0.001
Study 2 90 days treatment	18/53 (34%)	10/55 (18%)	0.061
Study 3 60 days treatment	15/48 (31%)	5/49 (10%)	0.021
30 days treatment	7/49 (14%)	2/49 (4%)	0.221

Complete Clearance of Actinic Keratosis Lesions 30 Days Post-Treatment (by location)

	Scalp	Forehead	Face	Arm/Forearm	Back of Hand
Study 1 90 days treatment					
Diclofenac Sodium Gel, 3%	1/4 (25%)	17/30 (57%)	9/17 (53%)	4/12 (33%)	6/16 (38%)
Vehicle	3/9 (33%)	8/24 (33%)	5/17 (29%)	4/12 (33%)	0/14 (0)
p-value	0.7646	0.0908	0.1682	1.000	0.0650
Study 2 90 days treatment					
Diclofenac Sodium Gel, 3%	2/6 (33%)	9/19 (47%)	4/5 (80%)	5/8 (63%)	1/17 (6%)
Vehicle	0/4 (0)	6/22 (27%)	2/8 (25%)	0/5 (0)	3/16 (19%)
p-value	0.4235	0.1870	0.0727	0.0888	0.2818
Study 3 60 days treatment					
Diclofenac Sodium Gel, 3%	3/7 (43%)	13/31 (42%)	10/19 (53%)	0/1 (0)	2/8 (25%)
Vehicle	0/6 (0)	5/36 (14%)	2/13 (15%)	0/2 (0)	1/9 (11%)
p-value	0.2271	0.0153	0.0433	-	0.4637
30 days treatment					
Diclofenac Sodium Gel, 3%	2/5 (40%)	4/29 (14%)	3/14 (21%)	0/0 (0)	0/9 (0)
Vehicle	0/5 (0)	2/29 (7%)	2/18 (11%)	0/1 (0)	1/9 (11%)
p-value	0.2299	0.3748	0.4322	-	0.6521
All data combined					
Diclofenac Sodium Gel, 3%	8/22 (36%)	43/109 (39%)	26/55 (47%)	9/21 (43%)	9/50 (18%)
Vehicle	3/24 (13%)	21/111 (19%)	11/56 (20%)	4/20 (20%)	5/48 (10%)
p-value	0.0903	0.0013	0.0016	0.2043	0.3662

CONTRAINDICATIONS

Diclofenac Sodium Gel, 3% is contraindicated in patients with a known hypersensitivity to diclofenac, benzyl alcohol and/or polyethylene glycol monomethyl ether 350.

WARNINGS

As with other NSAIDs, anaphylactoid reactions may occur in patients without prior exposure to diclofenac. Diclofenac sodium should be given with caution to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs.

PRECAUTIONS

General

Diclofenac sodium gel, 3% should be used with caution in patients with active gastrointestinal ulceration or bleeding and severe renal or hepatic impairments. Diclofenac sodium gel, 3% should not be applied to open skin wounds, infections, or exfoliative dermatitis. It should not be allowed to come in contact with the eyes.

The safety of the concomitant use of sunscreens, cosmetics or other topical medications and diclofenac sodium gel, 3% is unknown.

Information for Patients

In clinical studies, localized dermal side effects such as contact dermatitis, exfoliation, dry skin and rash were found in patients treated with diclofenac sodium gel, 3% at a higher incidence than in those with placebo.

Patients should understand the importance of monitoring and follow-up evaluation, the signs and symptoms of dermal adverse reactions, and the possibility of irritant or allergic contact dermatitis. If severe dermal reactions occur, treatment with diclofenac sodium gel, 3% may be interrupted until the condition subsides. Exposure to sunlight and the use of sunlamps should be avoided.

Safety and efficacy of the use of diclofenac sodium gel, 3% together with other dermal products, including cosmetics, sunscreens, and other topical medications on the area being treated, have not been studied.

Drug Interactions

Specific interaction studies between diclofenac sodium gel, 3% and other topical or oral agents were not performed.

Oral Nonsteroidal Anti-Inflammatory Drugs

Although low, there is systemic exposure to diclofenac following labeled use of diclofenac sodium gel, 3%. Therefore, concomitant administration of diclofenac sodium gel, 3% with oral NSAIDS or aspirin may result in increased NSAID adverse effects.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There did not appear to be any increase in drug-related neoplasms following daily topical applications of diclofenac sodium gel for 2 years at concentrations up to 0.035% diclofenac sodium and 2.5% hyaluronate sodium in albino mice. (Note: diclofenac sodium gel, 3% contains 3% diclofenac sodium.) When administered orally for 2 years, diclofenac showed no evidence of carcinogenic potential in rats given diclofenac sodium at up to 2 mg/kg/day (3 times the estimated systemic human exposure*), or in mice given diclofenac sodium at up to 0.3 mg/kg/day in males and 1 mg/kg/day in females (25% and 83%, respectively, of the estimated systemic human exposure).

A photococarcinogenicity study with up to 0.035% diclofenac in the diclofenac sodium gel, 3% vehicle gel was conducted in hairless mice at topical doses up to 2.8 mg/kg/day. Median tumor onset was earlier in the 0.035% group (diclofenac sodium gel, 3% contains 3% diclofenac sodium).

Diclofenac was not genotoxic in *in vitro* point mutation assays in mammalian mouse lymphoma cells and Ames microbial test systems, or when tested in mammalian *in vivo* assays including dominant lethal and male germinal epithelial chromosomal studies in mice, and nucleus anomaly and chromosomal aberration studies in Chinese hamsters. It was also negative in the transformation assay utilizing BALB/3T3 mouse embryo cells.

Fertility studies have not been conducted with diclofenac sodium gel, 3%. Diclofenac sodium showed no evidence of impairment of fertility after oral treatment with 4 mg/kg/day (7 times the estimated systemic human exposure) in male or female rats.

* Based on body surface area and assuming 10% bioavailability following topical application of 2 g diclofenac sodium gel, 3% per day (1 mg/kg diclofenac sodium).

Pregnancy:

Teratogenic Effects: Pregnancy Category B

The safety of diclofenac sodium gel, 3% has not been established during pregnancy. However, reproductive studies performed with diclofenac sodium alone at oral doses up to 20 mg/kg/day (15 times the estimated systemic human exposure*) in mice, 10 mg/kg/day (15 times the estimated systemic human exposure) in rats, and 10 mg/kg/day (30 times the estimated systemic human exposure) in rabbits have revealed no evidence of teratogenicity despite the induction of maternal toxicity. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival.

* Based on body surface area and assuming 10% bioavailability following topical application of 2 g diclofenac sodium gel, 3% per day (1 mg/kg diclofenac sodium).

Diclofenac has been shown to cross the placental barrier in mice and rats. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy unless the benefits to the mother justify the potential risk to the fetus. Because of the risk to the fetus resulting in premature closure of the ductus arteriosus, diclofenac should be avoided in late pregnancy.

Labor and Delivery

The effects of diclofenac on labor and delivery in pregnant women are unknown. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), use of diclofenac during late pregnancy should be avoided and, as with other nonsteroidal anti-inflammatory drugs, it is possible that diclofenac may inhibit uterine contractions and delay parturition.

TOLMAR Inc.
701 Centre Avenue
Fort Collins, CO 80526

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Shown at 100%

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Nursing Mothers
Because of the potential for serious adverse reactions in nursing infants from diclofenac sodium, 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.

Pediatric Use
Actinic keratoses is not a condition seen within the pediatric population. Diclofenac sodium gel, 3% should not be used by children.

Geriatric Use
Of the 211 subjects treated with diclofenac sodium gel, 3% in controlled clinical studies, 143 subjects were 65 and over. Of those 143 subjects, 55 subjects were 75 and over. 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.

ADVERSE REACTIONS
Of the 423 patients evaluable for safety in adequate and well-controlled trials, 211 were treated with diclofenac sodium gel, 3% drug product and 212 were treated with a vehicle gel. Eighty-seven percent (87%) of the diclofenac sodium gel, 3%-treated patients (183 patients) and 84% of the vehicle-treated patients (178 patients) experienced one or more adverse events (AEs) during the studies. The majority of these reactions were mild to moderate in severity and resolved upon discontinuation of therapy.

Of the 211 patients treated with diclofenac sodium gel, 3%, 172 (82%) experienced AEs involving skin and the application site compared to 160 (75%) vehicle-treated patients. Application site reactions (ASRs) were the most frequent AEs in both diclofenac sodium gel, 3%-and vehicle-treated groups. Of note, four reactions, *contact dermatitis, rash, dry skin and exfoliation* (scaling) were significantly more prevalent in the diclofenac sodium gel, 3% group than in the vehicle-treated patients.

Eighteen percent of diclofenac sodium gel, 3%-treated patients and 4% of vehicle-treated patients discontinued from the clinical trials due to adverse events (whether considered related to treatment or not). These discontinuations were mainly due to skin irritation or related cutaneous adverse reactions.

Table 1 below presents the AEs reported at an incidence of >1% for patients treated with either diclofenac sodium gel, 3% or vehicle (60- and 90-day treatment groups) during the phase 3 studies.

Table 1. Adverse Events Reported (>1% in Any Treatment Group) During Diclofenac Sodium Gel, 3% Phase 3 Clinical Trials Incidences for 60-Day and 90-Day Treatments

	60-day Treatment		90-day Treatment	
	Diclofenac Sodium Gel, 3% (%) N=48	Gel Vehicle (%) N=49	Diclofenac Sodium Gel, 3% (%) N=114	Gel Vehicle (%) N=114
BODY AS A WHOLE	**21**	**20**	**20**	**18**
Abdominal Pain	2	0	1	0
Accidental Injury	0	0	4	2
Allergic Reaction	0	0	1	3
Asthenia	0	0	2	0
Back Pain	4	0	2	2
Chest Pain	2	0	1	0
Chills	0	2	0	0
Flu Syndrome	10	6	1	4
Headache	0	6	7	6
Infection	4	6	4	5
Neck Pain	0	0	2	0
Pain	2	0	2	2
CARDIOVASCULAR SYSTEM	**2**	**4**	**3**	**1**
Hypertension	2	0	1	0
Migraine	0	2	1	0
Phlebitis	0	2	0	0
DIGESTIVE SYSTEM	**4**	**0**	**6**	**8**
Constipation	0	0	0	2
Diarrhea	2	0	2	3
Dyspepsia	2	0	3	4
METABOLIC AND NUTRITIONAL DISORDERS	**2**	**8**	**7**	**2**
Creatine Phosphokinase Increased	0	0	4	1
Creatinine Increased	2	2	0	1
Edema	0	2	0	0
Hypercholesteremia	0	2	1	0
Hyperglycemia	0	2	1	0
SGOT Increased	0	0	3	0
SGPT Increased	0	0	2	0
MUSCULOSKELETAL SYSTEM	**4**	**0**	**3**	**4**
Arthralgia	2	0	0	2
Arthrosis	2	0	0	0
Myalgia	2	0	3	1
NERVOUS SYSTEM	**2**	**2**	**2**	**5**
Anxiety	0	2	0	1
Dizziness	0	0	0	4
Hypokinesia	2	0	0	0
RESPIRATORY SYSTEM	**8**	**8**	**7**	**6**
Asthma	2	0	0	0
Dyspnea	2	0	2	0
Pharyngitis	2	8	2	4
Pneumonia	2	0	0	1
Rhinitis	2	2	2	2
Sinusitis	0	0	2	0
SKIN AND APPENDAGES	**75**	**86**	**86**	**71**
Acne	0	2	0	1
Application Site Reaction	75	71	84	70
Acne	0	4	1	0
Alopecia	2	0	1	1
Contact Dermatitis	19	4	33	4
Dry Skin	27	12	25	17
Edema	4	0	3	0
Exfoliation	6	4	24	13
Hyperesthesia	0	0	3	1
Pain	15	22	26	30
Paresthesia	8	4	20	20
Photosensitivity Reaction	0	2	3	0
Pruritus	31	59	52	45
Rash	35	20	46	17
Vesiculobullous Rash	0	0	4	1
Contact Dermatitis	2	0	0	0
Dry Skin	0	4	3	0
Herpes Simplex	0	2	0	0
Maculopapular Rash	0	2	0	0
Pain	2	2	1	0
Pruritus	4	6	4	1
Rash	2	10	4	0
Skin Carcinoma	0	6	2	2
Skin Nodule	0	2	0	0
Skin Ulcer	2	0	1	0
SPECIAL SENSES	**2**	**0**	**4**	**2**
Conjunctivitis	2	0	4	1
Eye Pain	0	2	2	0
UROGENITAL SYSTEM	**0**	**0**	**4**	**5**
Hematuria	0	0	2	1
OTHER	**0**	**0**	**0**	**3**
Procedure	0	0	0	3

Skin and Appendages Adverse Events Reported for diclofenac sodium gel, 3% at Less Than 1% Incidence in the Phase 3 Studies: skin hypertrophy, paresthesia, seborrhea, urticaria, application site reactions (skin carcinoma, hypertonia, skin hypertrophy lacrimation disorder, maculopapular rash, purpuric rash, vasodilation).

Adverse Reactions Reported for *Oral* Diclofenac Dosage Form (not topical diclofenac sodium gel, 3%):
*Incidence greater than 1% marked with asterisk.
Body as a Whole: abdominal pain or cramps*, headache*, fluid retention*, abdominal distention*, malaise, swelling of lips and tongue, photosensitivity, anaphylaxis, anaphylactoid reactions, chest pain.

Cardiovascular: hypertension, congestive heart failure, palpitations, flushing, tachycardia, premature ventricular contractions, myocardial infarction, hypotension.

Digestive: diarrhea*, indigestion*, nausea*, constipation*, flatulence*, liver test abnormalities*, PUB*, i.e., peptic ulcer, with or without bleeding and/or perforation, or bleeding without ulcer, vomiting, jaundice, melena, esophageal lesions, aphthous stomatitis, dry mouth and mucous membranes, bloody diarrhea, hepatitis, hepatic necrosis, cirrhosis, hepatorenal syndrome, appetite change, pancreatitis with or without concomitant hepatitis, colitis, intestinal perforation.

Hemic and Lymphatic: hemoglobin decrease, leukopenia, thrombocytopenia, eosinophilia, hemolytic anemia, aplastic anemia, agranulocytosis, purpura, allergic purpura, bruising.

Metabolic and Nutritional Disorders: azotemia, hypoglycemia, weight loss.

Nervous System: dizziness*, insomnia, drowsiness, depression, diplopia, anxiety, irritability, aseptic meningitis, convulsions, paresthesia, memory disturbance, nightmares, tremor, tic, abnormal coordination, disorientation, psychotic reaction.

Respiratory: epistaxis, asthma, laryngeal edema, dyspnea, hyperventilation, edema of pharynx.

Skin and Appendages: rash*, pruritus*, alopecia, urticaria, eczema, dermatitis, bullous eruption, erythema multiforme major, angioedema, Stevens-Johnson syndrome, excess perspiration, exfoliative dermatitis.

Special Senses: tinnitus*, blurred vision, taste disorder, reversible and irreversible hearing loss, scotoma, vitreous floaters, night blindness, amblyopia.

Urogenital: nephrotic syndrome, proteinuria, oliguria, interstitial nephritis, papillary necrosis, acute renal failure, urinary frequency, nocturia, hematuria, impotence, vaginal bleeding.

OVERDOSAGE
Due to the low systemic absorption of topically-applied diclofenac sodium gel, 3%, overdosage is unlikely. There have been no reports of ingestion of diclofenac sodium gel, 3%. In the event of oral ingestion, resulting in significant systemic side effects, it is recommended that the stomach be emptied by vomiting or lavage. Forced diuresis may theoretically be beneficial because the drug is excreted in the urine. The effect of dialysis or hemoperfusion in the elimination of diclofenac (99% protein-bound) remains unproven. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption of diclofenac. Supportive and symptomatic treatment should be given for complications such as renal failure, convulsions, gastrointestinal irritation and respiratory depression.

DOSAGE AND ADMINISTRATION
Diclofenac Sodium Gel, 3% is applied to lesion areas twice daily. It is to be smoothed onto the affected skin gently. The amount needed depends upon the size of the lesion site. Assure that enough Diclofenac Sodium Gel, 3% is applied to adequately cover each lesion. Normally 0.5 g of gel is used on each 5 cm x 5 cm lesion site. The recommended duration of therapy is from 60 days to 90 days. Complete healing of the lesion(s) or optimal therapeutic effect may not be evident for up to 30 days following cessation of therapy. Lesions that do not respond to therapy should be carefully re-evaluated and management reconsidered.

HOW SUPPLIED
Available in tubes of 100 g and 50 g. Each gram of gel contains 30 mg of diclofenac sodium.
100 g tube – NDC 0115-1483-61
50 g tube – NDC 0115-1483-56

Storage: Store at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature]. Protect from heat. Avoid freezing.

‡Voltaren® is a registered trademark of Novartis.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Manufactured by: TOLMAR Inc.
Fort Collins, CO 80526
Distributed by: Global Pharmaceuticals, Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124

44488 Rev. 1 06/13

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200936

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 200936

Date of Submission: October 08, 2013

Applicant's Name: Tolmar, Inc.

Established Name: Diclofenac Sodium Gel, 0.3%

Labeling Comments below are considered:

☐ Minor Deficiency*
*Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.

☒ No Comments **(**Labeling Approval Summary #1)

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions at this time based on your labeling Submission dated October 08, 2013.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Note RPM - Labeling comments end here

REMS required? NO

MedGuides and/or PPIs (505-1(e))	☐ Yes	☐ No
Communication plan (505-1(e))	☐ Yes	☐ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☐ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☐ No
Timetable for assessment (505-1(d))	☐ Yes	☐ No

ANDA REMS acceptable?

☐ Yes ☐ No ☒ N/A

APPROVAL SUMMARY
(List the package size, strength(s), and date of submission for approval):
Do you have Final Printed Labels and Labeling? Yes

Container

50 g – Satisfactory in FPL as of October 08, 2013 electronic submission.

100 g – Satisfactory in FPL as of October 08, 2013 electronic submission.

Carton

50 g – Satisfactory in FPL as of October 08, 2013 electronic submission.

100 g – Satisfactory in FPL as of October 08, 2013 electronic submission.

Package Insert: Satisfactory in FPL as of October 08, 2013 electronic submission.

Patient insert: Satisfactory in FPL as of October 08, 2013 electronic submission.

SPL Data Elements: Satisfactory as of October 08 2013 electronic submission.

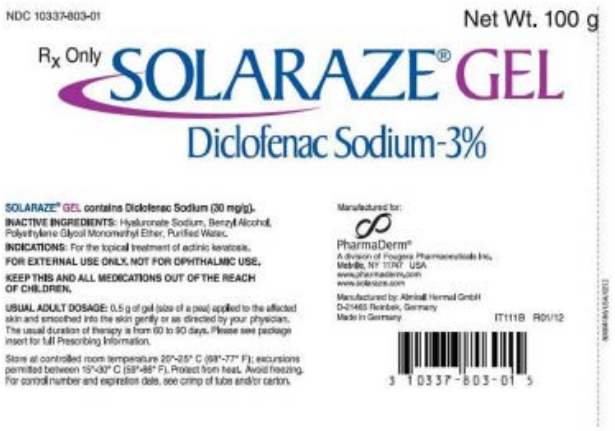
BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Diclofenac Sodium Gel, 3%
- NDA Number: 021005/S-013
- NDA Drug Name: Solaraze® Gel, 3%
- NDA Firm: Fougera Pharms
- Date of Approval of NDA Insert and supplement: 021005/S-013: Approved: December 08, 2011
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Revisions needed post-approval: NO
- Patents/Exclusivities: Refer to chart in FOR THE RECORD.

FOR THE RECORD:

1. **MODEL LABELING:** Review based on the labeling for the reference listed drug, Solaraze® (diclofenac sodium) Gel, 3% [NDA 021005/S-013: Approved December 08, 2011]. This Prior Approval supplemental new drug application provides for changes to the "Absorption" and "Drug Interactions" subsections of the package insert.

2. RLD CARTON AND CONTAINER: 100 g displayed:



3. PATIENTS/EXCLUSIVTIES:

Patent Data – NDA 021005

No	Expiration	Use Code	Use	File
5639738	June 17, 2014	U-402	Treatment of Actinic Keratoses	IV*
5792753	August 11, 2015			IV*
5852002	June 17, 2014	U-402	Treatment of Actinic Keratoses	IV*
5914322	August 11, 2015			IV*
5929048	July 27, 2016	U-402	Treatment of Actinic Keratoses	IV*
5985850	Nov 16, 2016			IV*

*On September 14, 2012, the firm informs the Agency that as of September 13, 2012, the suit was dismissed and the case is closed. Due to the subsequent dismissal of the patent litigation, this application is no longer subject to the provisions the 30-month stay and final approval may now be granted.

Exclusivity Data – NDA 021005

Code/sup	Expiration	Use Code	Description	Labeling Impact
			There are no unexpired exclusivities	

3. INACTIVE INGREDIENTS

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

Composition of Diclofenac Sodium Gel, 3%

Ingredient	Grade	Function	IIG Limit[a] (%)	% w/w
Diclofenac Sodium	USP	Active	NA	3.0
Methoxypolyethylene Glycol 350	NF	(b) (4)		
Benzyl Alcohol	NF			
PEG-60 Hydrogenated Castor Oil	NA			
Hydroxyethyl Cellulose	NF			
Purified Water	USP			

(b) (4)

Chemistry review: The generic formulation does not match the RLD qualitatively or quantitatively. One ingredient in the RLD, hyaluronate sodium, has been removed, and it has been replaced with two ingredients not present in the RLD, PEG-60 hydrogenated castor oil and hydroxyethyl cellulose. The effect of this qualitative change to the RLD is addressed by the results for clinical equivalence between the RLD and the generic product. Please note that the formulation design (which is different from the RLD) is pending outcome of DBEs review of the skin cadavear permeation study.

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: None
- RLD: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
- ANDA: Store between 20° - 25°C (68° and 77°F) excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from heat. Avoid freezing.

5. DISPENSING STATEMENT COMPARISON

- USP: Preserve in well closed containers
- RLD: None.
- ANDA: None.

6. PACKAGE CONFIGURATION

- RLD: 50 and 100 gram tubes
- ANDA: 50 and 100 gram (b) (4) tubes with polypropylene caps.

7. CONTAINER/CLOSURE - Laminate tube (b) (4)

8. FNISHED DOSAGE FORM

- RLD: Gel
- ANDA: White to off-white gel

9. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Tolmar Inc
Fort Collins, CO 80526

10. CONTACT INFORMATION:

Michelle Ryder
Phone: 970 212-4901
Fax 970 212-4950
Email: mryder@tolmar.com

Date of Submission: October 08, 2013

Primary Reviewer: B. Weitzman

Team Leader: J. Grace

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

/s/

BEVERLY WEITZMAN
10/18/2013

JOHN F GRACE
10/18/2013

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 200936

Date of Submission: December 04, 2009, May 11, 2012 and January 24, 2013

Applicant's Name: Tolmar, Inc.

Established Name: Diclofenac Sodium Gel, 0.3%

Labeling Comments below are considered:

☐ NOT easily correctable (applicant cannot respond within 10 business days)

☒ Easily correctable (respond within 10 business days)

☐ No Comments **(**Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

Labeling Deficiencies/Comments: Completed on June 04, 2013.
Date of Submission: December 04, 2009, May 11, 2012 and January 24, 2013.

1. **CONTAINER:** (50 g and 100 g):
   a. The established name and strength should be the most prominent information on the container label. Please decrease the prominence of your company logo. In addition, we recommend relocating the logo to the bottom of the principle display panel.
   b. Please assure that your container labels are of actual size, color and clarity when submitting in final print.
2. **CARTON:** (50 g and 100 g): Please refer to container comment (a).
3. **INSERT:**

   CONTRAINDICATIONS: Revise to be the same as the reference listed drug except for the inclusion of "hyaluronate sodium" as your drug product does not contain this inactive ingredient.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug insert labeling and a side-by-side comparison of your container and carton labeling with your last submission, with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Note RPM - Labeling comments end here

REMS required? NO

MedGuides and/or PPIs (505-1(e))	☐ Yes	☐ No
Communication plan (505-1(e))	☐ Yes	☐ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☐ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☐ No
Timetable for assessment (505-1(d))	☐ Yes	☐ No

ANDA REMS acceptable?

☐ Yes ☐ No ☒ n/a

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have Final Printed Labels and Labeling? Yes

Container

50 g – Satisfactory in FPL as of electronic submission.

100 g – Satisfactory in FPL as of electronic submission.

Carton

50 g – Satisfactory in FPL as of electronic submission.

100 g – Satisfactory in FPL as of electronic submission.

Package Insert: Satisfactory in FPL as of electronic submission.

Patient insert: Satisfactory in FPL as of electronic submission.

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Diclofenac Sodium Gel, 3%
- NDA Number: 021005/S-013
- NDA Drug Name: Solaraze® Gel, 3%
- NDA Firm: Fougera Pharms
- Date of Approval of NDA Insert and supplement: 021005/S-013: Approved: December 08, 2011
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Revisions needed post-approval: NO
- Patents/Exclusivities: Refer to chart in FOR THE RECORD.

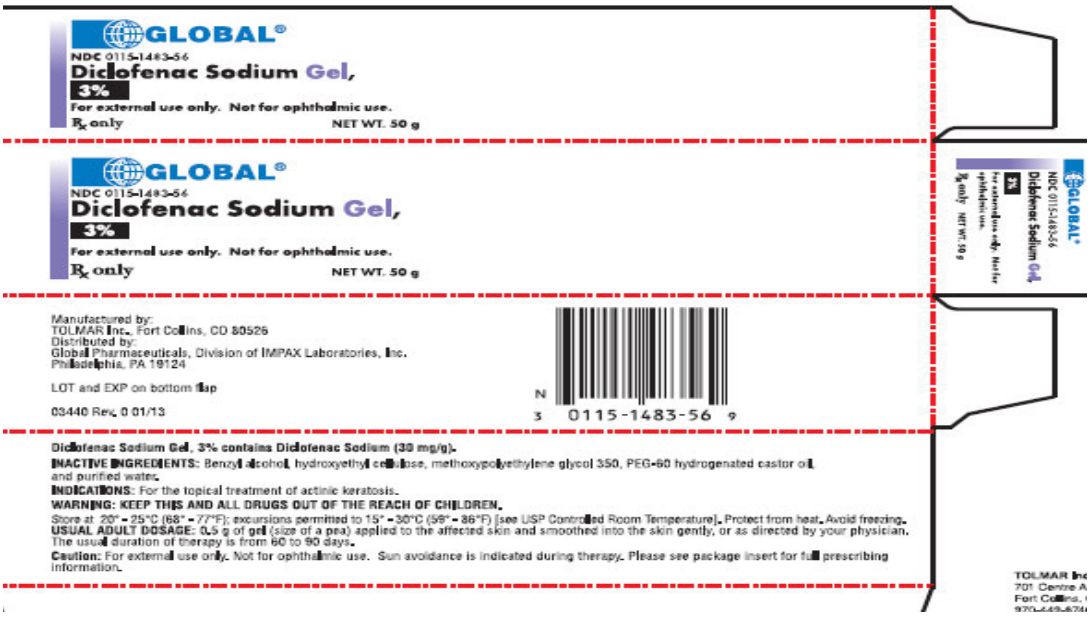
FOR THE RECORD:

1. **MODEL LABELING:** Review based on the labeling for the reference listed drug, Solaraze® (diclofenac sodium) Gel, 3% [NDA 021005/S-013: Approved December 08, 2011]. This Prior Approval supplemental new drug application provides for changes to the “Absorption” and “Drug Interactions” subsections of the package insert.

2. RLD CARTON AND CONTAINER: 100 g displayed:

ANDA CONTAINER AND CARTON: Submitted January 24, 2013 – Not satisfactory

50 gram displayed:




GLOBAL®
NDC 0115-1483-66
Diclofenac Sodium Gel,
3%
FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.
℞ only
NET WT. 50 g
Diclofenac Sodium Gel, 3% contains Diclofenac Sodium (30 mg/g).
INACTIVE INGREDIENTS: Benzyl alcohol, hydroxyethyl cellulose, methoxypolyethylene glycol 350, PEG-60 hydrogenated castor oil, and purified water.
INDICATIONS: For the topical treatment of actinic keratosis.
WARNING: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
USUAL ADULT DOSAGE: 0.5 g of gel (size of a pea) applied to the affected skin and smoothed into the skin gently, or as directed by your physician. The usual duration of therapy is from 60 to 90 days. Please see package insert for full prescribing information.
Store at 20° – 25°C (68° – 77°F); excursions permitted to 15° – 30°C (59° – 86°F) [see USP Controlled Room Temperature]. Protect from heat. Avoid freezing. See crimp of tube and/or carton for lot number and expiration date.
Manufactured by: TOLMAR Inc., Fort Collins, CO 80526
Distributed by: Global Pharmaceuticals, Division of IMPAX Laboratories, Inc., Philadelphia, PA 19124 02249 Rev. 0 01/13

3. PATIENTS/EXCLUSIVTIES:

Patent Data – NDA 021005

No	Expiration	Use Code	Use	File
5639738	June 17, 2014	U-402	Treatment of Actinic Keratoses	IV*
5792753	August 11, 2015			IV*
5852002	June 17, 2014	U-402	Treatment of Actinic Keratoses	IV*
5914322	August 11, 2015			IV*
5929048	July 27, 2016	U-402	Treatment of Actinic Keratoses	IV*
5985850	Nov 16, 2016			IV*

*On September 14, 2012, the firm informs the Agency that as of September 13, 2012, the suit was dismissed and the case is closed. Due to the subsequent dismissal of the patent litigation, this application is no longer subject to the provisions the 30-month stay and final approval may now be granted.

Exclusivity Data – NDA 021005

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There are no unexpired exclusivities		

3. INACTIVE INGREDIENTS

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

Composition of Diclofenac Sodium Gel, 3%

Ingredient	Grade	Function	IIG Limit[a] (%)	% w/w
Diclofenac Sodium	USP	Active	NA	3.0
Methoxypolyethylene Glycol 350	NF	(b) (4)		
Benzyl Alcohol	NF			
PEG-60 Hydrogenated Castor Oil	NA			
Hydroxyethyl Cellulose	NF			
Purified Water	USP			

(b) (4)

Chemistry review: The generic formulation does not match the RLD qualitatively or quantitatively. One ingredient in the RLD, hyaluronate sodium, has been removed, and it has been replaced with two ingredients not present in the RLD, PEG-60 hydrogenated castor oil and hydroxyethyl cellulose. The effect of this qualitative change to the RLD is addressed by the results for clinical equivalence between the RLD and the generic product. Please note that the formulation design (which is different from the RLD) is pending outcome of DBEs review of the skin cadavear permeation study.

4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**
   - USP: None
   - RLD: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
   - ANDA: Store between 20° - 25°C (68° and 77°F) excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from heat. Avoid freezing.

5. DISPENSING STATEMENT COMPARISON
   - USP: Preserve in well closed containers
   - RLD: None.
   - ANDA: None.

6. PACKAGE CONFIGURATION
   - RLD: 50 and 100 gram tubes
   - ANDA: 50 and 100 gram [redacted] (b) (4) tubes with polypropylene caps.

7. CONTAINER/CLOSURE - Laminate tube [redacted] (b) (4)

8. FNISHED DOSAGE FORM
   - RLD: Gel
   - ANDA: White to off-white gel

9. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
Tolmar Inc
Fort Collins, CO 80526

10. CONTACT INFORMATION:
Michelle Ryder
Phone: 970 212-4901
Fax 970 212-4950
Email: mryder@tolmar.com

Date of Submission: December 04, 2009, May 11, 2012 and January 24, 2013

Primary Reviewer: B. Weitzman

Team Leader: J. Grace

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

/s/

BEVERLY WEITZMAN
06/10/2013

JOHN F GRACE
06/10/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200936

CHEMISTRY REVIEWS

ANDA 200936

Diclofenac Sodium Gel, 3%

Tolmar, Inc.

Richard Chang
Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 200936

2. REVIEW #: 3

3. REVIEW DATE: October 30, 2012, December 13, 2012

4. REVIEWER: Richard Chang

5. PREVIOUS DOCUMENTS: N/A

Submission(s) Reviewed	Document Date
Original	December 14, 2009
Patent & Exclusivity/Patent Information	April 12, 2010
Patent & Exclusivity/Patent Information	November 08, 2010
Amendment	December 21, 2010
Dispute resolution/request for resolution	September 27, 2011
Unsolicited amendment	March 23, 2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Patent & Exclusivity/Patent Information	September 14, 2012
Minor Amendment	September 28, 2012
Telephone Amendment	December 12, 2012

7. NAME & ADDRESS OF APPLICANT:

Name: Tolmar, Inc.
Address: 701 Centre Avenue
Fort Collins, CO 80526

US Agent: N/A

Representative: Michelle R. Ryder

Telephone: (970) 212-4901

A. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
Non-Proprietary Name (USAN): Diclofenac Sodium Gel

9. LEGAL BASIS FOR SUBMISSION:

The Reference Listed Drug is Solaraze® (diclofenac sodium) Gel, 3% NDA 021005, manufactured by Nycomed US Inc.

PATENT CERTIFICATION STATEMENT

Tolmar, Inc. provided a statement of patent certification for the Abbreviated New Drug Application for diclofenac sodium gel, 3%.

Also presented is the Statement of Exclusivity required under 21 CFR Section 314.94(a)(3)(ii).

PATENT INFORMATION

Tolmar's proposed drug product is the generic version of Nycomed's Solaraze®, pursuant to NDA 021005. Nycomed's drug product appears in the FDA listing titled Electronic Orange Book- Approved Drug Products with Therapeutic Equivalence Evaluations as follows:

Product #	Patent #	Patent Expiration	Patent Use Code
001	5639738	June 17, 2014	U-402
001	5792753	Aug 11, 2015	
001	5852002	June 17, 2014	U-402
001	5914322	Aug 11, 2015	
001	5929048	July 27, 2016	U-402
001	5985850	Nov 16, 2016	

U-402: Treatment of Actinic Keratoses

Tolmar also provides a Paragraph IV certification to certify that U. S. Patent 5639738, 5792753, 5852002, 5914322, 5929048, and 5985850 will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

On September 14, 2012, the firm informs the Agency that as of September 13, 2012, the suit was dismissed and the case is closed. Due to the subsequent dismissal of the patent litigation, this

application is no longer subject to the provisions the 30-month stay and final approval may now be granted.

EXCLUSIVITY STATEMENT

Tolmar, Inc. certifies that to the best of its knowledge, there is no unexpired exclusivity is associated with the Approved Listed Drug Product, Solaraze® (diclofenac sodium) Gel, 3%.

10. PHARMACOL. CATEGORY:

Diclofenac sodium gel has clinical utility in the treatment of actinic keratosis.

11. DOSAGE FORM: Topical Gel

12. STRENGTH/POTENCY: 3%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

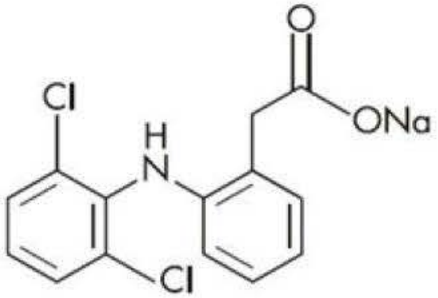
___x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: Sodium [o-(2,6-dichloroanilino)phenyl]acetate

CAS Registry Number: [15307-79-6]
Molecular Formula: $C_{14}H_{10}Cl_2NNaO_2$
Molecular Mass: 381.13 g/mol

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Item referenced	Holder	Code[1]/ Status[2]	Date review completed	Comments
(b) (4)	II		(b) (4)	3/Adequate	10/29/12	Reviewed by R. Chang
	II			3/Adequate	07/10/12	Reviewed by R. Chang
	III			4		

[1] Action codes for DMF Table: 1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF; 3 – Reviewed previously and no revision since last review; 4 – Sufficient information in application; 5 – Authority to reference not granted; 6 – DMF not available; 7 – Other (explain under "Comments"); [2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending	04/19/12	P. Chandaroy
Clinical Bioequivalence	Pending		
EA	Satisfactory (exclusion requested)		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X___ Yes ____ No If no, explain reason(s) below:

THIS WAY ON ORIGINAL

The Chemistry Review for ANDA 200936

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on approvability

This ANDA is presently non-approvable, because of pending review of bioequivalency, labeling, and clinical. The acceptability of the formulation design (which is different from RLD) is pending the outcome of DBEs review of the skin cadavear permeation study. CMC is complete.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Diclofenac Sodium Gel is supplied as a topical gel for the treatment of actinic keratosis. Each gram of Diclofenac Sodium Gel contains 30 mg active ingredient diclofenac sodium with the inactive ingredients methoxypolyethylene glycol 350, benzyl alcohol, PEG-60 hydrogenated castor oil, hydroxyethyl cellulose, and purified water.

Diclofenac sodium gel, 3% is packaged in 50 gram and 100 gram (b) (4) tubes with polypropylene caps. Store between 20°-25°C (59°-77°F). Protect from heat. The proposed expiration dating for the drug product is 24 months, when stored at controlled room temperature.

Diclofenac sodium is described in the USP Monograph. Diclofenac sodium appears as white to slightly yellowish hygroscopic crystalline powder and is sparingly soluble in water.

B. Description of How the Drug Product is Intended to be Used

The recommended dose is 0.5 gram of diclofenac sodium gel to treat an area of 25 cm^2.

(b) (4)

(b) (4)

	IT	QT
DS	0.10%	0.15%
DP	0.2%	0.2%

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(b) (4)

[redacted]

I. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Tolmar, Inc. is claiming a categorical exclusion from the requirement of an environmental impact analysis statement pursuant to 25.31(a) since Diclofenac Sodium Gel, 3% has the same indications, level of dosage, and duration of administration that is currently marketed and to their knowledge will not increase the use of the active moiety. Tolmar also certifies that it is in compliance with all federal, state, and local environmental protection requirements and that it has a certified waste disposal program.

Satisfactory

cc: ANDA 200936
ANDA DUP 200936
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/R. Chang/10/30/12, 12/13/2012
HFD-627/J. Fan/12/22/12
HFD-617/T. Tran/12/31/12

V:\Chemistry Division I\Team 13\FIRMSNZ\Tolmar \LTRS&REV\200936.R3.DOC

TYPE OF LETTER: CMC is complete. Pending all others.

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

/s/

RICHARD R CHANG
01/02/2013

TRANG Q TRAN
01/07/2013

JAMES M FAN
01/07/2013

ANDRE S RAW
01/08/2013

ANDA 200936

Diclofenac Sodium Gel, 3%

Tolmar, Inc

Richard Chang
Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 200936

2. REVIEW #: 2

3. REVIEW DATE: July 10, 2012

4. REVIEWER: Richard Chang

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	December 14, 2009
Patent & Exclusivity/Patent Information	April 12, 2010
Patent & Exclusivity/Patent Information	November 08, 2010
Amendment	December 21, 2010
Dispute resolution/request for resolution	September 27, 2011
Unsolicited amendment	March 23, 2012

7. NAME & ADDRESS OF APPLICANT:

Name: Tolmar, Inc.
Address: 701 Centre Avenue
Fort Collins, CO 80526

US Agent: N/A

Representative: Michelle R. Ryder

Telephone: (970) 212-4901

A. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

9. LEGAL BASIS FOR SUBMISSION:

The Reference Listed Drug is Solaraze® (diclofenac sodium) Gel, 3% NDA 021005, manufactured by Nycomed US Inc.

PATENT CERTIFICATION STATEMENT

Tolmar, Inc. provided a statement of patent certification for the Abbreviated New Drug Application for diclofenac sodium gel, 3%.

Also presented is the Statement of Exclusivity required under 21 CFR Section 314.94(a)(3)(ii).

PATENT INFORMATION

Tolmar's proposed drug product is the generic version of Nycomed's Solaraze®, pursuant to NDA 021005. Nycomed's drug product appears in the FDA listing titled Electronic Orange Book- Approved Drug Products with Therapeutic Equivalence Evaluations as follows:

Product #	Patent #	Patent Expiration	Patent Use Code
001	5639738	June 17, 2014	U-402
001	5792753	Aug 11, 2015	
001	5852002	June 17, 2014	U-402
001	5914322	Aug 11, 2015	
001	5929048	July 27, 2016	U-402
001	5985850	Nov 16, 2016	

U-402: Treatment of Actinic Keratoses

Tolmar also provides a Paragraph IV certification to certify that U. S. Patent 5639738, 5792753, 5852002, 5914322, 5929048, and 5985850 will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

EXCLUSIVITY STATEMENT

Tolmar, Inc. certifies that to the best of its knowledge, there is no unexpired exclusivity is associated with the Approved Listed Drug Product, Solaraze® (diclofenac sodium) Gel, 3%.

10. PHARMACOL. CATEGORY:

Diclofenac sodium gel has clinical utility in the treatment of actinic keratosis.

11. DOSAGE FORM: Topical Gel

12. STRENGTH/POTENCY: 3%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

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___x__Not a SPOTS product

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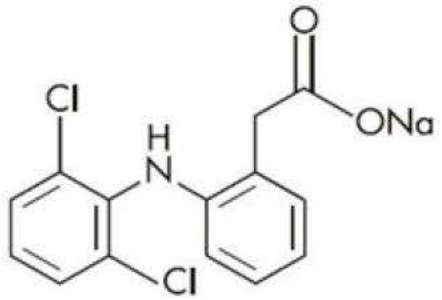
Chemical name: Sodium [o-(2,6-dichloroanilino)phenyl]acetate

CAS Registry Number: [15307-79-6]
Molecular Formula: $C_{14}H_{10}Cl_2NNaO_2$
Molecular Mass: 381.13 g/mol

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Item referenced	Holder	Code[1]/ Status[2]	Date review completed	Comments
(b) (4)	II		(b) (4)	3/Adequate	06/29/11	Reviewed by R. Chang
	II			3/Adequate	07/10/12	Reviewed by R. Chang

(b) (4)	III	(b) (4)	4		

[1] Action codes for DMF Table: 1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
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B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Deficient	04/19/12	P. Chandaroy
Clinical Bioequivalence	Pending		
EA	Satisfactory (exclusion requested)		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X___ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 200936

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on approvability

This ANDA is presently non-approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Diclofenac Sodium Gel is supplied as a topical gel for the treatment of actinic keratosis. Each gram of Diclofenac Sodium Gel contains 30 mg active ingredient diclofenac sodium with the inactive ingredients methoxypolyethylene glycol 350, benzyl alcohol, PEG-60 hydrogenated castor oil, hydroxyethyl cellulose, and purified water.

Diclofenac sodium gel, 3% is packaged in 50 gram and 100 gram (b) (4) tubes with polypropylene caps. Store between 20°-25°C (59°-77°F). Protect from heat. The proposed expiration dating for the drug product is 24 months, when stored at controlled room temperature.

Diclofenac sodium is described in the USP Monograph. Diclofenac sodium appears as white to slightly yellowish hygroscopic crystalline powder and is sparingly soluble in water.

B. Description of How the Drug Product is Intended to be Used

The recommended dose is 0.5 gram of diclofenac sodium gel to treat an area of 25 cm^2.

(b) (4))

(b) (4)

	IT	QT
DS	0.10%	0.15%
DP	0.2%	0.2%

50 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

3. We encourage you to apply Quality by Design (QbD) principles to the pharmaceutical development of your future original ANDA product submissions. A risk-based, scientifically sound submission would be expected to include the following:

   - Quality target product profile (QTPP)
   - Critical quality attributes (CQAs) of the drug product
   - Product design and understanding including identification of critical attributes of excipients, drug substance(s), and/or container closure systems
   - Process design and understanding including identification of critical process parameters and in-process material attributes
   - Control strategy and justification

   An example illustrating QbD concepts can be found online at FDA's **Generic Drugs: Information for Industry** webpage: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf

Sincerely yours,

{See appended electronic signature page}

Andre Raw, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 200936
ANDA DUP 200936
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/R. Chang/May 22, 2012; 7/11/12
HFD-627/J. Fan/6/5/12; 7/20/12
HFD-617/T. Tran/7/6/12; 7/27/12

V:\Chemistry Division I\Team 13\FIRMSNZ\Tolmar \LTRS&REV\200936.R2.DOC

TYPE OF LETTER: NOT APPROVABLE

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

/s/

RICHARD R CHANG
07/30/2012

TRANG Q TRAN
07/30/2012

JAMES M FAN
07/30/2012

ANDA 200936

Diclofenac Sodium Gel, 3%

Tolmar, Inc

Richard Chang
Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 200936

2. REVIEW #: 1

3. REVIEW DATE: June 27, 2011

4. REVIEWER: Richard Chang

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	December 14, 2009
Accepted for filing	December 16, 2009
Amendment	March 10, 2010
Amendment	April 12, 2010

7. NAME & ADDRESS OF APPLICANT:

Name: Tolmar, Inc.
Address: 701 Centre Avenue
Fort Collins, CO 80526

US Agent: N/A

Representative: Michelle R. Boyer

Telephone: (970) 212-4901

A. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
Non-Proprietary Name (USAN): Diclofenac Sodium Gel

9. LEGAL BASIS FOR SUBMISSION:

The Reference Listed Drug is Solaraze® (diclofenac sodium) Gel, 3% NDA 021005, manufactured by Nycomed US Inc.

PATENT CERTIFICATION STATEMENT

Tolmar, Inc. provided a statement of patent certification for the Abbreviated New Drug Application for diclofenac sodium gel, 3%.

Also presented is the Statement of Exclusivity required under 21 CFR Section 314.94(a)(3)(ii).

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U-402: Treatment of Actinic Keratoses

Tolmar also provides a Paragraph IV certification to certify that U. S. Patent 5639738, 5792753, 5852002, 5914322, 5929048, and 5985850 will not be infringed by the manufacture, use, or sale of the drug product for which this application is submitted.

EXCLUSIVITY STATEMENT

Tolmar, Inc. certifies that to the best of its knowledge, there is no unexpired exclusivity is associated with the Approved Listed Drug Product, Solaraze® (diclofenac sodium) Gel, 3%.

10. PHARMACOL. CATEGORY:

Diclofenac sodium gel has clinical utility in the treatment of actinic keratosis.

11. DOSAGE FORM: Topical Gel

12. STRENGTH/POTENCY: 3%

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Chemical name: Sodium [o-(2,6-dichloroanilino)phenyl]acetate

CAS Registry Number: [15307-79-6]
Molecular Formula: $C_{14}H_{10}Cl_2NNaO_2$
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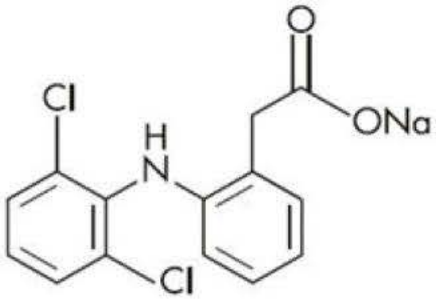
Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Item referenced	Holder	Code[1]/ Status[2]	Date review completed	Comments
(b) (4)	II		(b) (4)	3/Adequate	06/29/11	Reviewed by R. Chang
	III			4		

[1] Action codes for DMF Table: 1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
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B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	11/29/10	
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Deficient		
EA	Satisfactory (exclusion requested)		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X___ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 200936

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on approvability

This ANDA is presently non-approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Diclofenac Sodium Gel is supplied as a topical gel for the treatment of actinic keratosis. Each gram of Diclofenac Sodium Gel contains 30 mg active ingredient diclofenac sodium with the inactive ingredients methoxypolyethylene glycol 350, benzyl alcohol, PEG-60 hydrogenated castor oil, hydroxyethyl cellulose, and purified water.

Diclofenac sodium gel, 3% is packaged in 50 gram and 100 gram (b) (4) tubes with polypropylene caps. Store between 20°-25°C (59°-77°F). Protect from heat. The proposed expiration dating for the drug product is 24 months, when stored at controlled room temperature.

Diclofenac sodium is described in the USP Monograph. Diclofenac sodium appears as white to slightly yellowish hygroscopic crystalline powder and is sparingly soluble in water.

B. Description of How the Drug Product is Intended to be Used

The recommended dose is 0.5 gram of diclofenac sodium gel to treat an area of 25 cm^2.

(b) (4)

(b) (4)

	IT	QT
DS	0.10%	0.15%
DP	0.2%	0.2%

47 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

2. All facilities referenced in your ANDA should be in compliance with cGMP at the time of approval. We have requested an evaluation from the Office of Compliance.

Sincerely yours,

{See appended electronic signature page}

Paul Schwartz, Ph.D.
Acting Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 200936
ANDA DUP 200936
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/R. Chang/April 15, 2010, 06/27/2011
HFD-627/J. Fan/7/12/10; 6/30/11
HFD-617/T. Tran/7/13/10; 7/6/11

V:\Chemistry Division I\Team 3\FIRMSNZ\Tolmar \LTRS&REV\200936.R1.DOC

TYPE OF LETTER: NOT APPROVABLE – FATAL FLAW

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

/s/

RICHARD CHANG
07/09/2011

TRANG Q TRAN
07/11/2011

JAMES M FAN
07/11/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200936

STATISTICAL REVIEW

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ANDA/Serial Number: 200936

Drug Name: Diclofenac Sodium Gel, 3%

Indication(s): Treatment of Actinic Keratoses (AK)

Reference Listed Drug: Solaraze® (diclofenac sodium), Nycomed US

Applicant: Tolmar Inc.

Date(s): Submitted: 12/14/09, 6/3/10, 7/8/10, 4/19/11, 9/27/11 and 3/23/12

Biometrics Division: DB6

Statistical Reviewer: Huaixiang Li, Ph.D.

Concurring Reviewers: Stella Grosser, Ph.D.

Medical Division: Division of Clinical Review in OGD

Clinical Team: Brenda S. Gierhart, M.D.

Keywords: Bioequivalence, AK, Success rate

TABLE OF CONTENTS

List of Tables

1 Executive Summary

1.1 Conclusions and Recommendations

The equivalence test passed for the success rate in the FDA's per-protocol (FPP) population. Also, the two active treatments are statistically significantly better than the vehicle for the success rate in the FDA's intent-to-treat (FITT) population (see 1.2, below).

1.2 Brief Overview of the Clinical Study

The study TOL-AK-2008-02 was a multicenter, double-blind, randomized, vehicle-controlled, parallel-group study comparing Diclofenac Sodium Topical Gel, 3% (Tolmar Inc.) to Solaraze ® (Diclofenac sodium) Gel, 3% (Nycomed US) and both active treatments to vehicle (Tolmar Inc.) in the treatment of actinic keratoses (AK).

Six hundred and nine (609) subjects were randomized in a 2:2:1 ratio to receive one of 3 treatments. Subjects were instructed to gently apply the assigned study medication twice daily to the designated area(s) for 84 days (12 weeks). There were total of six study visits: Visit 1/Day 1 (Baseline), Visit 2/Day 14 (±3 days), Visit 3/Day 28 (±3 days), Visit 4/Day 56 (±5 days), Visit 5/Day 84 (±5 days) (End of Treatment), and Visit 6/Day 112 (±5days) (Follow-up). If the subject left the study early, the subject's final visit would recorded as "Visit 6."

The clinical endpoint is the success rate, defined as the proportion of subjects with treatment success (100% clearance of all AK lesions within the treatment area) at Visit 6/Day 112 (±5days). Noted: All actinic keratoses (i.e., baseline actinic keratoses and any new actinic keratoses) within the treatment area are to be treated and included in the efficacy lesion count for each visit.

1.3 Statistical issues and findings

Efficacy: The test and reference treatments were statistically significantly better than vehicle for the success rates, 22.41% (test), 28.63% (reference), and 10.43% (vehicle), at Visit 6/Day 112 for the FDA's intent-to-treat (FITT) population.

Equivalence: The test and reference treatments were found to be clinically equivalent for the success rates, 26.14% (test) and 32.32% (reference), at Visit 6/Day 112 for the FDA's per-protocol (FPP) population.

2 Introduction

2.1 Overview

Actinic or solar keratosis is common in severely sun-damaged areas of the face, scalp, and hands. Lesions occur as skin colored to reddish brown or yellowish black with ill-defined macules or papules varying in size from approximately 1 millimeter to several centimeters in diameter.

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that is a potent inhibitor of inducible cyclo-oxygenase (COX-2), resulting in a reduction of prostaglandin synthesis. Sun damage and actinic keratosis (AK) have been linked with elevated prostaglandins in exposed skin. The mechanism of action in treating AK lesions is unknown.

Solaraze® (diclofenac sodium) Gel, 3% is a topical nonsteroidal anti-inflammatory drug (NSAID) approved under NDA 021005 for the treatment of AK.

According to the approved labeling, systemic absorption of diclofenac in subjects treated topically with Solaraze® is much lower than that occurring after oral daily dosing of diclofenac sodium. Blood was drawn at the end of treatment from 60 subjects with AK lesions treated with Solaraze® in three adequate and well-controlled clinical trials. Each subject was administered 0.5 g of Solaraze Gel twice a day for up to 105 days. There were up to three 5 cm x 5 cm treatment sites per subject on the face, forehead, hands, forearm and scalp. Serum concentrations of diclofenac were on average at, or below 20 ng/mL.

In clinical studies, localized dermal side effects such as contact dermatitis, exfoliation, dry skin, and rash were found in subjects treated with Solaraze® at a higher incidence than in those with vehicle.

Regulatory Background

Tolmar Inc has not submitted any INDs, Protocols, Controlled Correspondences, or additional ANDAs to the OGD for Diclofenac Sodium Gel, 3%. No INDs have been submitted to the OGD for Diclofenac Sodium Gel, 3%.

There are several ANDAs submitted to the OGD for Diclofenac Sodium Gel, 3%. Details may be found in the clinical review.

2.2 Data Sources

The data were submitted electronically. The data files are located in the following directory:

\\cdsesub1\EVSPROD\ANDA200936**0003**\m5**53**-clin-stud-rep**531**-rep-biopharm-stud**5312**-compar-ba-be-stud-rep

3 Statistical Evaluation

3.1 Study Design and Endpoints Objectives

To evaluate the therapeutic equivalence and safety of the Test Treatment, Diclofenac Sodium Gel, 3% (Tolmar Inc.), and the Reference Treatment, Solaraze® (diclofenac sodium) Gel, 3% (Nycomed US), in the treatment of actinic keratoses (AK).

To demonstrate the superiority of the efficacy of the Test and Reference Treatments over the vehicle control (Tolmar Inc.) in the treatment of actinic keratoses (AK).

Study Design

The study TOL-AK-2008-02 was a multicenter, double-blind, randomized, vehicle-controlled, parallel-group study. Subjects were assigned in a 2:2:1 ratio to treatment with the Test treatment, Diclofenac Sodium Topical Gel, 3% (Tolmar Inc.), the Reference treatment, Solaraze ® (diclofenac sodium) Gel, 3% (Nycomed US), the Vehicle control (Tolmar Inc.) in this study.

Male and female subjects, at least 18 years of age, with AK, were enrolled in this study. For inclusion into this study, the subjects must have had 5 or more clinically typical visible, discrete, nonhyperkeratotic, non-hypertrophic lesions contained in one 25 cm^2 treatment area in one major body area (as defined in this study: forehead, central face, scalp, back of hands, and forearms). The location of each lesion was recorded on an anatomical diagram. At each subsequent visit, AK lesions within the designated treatment area were evaluated and results recorded.

Six hundred and nine subjects (609) who met the entry criteria were enrolled in this study.

There were a total of six study visits Visit 1/Day 1 (Baseline), Visit 2/Day 14 (±3 days), Visit 3/Day 28 (±3 days), Visit 4/Day 56 (±5 days), Visit 5/Day 84 (±5 days) (End of Treatment [EOT]), and Visit 6/Day 112 (±5days) (Follow-up). If the subject left the study early (Early Discontinuation), the subject's final visit would recorded as "Visit 6."

Treatments

Subjects were instructed to wash treatment area with cold water and pat dry prior to applying study drug. Subjects were instructed to gently apply the assigned study medication twice daily to the designated area(s) for 84 days (12 weeks). The amount of study drug needed depended upon the size of the treatment area. Subjects were instructed to apply enough study drug to adequately cover each lesion. Normally, 0.5 gram (pea size) of gel was used on the 5 cm × 5 cm area. Subjects used a diary to record each date (i.e., mm/dd/yy) of treatment and whether or not study treatment as applied in the AM and in the PM on that specific date. There were a total of six study visits in this study. The same investigator, to the greatest extent possible, performed the dermatologic assessments for any given subject (i.e., at Visits 1 and 6, identified, counted, and located the target/baseline AK lesions).

Article	Description
Test	Diclofenac Sodium Gel, 3% (Tolmar Inc.) Batch/Lot #3241A, manufactured 11/08
Reference	Solaraze ® (diclofenac sodium) Gel, 3% (Nycomed US) Batch/Lot #8064201 - #8346601*
Vehicle	Vehicle (Tolmar Inc.) Batch/Lot #3240

*: Please see details in the clinical review report.

Outcome Variable

At each study visit, AK lesions within the designated treatment area were evaluated and results recorded. The number of visible lesions within the designated treatment area was recorded on the source document.

Endpoint

Success rate: Proportion of subjects with treatment success (100% clearance of all AK lesions within the treatment area) at Visit 6/Day 112 (±5days). Complete (100%) clearance required that all baseline lesions as well as new or subclinical AK lesions which appeared during treatment within the designated treatment area were no longer present.

3.2 Subject Disposition

Six hundred and nine (609) subjects were enrolled and randomized. The sponsor's Modified Intent-to-Treat (MITT) and Per-Protocol (PP) populations[1] had 605 and 460 subjects respectively. The FDA's Intent-to-Treat (FITT) and Per-Protocol (FPP) populations had 581 and 427 subjects respectively.

The subject disposition for the sponsor's and the FDA's populations are given in Table 1.

Remark: The clinical reviewer states that, in her opinion,

> *"the deletion of an additional 40 subjects, in order to comply with OGD recommendations regarding the designated visit window ± **4** days for the primary endpoint evaluation (which were not posted until after this study was completed), is unreasonable. Thus, [she] accepts the sponsor's proposal to include subjects in the PP population if Visit 6 occurred on Day 112 ± **5** days."*

[1]: **MITT**: 1) enrolled into the study, 2) applied at least one dose of study drug, 3) had a baseline lesion count, AND 4) had at least one post-baseline lesion count.
PP: 1) enrolled into the study, 2) met inclusion/exclusion criteria, 3) maintained compliance with study drug applications (applied at least 80% and not more than 120% of doses and did not miss 10 or more consecutive applications of study drug), 4) took no concomitant medications prohibited by the protocol, 5) had no other significant protocol violations, AND 6) returned for visit 6/day 112 within the visit window and had a lesion count in this visit, OR 7) were discontinued early due to insufficient therapeutic response (after completing at least 28 days of study drug use, with a compliance rate of at least 80%).

Table 1 Subject disposition - Sponsor's MITT and PP, FDA's FITT and FPP Populations*

	Total	Test	Reference	Vehicle
Enrolled and Randomized	**609**	**242**	**246**	**121**
Total sponsor's MITT population (MITT)	**605**	**241**	**244**	**120**
Total exclusion from the sponsor's MITT population	4	1	2	1
Reason for exclusion from sponsor's MITT				
No study medicine applied	1	1		
No post-baseline lesion count	3		2	1
Total sponsor's PP population (PP)	**460**	**187**	**180**	**93**
Total Exclusion from the sponsor's PP population				
Reason for exclusion from sponsor's PP	149	55	66	28
Not in MITT population	4	1	2	1
Did not meet inclusion criteria	6	3	3	
Not compliant with study medication apply	18	6	5	7
Lost diary card or miss visit	2	1	1	
Non-efficacy related discontinuation	80	31	37	12
Visit 6 outside of window	39	13	18	8
Total FDA's ITT population (FITT)	**581**	**232**	**234**	**115**
Total exclusion from the FDA's FITT population	28	10	12	6
Reason for exclusion from FDA's FITT				
Exclusion from sponsor's MITT	4	1	2	1
DSI site inspection results[@1]	21	8	9	4
Clinical reviewer's comment[#1]	5	1	3	1
Clinical reviewer's comment[#2]	+2		+2	
Total FDA's PP population (FPP)	**427**	**176**	**164**	**87**
Total Exclusion from the FDA's PP population	182	66	82	34
Reason for exclusion from FDA's FPP				
Exclusion from sponsor's PP	149	55	66	28
DSI site inspection results[@1]	15	5	6	4
Visit 6 outside window on Day 112±5 days[@2]	25	10	11	4
Clinical reviewer's comment[#3]	+7	+4	+1	+2

*: Subject may have multiple reasons to be excluded from the MITT, PP, FITT, and FPP populations.
@1: Subject (b) (6) in the reference group and all of 20 subjects in site 5 were excluded from FITT and FPP populations based on DSI inspection results. Six subjects among 21 subjects were already excluded from the PP population due to other reasons.
#1: Subject (b) (6) in the test group, (b) (6) in the reference group, (b) (6) in the vehicle group were exclude from FITT population based on the OGD clinical reviewer's comment.
#2: Subject (b) (6) in the reference group were included into the FITT population based on the OGD clinical reviewer's comment.
@2: See Remark, above. We include subjects in the FPP population if Visit 6 occurred on Day 112±5 days, i.e., [107, 117] days. Twenty-five subjects who had visit day 106 at Visit 6 were excluded from the FPP population: (b) (6) (b) (6) in the test group, (b) (6) (b) (6) in the reference group, and, (b) (6) in the vehicle group.
#3: Subject (b) (6) in the test group (b) (6) in the reference group, (b) (6) (b) (6) in the vehicle group were included into the FPP population based on the OGD clinical reviewer's comment.

3.3 Demographics and Baseline

The demographic characteristics for the FITT population at baseline are presented below. Gender and race were analyzed using a Chi-square test. Age was analyzed using a general linear model. Demographic and baseline characteristics for the FPP population were similar to that of the FITT population.

Table 2 Demographic characteristics in the FDA's FITT population

	Total N=581	Test N=232	Reference N=234	Vehicle N=115	p-value
Gender					
Female	115	50	43	22	0.6771
Male	466	182	191	93	
Race					
White	579	230	234	115	0.5546
Native Hawaiian or other	1	1			
American India or Alaska	1	1			
Age (years)					
Mean (STD)	65.2 (10.64)	65.7 (10.32)	65.2(11.0)	64.2 (10.55)	0.4910
Median	65	66	65	63	
Range	21-95	36-95	32-99	21-84	

An analysis for homogeneity of the actinic keratoses (AK) lesion count at baseline visit for the FITT and FPP populations was performed. There were no statistically significant differences among treatment arms for two populations.

3.4 Statistical Methodologies

Statistical Analysis Methods

Binary endpoint

The success rate based on the 100% clearance of all AK lesions within the treatment area at Visit 6/Day 112 (week 16) in the FITT/FPP populations was used for the statistical analysis.

Efficacy Analysis

Tests for superiority of each active treatment over the vehicle were conducted using a two-sided Fisher's exact test at the 5% level of significance. The efficacy of each active treatment was tested separately by comparing it with the vehicle. The active treatment should be better than vehicle.

Equivalence Analysis

Based on the usual method used in the Office of Generic Drugs (OGD) for binary outcomes, the 90% confidence interval for the difference in proportions between the test and reference treatments should be contained within -0.20 to 0.20 in order to establish equivalence.

The compound hypothesis to be tested is:

H_0: $p_T - p_R < -0.20$

or $p_T - p_R > 0.20$

versus

H_A : $-0.20 \leq p_T - p_R \leq 0.20$

where

p_T = success rate of test treatment and p_R = success rate of reference treatment.

Let

n_T = sample size of test treatment, n_R = sample size of reference treatment,

and

$$se = (\hat{p}_T(1-\hat{p}_T)/n_T + \hat{p}_R(1-\hat{p}_R)/n_R)^{1/2}$$

where

$\hat{p}_T$ = observed success rate for the test treatment and

$\hat{p}_R$ = observed success rate for the reference treatment.

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2$$
$$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$$

We reject H_0 if $L \geq -0.20$ and $U \leq 0.20$. Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two treatments.

3.5 Results and Conclusions

3.5.1 Sponsor's Analysis Results

The sponsor evaluated the proportion of subjects achieving success [defined as achieving complete (100%) clearance of AK lesions in the designated treatment area(s) at Visit 6/day 112] in the PP and MITT populations. Complete clearance was defined as subjects who have no (zero) clinically visible AK lesions in the designated treatment area(s) at Visit 6/Day 112 (28 days post-last application visit). Complete (100%)

clearance requires that all baseline lesions as well as new or subclinical AK lesions which appeared in the treatment area during therapy are no longer present.

The sponsor's summary of the result is shown below.

Primary Efficacy Analysis: Complete Clearance of AK lesions at visit 6/Day 112 (4 weeks follow-up); per Sponsor*

Parameter	Test	Reference	Vehicle	90% C.I. for Bioequivalence of Test to Reference	p-values	
					Test vs. Vehicle	Reference vs. Vehicle
Per-Protocol Subjects (n, %)						
	n=187	n=180	n=93			
Success	43 (23.0%)	57 (31.7%)	11 (11.8%)	(-16.8%, -0.5%)	NA	NA
Failure	144 (77.0%)	123 (68.3%)	82 (88.2%)			
Modified Intent-to-Treat Subjects (n, %)						
	n=241	n=244	n=120			
Success	53 (22.0%)	70 (28.7%)	12 (10.0%)	NA	0.0081	0.0001
Failure	188 (78.0%)	174 (71.3%)	108 (90.0%)			

*: Source: Final Study Report TOL-AK-2008-02, Table 14.2.1, pg. 87.

Sponsor concluded the test and reference treatments were statistically significantly better than vehicle for the success rate at visit 6/Day 112 for their modified intent-to-treat (MITT) population and the test and reference treatments were clinically equivalent for the success rate at visit 6/Day 112 for their per-protocol (PP) population.

3.5.2 Reviewer's Results

The test and reference treatments were statistically significantly better than vehicle for the success rate at Visit 6/Day 112 for the FITT population.

Table 3 Efficacy analyses for the success rate at visit 6/Day 112 per FDA's FITT population

			P-value*	
Test	Reference	Vehicle	Test vs. Vehicle	Reference vs. Vehicle
22.41% (52/232)	28.63% (67/234)	10.43% (12/115)	0.0078	<0.0001

*: p-values were derived from the two-sided Fisher's exact test.

The test and reference treatments were found to be clinically equivalent for the success rate at Visit 6/Day 112 for the FPP population.

Table 4 Equivalence analyses for the success rate at visit 6/Day 112 per FDA's FPP population

Test	Reference	The 90% CI for the Test versus Reference	Is the 90% CI within [-20%, 20%]
26.14% (46/176)	32.32% (53/164)	-14.88%, 2.52%	Yes

4 Conclusions

4.1 Comments on the Sponsor's Analyses

Sponsor and FDA use same definition for the same success rate. There are minor differences between our and the sponsor's analyses results due to the differences between the sponsor's and the FDA's intent-to-treat and per-protocol populations.

4.2 Conclusions

Efficacy: The test and reference treatments were statistically significantly better than vehicle for the success rates (100% clearance of all AK lesions within the treatment area) at Visit 6/Day 112 for the FDA's intent-to-treat (FITT) population.

Equivalence: The test and reference treatments were found to be clinically equivalent for the success rates (100% clearance of all AK lesions within the treatment area) at Visit 6/Day 112 for the FDA's per-protocol (FPP) population.

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5 References

Joseph L. Fleiss, Bruce Levin, and MyungHee Cho Paik. (1981). Statistical Methods for Rates and Proportions (2nd edition). New York: Wiley-Interscience.

Clopper, C. and Pearson, S. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-413.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200936

CLINICAL PHARM/BIO REVIEW

Review #2 of a Bioequivalence Study with a Clinical Endpoint

ANDA 200936
Tolmar Inc.

Diclofenac Sodium Gel, 3%

Brenda S. Gierhart, M.D.
Medical Officer
Division of Clinical Review
Office Generic Drugs

Submission dates reviewed:
12/14/09, 6/3/10, 7/8/10, 4/19/11, 9/27/11 & 3/23/12
(DARRTS letter dates)

Date of Review: 6/10/13

Table of Contents

Review of a Bioequivalence Study with a Clinical Endpoint: ANDA 200936

Executive Summary

I. Summary

ANDA 200936 was originally submitted on December 14, 2009 and the OGD issued a letter acknowledging receipt of the application on March 18, 2010. However, a filing review by the Clinical Review Team (currently Division of Clinical Review [DCR]) completed on April 12, 2010 found the submitted bioequivalence study with a clinical endpoint unacceptable because the study design was not adequately sensitive for detecting differences in formulation performance. Therefore, the OGD rescinded the acknowledgement letter of March 18, 2010 and issued a Refuse to Receive letter on April 26, 2010. The firm responded on June 3, 2010 with their justification for the study design, and, after reconsideration, the OGD reversed the prior decision and officially received the application for review on June 11, 2010, affirming the original date of receipt.

Tolmar's generic version of Diclofenac Sodium Gel, 3% has a markedly different formulation than that of the Reference Listed Drug (RLD). The RLD formulation contains (b) (4) sodium hyaluronate, (b) (4) The proposed generic version does not contain hyaluronate and instead contains hydroxyethyl cellulose as (b) (4) along with PEG-60 hydrogenated castor oil. The resulting viscosity is only (b) (4) of that of the RLD. This could result in a difference in efficacy that could be missed on a clinical endpoint study that is not adequately sensitive. To address the OGD concerns regarding this potential difference in efficacy, the sponsor conducted the in vitro Study R12-0512 entitled "HPLC analytical method of qualification with sample matrices relevant to the evaluation of the in vitro percutaneous absorption of diclofenac sodium from a gel formulations into and through human torso skin using the Franz finite dose model", which was submitted to ANDA 200936, with letter date October 31, 2012 and reviewed by the Division of Bioequivalence II, with the conclusion of "inadequate" because it did not show bioequivalence at the first stage, based on a Confidence Interval approach of 75% to 133.33%, between the test and reference product for deposition of the drug within the epidermal layer.[1]

The sponsor also conducted a double-blind, randomized, multicenter, parallel-group study in the treatment of actinic keratoses (AK) to demonstrate that Tolmar Inc.'s Diclofenac Sodium Gel, 3% is bioequivalent to the RLD, Nycomed US's Solaraze® Gel, 3% and its Final Study Report TOL-AK-2008-02 was submitted to the OGD in Original ANDA 200936. The protocol for this study incorporated an 84-day treatment period, whereas the Agency recommends a treatment duration of 60 days, with subject evaluation for the primary endpoint, i.e., complete clearance of

[1] ANDA 200936 Division of Bioequivalence Review Diclofenac Sodium Topical Gel, 3% by Josephine Aimiuwu, Ph.D. finalized in DARRTS on 4/3/13.

all AK lesions within the treatment area, to occur 30 days after the end of treatment. It should be noted that the draft Bioequivalence (BE) Recommendations for this specific product had not been posted at the time when this application was submitted. Review of this BE study with clinical endpoint was assigned to the OGD Division of Clinical Review and it is reviewed in this document.

In the safety and efficacy studies conducted to support approval of the RLD, the Solaraze® Gel was statistically superior to vehicle (placebo) 30 days after completion of the 60-day treatment period. In separate studies of 90 days treatment duration, the treatment efficacy was somewhat higher, but the vehicle success rate was also higher, resulting in one study showing a non-significant difference between active treatment and vehicle. Based on these results, the OGD has concluded that the optimum duration of treatment for a bioequivalence study in the treatment of AK is 60 days.

It should be noted per 21 CFR 320.24 (b)(4), well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for the purposes of demonstrating bioequivalence, are the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence. Clinical trials as an approach to demonstrate bioequivalence generally are considered insensitive.[2] To improve the sensitivity of comparative clinical trials, the dosing regimen and period of dosing must be carefully selected. If the doses chosen for both agents are too high then subjects may reach an upper threshold in response, leading to a false conclusion of equivalence.[3] The same may be true of a longer treatment duration.

In all three of the Innovator's pivotal Phase 3 clinical studies supporting approval (see Tables 1 and 2), the primary efficacy variable was evaluated at the 30-day post-treatment visit and the dosing regimen was twice daily with approximately 0.5 gram of gel per "block" of affected skin. The primary difference between the three pivotal Phase 3 clinical studies supporting approval was the duration of treatment (i.e., 30, 60 or 90 days) and the shortest treatment duration demonstrating a statistically significant difference for the primary endpoint was 60 days of treatment. Increasing the treatment duration to 90 days resulted in an overall higher complete clearance rate for the vehicle. Thus, the 90 day treatment duration is more likely to capture only the maximum effect and not the rate and extent of drug delivery to the site of action. Diclofenac Sodium Gel/Topical 3% administered twice daily for 60 days with the primary efficacy endpoint evaluated at the 30-day post-treatment assessment is recommended by the OGD in the individual product guidance for a bioequivalence study with clinical endpoint. Thus, the study design of TOL-AK-2008-02 with an 84-day treatment duration was not considered to be not acceptable because the longer, 84-day treatment duration is likely to minimize any differences between the test and reference treatments with regard to rate and/or extent of drug delivery to the site of action.

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[2] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Bioavailability and bioequivalence studies for orally administered drug products-general considerations. March 2003; pg. 9.
[3] Jones B et al. Trials to assess equivalence: the importance of rigorous methods. *BMJ.* 1996; 313: 36-9.

Table 1: Complete Clearance of Actinic Keratosis Lesions at 30 Days Post-Treatment (all locations)

		Solaraze® Gel	Vehicle	p-value
Study 1	90 days treatment	27/58 (47%)	11/59 (19%)	<0.001
Study 2	90 days treatment	18/53 (34%)	10/55 (18%)	0.061
Study 3	60 days treatment	15/48 (31%)	5/49 (10%)	0.021
	30 days treatment	7/49 (14%)	2/49 (4%)	0.221

Source: Solaraze® Approved Labeling dated 11/06 available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=2508

Table 2: Complete Clearance of Actinic Keratosis Lesions at 30 Days Post-Treatment (by location)

		Scalp	Forehead	Face	Arm/Forearm	Back of Hand
Study 1	**90 days treatment**					
	Solaraze®	1/4 (25%)	17/30 (57%)	9/17 (53%)	4/12 (33%)	6/16 (38%)
	Vehicle	3/9 (33%)	8/24 (33%)	5/17 (29%)	4/12 (33%)	0/14 (0)
	p-value	0.7646	0.0908	0.1682	1.000	0.0650
Study 2	**90 days treatment**					
	Solaraze	2/6 (33%)	9/19 (47%)	4/5 (80%)	5/8 (63%)	1/17 (6%)
	Vehicle	0/4 (0)	6/22 (27%)	2/8 (25%)	0/5 (0)	3/16 (19%)
	p-value	0.4235	0.1870	0.0727	0.0888	0.2818
Study 3	**60 days treatment**					
	Solaraze	3/7 (43%)	13/31 (42%)	10/19 (53%)	0/1 (0)	2/8 (25%)
	Vehicle	0/6 (0)	5/36 (14%)	2/13 (15%)	0/2 (0)	1/9 (11%)
	p-value	0.2271	0.0153	0.0433	–	0.4637
	30 days treatment					
	Solaraze	2/5 (40%)	4/29 (14%)	3/14 (21%)	0/0 (0)	0/9 (0)
	Vehicle	0/5 (0)	2/29 (7%)	2/18 (11%)	0/1 (0)	1/9 (11%)
	p-value	0.2299	0.3748	0.4322	–	0.6521
All data combined	Solaraze	8/22 (36%)	43/109 (39%)	26/55 (47%)	9/21 (43%)	9/50 (18%)
	Vehicle	3/24 (13%)	21/111 (19%)	11/56 (20%)	4/20 (20%)	5/48 (10%)
	p-value	0.0903	0.0013	0.0016	0.2043	0.3662

Source: Solaraze® Approved Labeling dated 11/06 available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=2508

Tolmar's subject population for their BE study with clinical endpoint is also not optimal for ensuring adequate sensitivity of the study to detect differences between the test and reference

products. Although Tolmar specified an appropriate lower limit to baseline lesion count (at least 5 AK lesions), no upper limit was set and a minimum size for the baseline lesions included in that count was not specified. The data presented show that more subjects receiving the reference product had lesion counts above 10 compared to subjects receiving the test product. This could have lowered the reference product success rate, thereby making the test and reference results more similar.

Tolmar also enrolled subjects with AK lesions on different body areas instead of enrolling only subjects with AK lesions on the face or balding forehead, as specified in the posted Draft BE guidance for this drug product. Although in the NDA studies fewer subjects had AK lesions on the back of the hands or forearms/arms, the success rate appears to be different for lesions in those areas than for lesions on the face or forehead. Therefore enrollment of subjects with lesions on the back of the hands or forearms/arms may have increased the variability in treatment response and confounded the study results.

The Final Study Report for Study TOL-AK-2008-02 states that 609 subjects were enrolled and randomized, 608 subjects were in the Intent-to-Treat (ITT; Safety) population, 605 subjects were included in the modified Intent-to-Treat (mITT) population and 460 subjects were included in the Per Protocol (PP) population.[4] Per the sponsor, complete clearance [defined as 100% clearance of AK lesion count in the designated treatment area(s)] was achieved in 43 subjects (23.0%) in the Diclofenac Sodium Gel treatment group and 57 subjects (31.7%) in the Solaraze® Gel treatment group in the PP population at visit 6/day 112 (i.e., week 16; 4 weeks after treatment ended).[5] The sponsor concluded that the 90% Confidence Interval (CI) of the difference in the success rate between the test and reference products at visit 6 in the PP population is (-0.168, -0.005), which is within the bioequivalence limits of (-0.20 to +0.20).[6] Per the sponsor, both test and reference products are shown to be statistically superior to vehicle (p=0.0081 and p=0.0001, respectively) at visit 6 in the mITT population, demonstrating that the study is sufficiently sensitive to discriminate differences between products.

Reviewer's comment: *Although the difference in success rates is within the established bioequivalence limits, a 90% confidence interval entirely below 0 suggests that the test and reference products may not be truly equivalent in performance. Furthermore, superiority over placebo (vehicle) only ensures study sensitivity at the lower end of the dose response curve and*

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[4] Per Final Study Report TOL-AK-2008-02 (pg. 32 of 217), the following analysis populations contained subjects who:
ITT (Safety Population): 1) enrolled into the study, AND 2) applied at least one dose of study drug.
mITT: 1) enrolled into the study, 2) applied at least one dose of study drug, 3) had a baseline lesion count, AND 4) had at least one post-baseline lesion count.
PP: 1) enrolled into the study, 2) met inclusion/exclusion criteria, 3) maintained compliance with study drug applications (applied at least 80% and not more than 120% of doses and did not miss 10 or more consecutive applications of study drug), 4) took no concomitant medications prohibited by the protocol, 5) had no other significant protocol violations, AND 6) returned for visit 6/day 112 within the visit window and had a lesion count in this visit, OR 7) were discontinued early due to insufficient therapeutic response (after completing at least 28 days of study drug use, with a compliance rate of at least 80%).
[5] Final Study Report TOL-AK-2008-02 (pg. 43 of 217).
[6] Per Final Study Report TOL-AK-2008-02 (pg. 43 of 217), the sponsor calculated the confidence interval using Wald's method with Yates' continuity correction.

does not address the limitations of a study with a longer treatment duration that may have reached an upper threshold in response and lead to a false conclusion of equivalence.

Thus, the assessment in the first Clinical Review of ANDA 200936 (finalized on July 10, 2011) was:

> The formulation differences between the test and reference products are substantial and may negatively impact the performance of the test product. Due to inadequate sensitivity of the study design, the Clinical Review Team concludes that the data submitted to ANDA 200936 are not adequate to demonstrate bioequivalence of Tolmar Inc.'s Diclofenac Sodium Gel, 3%, with the reference listed drug, Nycomed US's Solaraze® Gel, 3%. Therefore, the study is not adequate to support approval of the application. [7]

Therefore, the OGD issued the ANDA 200936 "fatal flaw" letter of July 11, 2011 which stated that the OGD had determined that this application could not be approved in its present form because: 1) one or more of the inactive ingredients of the proposed drug or its composition raise serious questions of safety or efficacy [21 CFR 314.127(a)(8)(ii)(A)], and 2) the bioequivalence study is not adequate to demonstrate that the test product is bioequivalent to the reference listed drug [21 CFR 314.127(a)(6)(i)]. The firm responded on September 27, 2011 by appealing the non-approval of ANDA 200936 to Helen N. Winkle, Director, Office of Pharmaceutical Science (OPS), FDA and requesting Dispute Resolution. After their submission was reviewed in detail by the Division of Clinical Review (DCR), the conclusion in the Addendum to the ANDA 200936 Clinical Review finalized on December 13, 2011 was:

> After re-review of the innovator Phase 3 efficacy and safety studies, the DCR revised their previous evaluation of Tolmar's submitted bioequivalence (BE) study with clinical endpoint based upon a similar mean difference between Solaraze Gel and vehicle at both after 60 days of treatment (i.e., mean difference 21%) and after 90 days of treatment (i.e., mean difference 22%).

Table 3: Complete Clearance of Actinic Keratosis Lesions at 30 Days Post-Treatment (all locations)

	Treatment duration	Solaraze® Gel	Vehicle	Difference in %	Mean Difference in %	p-value
Study 1	90 days	27/58 (47%)	11/59 (19%)	28%	22%	<0.001
Study 2	90 days	18/53 (34%)	10/55 (18%)	16%		0.061
Study 3	60 days	15/48 (31%)	5/49 (10%)	21%	21%	0.021
	30 days	7/49 (14%)	2/49 (4%)	10%	10%	0.221

Sources: Calculation of Difference in % and Mean Difference in % by this reviewer; Solaraze® Approved Labeling dated 11/06 available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=2508

> The DCR now concurs with Tolmar that their BE with clinical endpoint study is adequately sensitive to demonstrate whether their test drug product and the reference listed drug (RLD)

[7] ANDA 200936: Review #1 of a Bioequivalence Study with a Clinical Endpoint by Brenda S. Gierhart, M.D., finalized in DARRTS on 7/10/11; pg. 7 of 61.

> are bioequivalent or not. Thus, Tolmar's BE with clinical endpoint study is now eligible for a full review. The DCR will be sending a Request for Consultation to the Division of Scientific Information pertaining to study site inspections and also sending a request for a formal statistical review of Tolmar's study.[8]

Thus, the OPS issued the ANDA 200936 "Dispute Appeal – Denied" letter on December 20, 2011 which denied Tolmar's request that ANDA 200936 be approved; however, it also provided recommendations for addressing the July 11, 2011 "fatal flaw" letter, which included the following recommendations for addressing comment "4. Conduct a clinical endpoint study designed to have the maximum sensitivity for detecting differences in product performance between the test and reference products.":

> Regarding the above comment #4 from the July 11, 2011 letter, I requested that the OGD Division of Clinical Review (DCR) re-evaluate the study. After the re-evaluation of the innovator Phase 3 efficacy and safety studies, DCR has revised their previous evaluation of your submitted bioequivalence (BE) study with clinical endpoint. The DCR now concurs with you that your BE with clinical endpoint study is adequately sensitive to demonstrate whether your test drug product and the reference listed drug (RLD) are bioequivalent or not; thus, your BE with clinical endpoint study is now eligible for a full review. I concur with their finding. The DCR will be sending a Request for Consultation to the Division of Scientific Information pertaining to study site inspections and also sending a request for a formal statistical review of your study.[9]

On March 4, 2013, the Division of Scientific Information (DSI) finalized the results of their site inspections for ANDA 200936 and recommended that all data from Stephen Miller, MD's study site be deleted from the bioequivalence evaluation of Study TOL-AK-2008-02 because:

> As the blinding code was not maintained at the study site by Dr. Miller, the test and reference drug products used at site #3 cannot be positively identified. The quality and integrity of the study data from site# 3 cannot be assured as the site did not main adequate drug accountability records (FDA-483, Observations 2).[10]

The DCR concurred with the recommendations of the DSI and included all subjects from Dr. Miller's site in the listing of excluded subjects sent to the statisticians, i.e., the listing of subjects to be excluded from the FDA per-protocol and intent-to-treat subject populations when performing the FDA bioequivalence evaluation of Study TOL-AK-2008-02. On June 6, 2013, the statistical review of the BE study with clinical endpoint, i.e., Study TOL-AK-2008-02, was finalized with the conclusion that the equivalence test passed for the success rate in the FDA's

[8] ANDA 200936: Addendum to Clinical Review of a Bioequivalence Study with a Clinical Endpoint by Brenda S. Gierhart, M.D., finalized in DARRTS on 12/13/11; pg. 3 of 5.
[9] ANDA 200936 OPS Dispute Appeal – Denied Letter finalized in DARRTS on 12/20/11 on pg. 3-4 of 6.
[10] Review of EIRs covering ANDA 200936, Diclofenac Sodium Gel, 3%, sponsored by Tolmar Inc. by Arindam Dasgupta, Ph.D., Division of Bioequivalence and GLP Compliance, Office of Scientific Investigations, finalized in DARRTS on 3/4/13; pg. 8 of 26.

per-protocol (FPP) population and the two active treatment were statistically significantly better than the vehicle for the success rate in the FDA's intent-to-treat (FITT) population.[11]

II. Recommendation on Approval

The Division of Clinical Review (DCR) concurs with the FDA statisticians that when using data from the FDA-determined study populations for Study TOL-AK-2008-02, data submitted to ANDA 200936 confirms the sponsor's results. Thus, the DCR concludes that this study is adequate to support approval of the application. However, the formulation differences between the test and reference products are substantial and may negatively impact the performance of the test product. This deficiency is being addressed by the Division of Bioequivalence II.[12, 13]

III. Summary of Clinical Findings

Study TOL-AK-2008-02 was conducted to demonstrate that Tolmar Inc.'s Diclofenac Sodium Gel, 3%, is bioequivalent to the reference listed drug, Nycomed US's Solaraze® Gel, 3%, using the primary endpoint of complete clearance of AK lesions (zero clinically visible) in the treated area at visit 6/day 112 (i.e., week 16; 4 weeks after completion of 84 days of treatment).

A. Brief Overview of Clinical Program

Study TOL-AK-2008-02 was a randomized, double-blind, comparative study of Tolmar Inc.'s Diclofenac Sodium Gel, 3%, versus the reference listed drug, Nycomed US's Solaraze® Gel, 3%, in the treatment of AK. Six hundred and nine (609) subjects with five or more clinically typical visible, discrete, non-hyperkeratotic, non-hypertrophic AK lesions contained in one 25 cm^2 treatment area in one major body area as defined in this study: forehead, central face, scalp, back of hands, and forearms were randomized in a 2:2:1 ratio to receive the test, reference, or vehicle (placebo) gel twice daily for 84 days (12 weeks).

B. Comparative Efficacy

The primary endpoint of this study evaluated by the sponsor was the percentage of subjects in the PP population achieving complete clearance of AK lesions in the treated area at the 4-week follow-up visit (i.e., visit 6/day 112/week 16) after completion of 12 weeks of treatment. According to the sponsor, the success rate in the PP population at visit 6 was 23.0% in the test group and 31.7% in the reference group. The 90% CI of the difference in success rate between the two active products is (-0.168, -0.005), which is within the established bioequivalence limits of (-0.20 to +0.20). While this confidence interval is entirely below zero, suggesting a difference between products, despite meeting the established limits, this finding is insufficient to preclude the use of this study to support the approval of ANDA 200936.

[11] ANDA 200936 Office of Biostatistics Statistical Review and Evaluation by Huaxixiang Li, Ph.D. finalized in DARRTS on 6/6/13.
[12] ANDA 200936 OGD Bioequivalence Deficiencies Letter finalized in DARRTS on 4/19/12.
[13] ANDA 200936 Division of Bioequivalence Review Diclofenac Sodium Topical Gel, 3% by Josephine Aimiuwu, Ph.D. finalized in DARRTS on 4/3/13.

C. Comparative Safety

The sponsor concluded that the safety profile of the test product was not statistically or clinically different than that of the reference product in the treatment of actinic keratoses.[14]

A total of 158 subjects [i.e., 69 (28.6%) in the test group, 58 (23.6%) in the reference group, and 31 (25.6%) in the vehicle group] experienced one or more treatment-emergent adverse events. Twenty (3.3%) subjects (8 test, 9 reference, 3 vehicle) discontinued the study due to "withdrawal due to adverse event". An additional 15 subjects (11 test, 3 reference, 1 vehicle) withdrew due to a local skin reaction, which the sponsor coded as "Other". Local skin reactions recorded during the assessment of the treated area were not reported as AEs, unless, in the opinion of the Investigator, the event qualified as an AE.

Reviewer's comment: *The more than three-fold higher number of test subjects withdrawing due to a local skin reaction suggests that the test formulation may be more irritating than the RLD. However, this finding alone is insufficient to preclude the use of this study to support the approval of ANDA 200936. When comparing the safety findings of the two active treatment groups, the total number of adverse events, subjects prematurely discontinuing from the study due to a treatment-emergent adverse events, and skin-related adverse events are similar.*

Skin-related adverse events listed in the "Skin and subcutaneous tissue disorders" MedDRA system organ class, regardless of relationship to the study medication, occurred in 22 subjects (12 test, 8 reference, 2 vehicle). Skin-related adverse events probably or definitely related to study medication occurred in 17 subjects (9 test, 6 reference, 2 vehicle). Additionally, 3 skin-related adverse events listed in the "General disorders and administration site conditions" MedDRA system organ class occurred in 3 subjects (2 test, 1 reference) and all were considered to be related: the AE "application site erythema" was reported by 1 test subject, the AE "application site irritation" was reported by 1 reference subject and the AE "application site rash" was reported by 1 test subject. Severe "Skin and subcutaneous tissue disorders" AEs occurred in five subjects (4 test, 1 reference): severe contact dermatitis was reported in 2 test subjects; severe rash was reported in 1 test subject; severe skin erosion was reported in 1 reference subject; severe skin irritation was reported in 1 test subject.[15] According to the sponsor's analysis, there were no notable differences between the treatment groups in the percentage of subjects with skin reactions reported as AEs related to study drug, with the exception of hypersensitivity reactions related to study drug being more common in the reference group (n=5).[16]

No death occurred in the study. Thirteen serious adverse events were experienced by 13 subjects (5 test, 5 reference, 3 vehicle) and none were considered by the sponsor to be related to the study drug.

[14] ANDA 200936 Section 5.3.1.2 (pg. 1 of 1).
[15] Final Study Report TOL-AK-2008-02 (pg. 60 of 217).
[16] Final Study Report TOL-AK-2008-02 (pg. 70 of 217).

Clinical Review

I. Introduction and Background

Solaraze® (diclofenac sodium) Gel, 3% is a topical nonsteroidal anti-inflammatory drug (NSAID) approved under NDA 021005 for the treatment of actinic keratoses. The mechanism of action of diclofenac sodium for the treatment of actinic keratoses (AK) is unknown.[17]

According to the approved labeling, systemic absorption of diclofenac in subjects treated topically with Solaraze® is much lower than that occurring after oral daily dosing of diclofenac sodium. Blood was drawn at the end of treatment from 60 subjects with AK lesions treated with Solaraze® in three adequate and well-controlled clinical trials. Each subject was administered 0.5 g of Solaraze Gel twice a day for up to 105 days. There were up to three 5 cm x 5 cm treatment sites per subject on the face, forehead, hands, forearm and scalp. Serum concentrations of diclofenac were on average at, or below 20 ng/mL.

In clinical studies, localized dermal side effects such as contact dermatitis, exfoliation, dry skin, and rash were found in subjects treated with Solaraze® at a higher incidence than in those with vehicle (placebo).

A. Drug Established Name, Drug Class

Drug Established Name: Diclofenac Sodium Gel, 3%

Drug Class: Nonsteroidal anti-inflammatory drug (NSAID)

B. Trade Name of Reference Drug, NDA number, Date of approval, Approved Indication(s), Dose, Regimens

Reference Drug (NDA number): Solaraze® (diclofenac sodium) Gel, 3% (NDA 021005), Nycomed US (see Appendix, Table 29)

Date of approval: 10/16/00

Approved indication(s) based on label approved on 10/16/00: For the topical treatment of actinic keratoses (AK). Sun avoidance is indicated during therapy.

Recommended dosing regimens: Per the approved labeling, Solaraze® Gel, 3% should be applied to lesion areas twice daily. It is to be smoothed on the affected skin gently. The amount needed depends upon the size of the lesion site. Assure that enough Solaraze Gel is applied to adequately cover each lesion. Normally 0.5 g of gel is used on each 5 cm x 5 cm lesions site. The

[17] **CLINICAL PHARMACOLOGY** section of the Solaraze® (diclofenac sodium) Gel, 3% Approved Labeling,

recommended duration of therapy is from 60 days to 90 days. Complete healing of the lesion(s) or optimal therapeutic effect may not be evident for up to 30 days following cessation of therapy.

C. Regulatory Background

To date, Tolmar Inc. has not submitted any IND, Protocol, or Controlled Correspondence to the OGD for Diclofenac Sodium Gel, 3%. To date, no INDs have been submitted to the OGD for Diclofenac Sodium Gel, 3%.

To date, the following one Protocol (designated by "P" below; also see Appendix, Table 33) and seven Controlled Correspondence (designated by "C" below; also see Appendix, Table 34) have been submitted to the OGD for Diclofenac Sodium Gel, 3% by other sponsors:

Submission		Status
C02-592	(b) (4)	(b) (4)
C06-0132		
C06-0174		
C06-1336		
(b) (4)		
C09-0608		
C11-0632		
C12-0467		

The current submission is the only ANDA submitted to the OGD for Diclofenac Sodium Gel, 3% (see Appendix, Table 32). (b) (4) ANDAs have been submitted for the related drug product Diclofenac Sodium Gel, 1%, which has a different indication and different dosing regimen.

(b) (4)

D. Other Relevant Information

The treatment of AK is the only approved indication for Solaraze Gel, 3%. The clinical presentation of AK is straightforward, and clinical assessment is appropriate and reliable without the need for diagnostic biopsies at baseline or end of treatment. The recommended treatment regimen allows for a duration of treatment from 60 to 90 days. The OGD recommends a single bioequivalence study with a clinical endpoint in the treatment of AK for assessment of bioequivalence of generic Diclofenac Sodium Gel, 3% to the RLD. The recommended treatment duration is 60 days, the shortest labeled treatment duration.

II. Description of Clinical Data and Sources

Study Centers/Investigators: The study was conducted at the 37 sites that enrolled subjects. No subjects appear to have been enrolled at Sites #1, 2, 3 and 28. The sponsor certified that they did not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application. The sponsor also certified that neither they, nor any affiliated person responsible for the development or submission of the Diclofenac Sodium Gel, 3% ANDA, had sustained any convictions described under sections 306 (1) and 2306 (b) of the Act within the past 5 years.

Table 4: Study TOL-AK-2008-02 Sites, Principal Investigators and Number of Subjects per Site

Site Number *	Site Number **	Principal Investigator	Randomized n=609	Per-Protocol Analyses n=460	Modified Intent-to-Treat Analyses n=605	Intent-to-Treat Analyses n=608
1	4	Sunil S. Dhawan, MD	19	12	18	19
2	5	Marina I Peredo, MD	19	16	19	19
3	6	Elyse S Rafal, MD	15	13	15	15
4	7	Jonathan S Weiss, MD	13	8	13	13
5	8	Stephen Miller, MD	20	15	20	20
6	9	Krunal M Patel, MD	15	11	15	15
7	10	Dow B Stough, MD	14	10	14	14
8	11	Leonard Swinyer, MD	15	13	15	15
9	12	Stanley C Gilbert, MD	15	8	15	15
10	13	Robert S Haber, MD	4	3	4	4
11	14	David M Pariser, MD	15	13	15	15
12	15	Terry M Jones, MD	15	14	15	15
13	16	William B Harwell, MD	29	23	28	29
14	17	Joseph F Fowler, Jr, MD	15	12	15	15
15	18	Elizabeth A Arthur, MD	10	6	10	10
16	19	Keith H Loven, MD	6	5	6	6
17	20	Kenneth G Gross, MD	15	10	15	15
18	21	David L Kaplan, MD	11	5	10	11
19	22	Joel Schlessinger, MD	35	17	35	35
20	23	Michael Jarratt, MD	15	14	15	15
21	24	John H Tu, MD MS	25	21	25	25
22	25	Mark R Ling, MD PhD	15	6	15	15
23	26	Paul Yamauchi, MD, PhD	15	14	15	15
24	27	James M Swinehart, MD	15	11	15	15
26	29	Steven Kempers, MD	14	13	14	14
27	30	Eduardo Tschen, MD	18	14	18	18
28	31	Adnan Nasir, MD, PhD	20	15	20	20
29	32	Zoe Diana Draelos, MD	15	13	15	15
30	33	Linda Murray, DO	15	9	15	15

Site Number *	Site Number **	Principal Investigator	Randomized n=609	Per-Protocol Analyses n=460	Modified Intent-to-Treat Analyses n=605	Intent-to-Treat Analyses n=608
31	34	Frank E Dunlap, MD	15	10	15	15
32	35	Francisco Flores, MD	15	14	15	15
33	36	Hector Wiltz, MD	15	13	15	15
34	37	Robert T Matheson, MD	30	30	30	30
35	38	Linda Stein Gold, MD	15	11	15	15
36	39	J.. Michael Maloney, III, MD	15	11	15	15
37	40	David Kerr, MD	15	11	14	14
38	41	Phoebe Rich MD	22	16	22	22

*Site number per Subject2 dataset submitted in Original ANDA 200936
** Site number per Subject dataset submitted in Original ANDA 200936

Study Period: February 5, 2009 to August 25, 2009

Enrollment: A total of six hundred and nine (609) subjects were randomized into the study.

III. Clinical Review Methods

A. Overview of Materials Included in Review

Original Submission: Original ANDA 200936 electronic submission received on 12/16/09 (i.e., DARRTS Supp. Document No. 1; letter date 12/14/09) was reviewed.

ANDA Amendments:

1) DARRTS Supp. Document No. 4: On June 3, 2010 (DARRTS received date June 4, 2010), the lawyer representing the sponsor (i.e., Roger C. Thies, Hyman, Phelps & McNamara, P.C.) submitted an appeal of refusal to receive decision and it was reviewed.

2) DARRTS Supp. Document No. 5: On April 26, 2010, the OGD asked the sponsor to provide additional data regarding the submitted clinical endpoint study. In response, the sponsor submitted the additional data (cover letter dated June 30, 2010; DARRTS letter date July 8, 2010; DARRTS received date July 9, 2010) and it was reviewed.

3) DARRTS Supp. Document No. 8: On April 19, 2011, the OGD asked the sponsor to provide the total number of subjects enrolled at each site and the number of subjects in the Per Protocol Population at each site for the submitted BE with clinical endpoint study TOK-AK-2008-02. In response, the sponsor submitted a 3-page table containing the requested information (cover letter and DARRTS letter date April 19, 2010; DARRTS received date April 20, 2011) and it was reviewed. The table confirmed the number of randomized subjects per site and Per Protocol subjects per site provided in the above Table 4.

4) DARRTS Supp. Document No. 13: On September 27, 2011 (DARRTS received date September 27, 2011), Tolmar submitted a "Dispute Resolution/Request for Resolution", including two cover letters, an introduction, and nine exhibits, and it was reviewed.

5) DARRTS Supp. Document No. 15: On March 23, 2012 (DARRTS received date March 23, 2012), Tolmar submitted an unsolicited amendment to clarify previously submitted information and it was reviewed

B. Overview of Methods Used to Evaluate Data Quality and Integrity

Division of Scientific Investigations (DSI) Report:

On December 15, 2011, DSI inspections were requested for three study sites (i.e., Sites 1, 2, and 5) and the report was finalized on 3/4/13. Based upon the inspections of Study TOL-AK-2008-02 sites conducted by the Division of Scientific Inspection (DSI), the Division of Clinical Review (DCR) concludes that data from Study Site 5: Stephen Miller, MD should be deleted from the bioequivalence evaluation. [**NOTE**: see Section VI of this review for additional details re: the DSI Inspection Report.]

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

This reviewer was unable to locate any information regarding approval of the study protocol by any Investigational Review Board (IRB). The Original Protocol (Version 1.8) is dated November 12, 2008 and Amendment #1 (Version 1.9) is dated January 15, 2009. It appears that the sponsor failed to provide a listing of all changes made in Amendment #1 to the protocol.

The sponsor reported that the standard subject informed consent form (13 pg.) was approved on January 19, 2009 by the (b) (4) IRB located (b) (4) and an amended subject informed consent form (13 pg.) was approved by the same IRB on January 26, 2009. This reviewer was unable to locate any information provided by the sponsor delineating the changes made to the amended consent form approved by the (b) (4) IRB. Specifically for the Henry Ford Health System site, a different subject informed consent form (12 pg.) Version 2 was approved on January 27, 2009 by the Henry Ford Health System IRB located in Detroit, MI.

Reviewer's comment: *The sponsor stated that the study protocol was approved by an IRB*[18] *but did not submit verification from the IRB. A listing of the* (b) (4) *IRB* (b) (4) *) Board Membership, a listing of the Henry Ford Health System IRB Membership and the informed consents approved by the two IRBs were located.*[19]

[18] TOL-AK-2008-02 Final Study Report pg. 13 of 217.
[19] TOL-AK-2008-02 Final Study Report Appendix 16.1.3. entitled "Ethics Committee(s)/Institutional Review Boards and Sample Informed Consents pg. 1-54 of 54.

D. Evaluation of Financial Disclosure

The sponsor declared that they had not entered into any financial arrangement with the 37 listed clinical investigators (who enrolled all of the subjects for Study TOL-AK-2008-02), whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2 (a).

IV. Review of Bioequivalence Study with Clinical Endpoints

A. Brief Statement of Conclusions

The DCR concurred with the recommendations of the DSI and included all subjects from Dr. Miller's site in the listing of excluded subjects sent to the statisticians, i.e., the listing of subjects to be excluded from the FDA per-protocol and intent-to-treat subject populations when performing the FDA bioequivalence evaluation of Study TOL-AK-2008-02. On June 6, 2013, the statistical review of the BE study with clinical endpoint, i.e., Study TOL-AK-2008-02, was finalized with the conclusion that the equivalence test passed for the success rate in the FDA's per-protocol (FPP) population and the two active treatment were statistically significantly better than the vehicle for the success rate in the FDA's intent-to-treat (FITT) population.[20]

The Division of Clinical Review (DCR) concurs with the FDA statisticians that when using data from the FDA-determined study populations for Study TOL-AK-2008-02, data submitted to ANDA 200936 confirms the sponsor's results. Thus, the DCR concludes that this study is adequate to support approval of the application. However, the formulation differences between the test and reference products are substantial and may negatively impact the performance of the test product. This deficiency is being addressed by the Division of Bioequivalence II.[21, 22]

B. General Approach to Review of the Comparative Efficacy of the Drug

The sponsor's study (protocol #TOL-AK-2008-02) was reviewed to evaluate the bioequivalence of the test product and the reference product. The primary endpoint of this study is the complete clearance of AK lesions (zero clinically visible actinic keratosis lesions in the treatment area) at 4-weeks post-treatment (week 16). The sponsor's proposed primary parameter was evaluated for bioequivalence and secondary parameters were considered as supportive information.

C. Detailed Review of Bioequivalence Studies with Clinical Endpoints

1. The sponsor's 52-page Original Protocol TOL-AK-2008-02 is dated November 12, 2008 (Version 1.8) and it was not reviewed by the OGD prior to the ANDA submission.

[20] ANDA 200936 Office of Biostatistics Statistical Review and Evaluation by Huaxixiang Li, Ph.D. finalized in DARRTS on 6/6/13.
[21] ANDA 200936 OGD Bioequivalence Deficiencies Letter finalized in DARRTS on 4/19/12.
[22] ANDA 200936 Division of Bioequivalence Review Diclofenac Sodium Topical Gel, 3% by Josephine Aimiuwu, Ph.D. finalized in DARRTS on 4/3/13.

2. Protocol TOL-AK-2008-02 was amended (Amendment #1) on January 15, 2009 (Version 1.9). Per the sponsor, it revised the treatment area from one to two 5 cm x 5 cm treatment areas to one 25 cm^2 treatment area and made other changes. The sponsor submitted a copy of this amended 51-page protocol; however, it did not include a listing of all changes made in Amendment #1 to the protocol.

3. The sponsor's standard subject informed consent form (13 pg.) was approved on January 19, 2009 by the (b) (4) IRB located (b) (4) and an amended subject informed consent form (13 pg.) was approved by the same IRB on January 26, 2009. This reviewer was unable to locate any information provided by the sponsor delineating the changes made to the amended consent form approved by the (b) (4) IRB. Specifically for the Henry Ford Health System site, a different subject informed consent form (12 pg.) Version 2 was approved on January 27, 2009 by the Henry Ford Health System IRB located in Detroit, MI.

Protocol Review (TOL-AK-2008-02):

Title: A Double-Blind, Randomized, Parallel-Group, Vehicle-Controlled, Multicenter Study to Evaluate the Safety and Bioequivalence of Diclofenac Sodium Gel, 3% (TOLMAR Inc.) to Solaraze® (Diclofenac sodium) Gel, 3% and Compare Both Active Treatments to a Vehicle Control in the Treatment of Actinic Keratosis

Objective: The objectives of this study were to demonstrate comparable safety, tolerability, and efficacy of Diclofenac Sodium Gel, 3% and Solaraze® (diclofenac sodium) Gel, 3% in the treatment of AK in order to demonstrate bioequivalence, and to demonstrate superiority of the two active gels over that of the vehicle control.

Study Design: This was a 16-week, 2:2:1 randomized, double-blind, parallel-group, vehicle-controlled, multicenter study design comparing the following three products (all supplied in 100 gram tubes) applied twice daily for 12 weeks (84 days):

1. Test: Diclofenac Sodium Gel, 3%, Tolmar Inc., Batch/Lot #3241A, manufactured 11/08.

2. Reference: Solaraze® (diclofenac sodium) Gel, 3%, Doak Dermatologics (current sponsor Nycomed US), Batch/Lot #8064201 expiration date 2/10; #8205201 expiration date 5/10; #8205301 expiration date 5/10; #8205401 expiration date 5/10; #8205101 expiration date 5/10; #8346401 expiration date 8/10; #8346301 expiration date 8/10; #8346601 expiration date 8/10.

3. Placebo (Vehicle): Tolmar Inc., Batch/Lot #3240.

The initial application of study drug was conducted under direct supervision of study drug dispenser. Subjects were instructed to wash treatment area with cold water and pat dry prior to applying study drug. Subjects were instructed to gently apply the assigned study medication twice daily to the designated area(s) for 84 days (12 weeks). The amount of study drug needed depended upon the size of the treatment area. Subjects were instructed to apply enough study drug to adequately cover each lesion. Normally, 0.5 gram (pea size) of gel was used on the 5 cm

× 5 cm area. Subjects used a diary to record each date (i.e., mm/dd/yy) of treatment and whether or not study treatment as applied in the AM (i.e., AM: □ Yes □ No) and in the PM (i.e., PM: □ Yes □ No) on that specific date.[23] There were a total of six study visits Visit 1/Day 1: Baseline, Visit 2/Day 14 (±3 days), Visit 3/Day 28 (±3 days), Visit 4/Day 56 (±5 days), Visit 5/Day 84 (±5 days) (End of Treatment [EOT]), and Visit 6/Day 112 (±5days): (Follow-up/Early Discontinuation).

Reviewer's comment: *The primary issue pertains to the design of the clinical endpoint study. It should be noted per 21 CFR 320.24 (b)(4), well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for the purposes of demonstrating bioequivalence, are the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence. It has been recommended that clinical trials as an approach to demonstrate bioequivalence generally are considered insensitive.[24] To improve the sensitivity of comparative clinical trials, the dosing regimen and period of dosing must be carefully selected. If the doses chosen for both agents are too high then subjects may reach an upper threshold in response, leading to a false conclusion of equivalence.[25] The same may be true of a longer treatment duration. In all 3 of the Innovator's pivotal Phase 3 clinical studies supporting approval (see above Tables 1 and 2), the primary efficacy variable was evaluated at the 30-day post-treatment visit and the dosing regimen was twice daily with approximately 0.5 gram of gel per "block" of affected skin. The primary difference between the 3 pivotal Phase 3 clinical studies supporting approval was the duration of treatment (i.e., 30, 60 or 90 days) and the shortest treatment duration demonstrating a statistically significant difference for the primary endpoint was 60 days of treatment. Increasing the treatment duration to 90 days resulted in an overall higher complete clearance rate for the vehicle. Thus, the 90 day treatment duration is more likely to capture only the maximum effect and not the rate and extent of drug delivery to the site of action. The OGD recommends that Diclofenac Sodium Gel/Topical 3% be administered twice daily for 60 days with the primary efficacy endpoint evaluated at the 30-day post-treatment assessment in the bioequivalence study with clinical endpoint. The longer, 84-day treatment duration is likely to minimize any differences between the test and reference treatments with regard to rate and/or extent of drug delivery to the site of action. However the DCR has revised their previous evaluation of Tolmar's submitted bioequivalence (BE) study with clinical endpoint (see above Table 3) based upon a similar mean difference between Solaraze Gel and vehicle at both after 60 days of treatment (i.e., mean difference 21%) and after 90 days of treatment (i.e., mean difference 22%). The minor difference of the post-treatment assessment occurring at 30-days post-treatment (as recommended by the OGD) or at 28-days post-treatment (as in TOL-AK-2008-02) is not considered to be an issue.*

[23] Amended Protocol TOL-AK-2008-02 (Version 1.9) pg. 44.
[24] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Bioavailability and bioequivalence studies for orally administered drug products-general considerations. March 2003; pg. 9.
[25] Jones B et al. Trials to assess equivalence: the importance of rigorous methods. *BMJ.* 1996; 313: 36-9.

Randomization:
Study personnel assigned a subject number to each enrolled subject. The subject number corresponded to a computer-generated randomization schedule assigning the number to one of the three treatment groups. The randomization scheme was generated so that Test Product, Reference Product, and Vehicle Gel were assigned in a 2:2:1 ratio, using a block of 5. The subject numbers were assigned sequentially in the order in which subjects were enrolled at each study center. Study drug was labeled and packaged so that neither the subject nor the Investigator could identify the treatment.

Blinding:
Per the sponsor, the study drug assigned to each subject number was determined by a computer-generated randomization schedule and the study drug was labeled and packaged, according to the random code, so that neither the subject nor the Investigator could identify the treatment. A three-part label was to be attached to each subject study kit box. The tear-off section of the label would be attached to the Study Drug Dispensing Log at the time the first tube was dispensed. The integrity of the randomization code-break tabs was checked periodically and at the conclusion of study, by the study monitor. The Investigator was not to open any code-break tabs unless absolutely necessary to provide medical treatment to a subject in an emergency and only with prior authorization from the Sponsor or designee. If the blind was broken for a subject, the subject was discontinued from the study and the reason recorded.

The study kit box contained three 100 gram tubes of study drug and one tube was dispensed at Visit 1/Baseline, Visit 2/day 28, and Visit 4/ day 56.[26] The test treatment and vehicle control were each described as being "transparent to translucent, colorless to light amber gel"; while the reference treatment was described as a "clear, transparent, colorless to slightly yellow gel".[27] Per the protocol, the study drug was blinded by covering the tubes of study drug with opaque material.[28] Per the protocol, each subject kit box was to bear a label showing the Sponsor's name, study protocol number, subject number, amount, date dispensed, dispensed by, directions for use and storage, and warnings: "For Dermatologic Use Only", "Not for Ophthalmic Use", "For External Use Only", "Keep Out of Reach of Children" and "Caution: New Drug - Limited by Federal (or United States) law to investigational use only."

Study Population:

Inclusion Criteria
To be eligible for the study, subjects were to have fulfilled all of the following criteria:
1. Subjects with a definite clinical diagnosis of AK, i.e., five or more clinically typical visible, discrete, non-hyperkeratotic, non-hypertrophic lesions contained in one 25 cm^2 treatment area in one major body area as defined in this study: forehead, central face, scalp, back of hands, and forearms;
2. Subjects must be male or a non-pregnant, non-lactating female and at least 18 years of age;

[26] Final Study Report TOL-AK-2008-02 (pg. 22 of 217).
[27] Final Study Report TOL-AK-2008-02 (pg. 22 of 217).
[28] Amended Protocol TOL-AK-2008-02 (Version 1.9) pg. 18.

3. Female subjects of childbearing potential (excluding subjects who are surgically sterilized or post menopausal for at least two years), in addition to having a negative urine pregnancy test, must be willing to use an acceptable form of birth control during the study. For the purpose of this study, the following are considered acceptable methods of birth control: oral contraceptives, contraceptive patches, Depo-Provera®, NuvaRing® (vaginal contraceptive) or Implanon™ (contraceptive implant); double barrier methods (e.g., condom and spermicide); intrauterine device (IUD); or abstinence with a documented second acceptable method of birth control if the subject were to become sexually active during the study;
4. Subjects 18 years of age or older must sign the IRB-approved written informed consent form (ICF) and HIPAA form;
5. Subjects must be willing and able to understand and comply with the requirements of the study, apply the study drug as instructed, return for the required treatment period visits, comply with therapy prohibitions, and be able to complete the study;
6. Subjects must be in good health and free from any clinically significant disease, other than AK, that might interfere with the study evaluations.

Reviewer's comments:

1) *The sponsor did not place an upper limit on the number of AKs contained in the treatment area and also did not prespecify a minimum size for the AKs counted in the treatment area, which will tend to increase the variability in study outcome. Subjects with >10 AKs may be less likely to achieve complete clearance. Per this reviewer's analysis of the baseline AK data submitted to ANDA 200936 in the DAS (lesion count) dataset, no subject was enrolled with less than 5 AKs within the treatment area; however, 23 subjects (7 test, 13 reference and 3 vehicle) in the mITT population[29][of which, 18 subjects (5 test, 11 reference and 2 vehicle) were in the PP population[30]) had 11-24 AKs within the treatment area at the baseline visit. The imbalance between the test and reference groups, with twice as many reference subjects than test subjects having >10 AKs within the treatment area at baseline, is likely to decrease the efficacy demonstrated by the reference group in achieving complete clearance of AKs. Per this reviewer's analysis (see Table 5), the success rates by treatment group for the 23 subjects with 11-24 baseline AKs in the mITT population were all lower than the success rates in the corresponding treatment groups for all subjects in the mITT population. In addition, the success rates by treatment group for the 18 subjects with 11-24 baseline AKs in the PP population were all lower than the success rates in the corresponding treatment groups for all subjects in the PP population.*

(b) (6)

Table 5: Success Rates (Complete Clearance at Visit 6/Day 112/EOT) by Treatment Group

Population (n)	Diclofenac Sodium	Solaraze	Vehicle
Subjects with 11-24 baseline AKs in mITT population (n=23)	1/7=14.3%	2/13=15.4%	0/3=0%
All subjects in mITT population (n=605)	53/241=22.0%	70/244=28.7%	12/120=10.0%
Subjects with 11-24 baseline AKs in PP population (n=18)	1/5=20.0%	2/11=18.2%	0/2=0%
All subjects in PP population (n=460)	43/187=23.0%	57/180=31.7%	11/93=11.8%

2) *The sponsor also enrolled 85 subjects (33 test, 31 reference, and 21 vehicle) with treatment areas where AKs may be more difficult to eradicate, i.e., on the arms or back of the hands (see Appendix, Tables 31, 35 and 36). Per this reviewer's analysis (see Table 6), the success rates by treatment group for the 85 subjects with AK treatment locations on the arms or back of the hands in the mITT population were all lower than the success rates in the corresponding treatment groups for all subjects in the mITT population. In addition, the success rates by treatment group for the 69 subjects with AK treatment locations on the arms or back of the hands in the PP population were all lower than the success rates in the corresponding treatment groups for all subjects in the PP population. The decreased efficacy of all three treatments for AKs located on the arms or back of the hands will tend to obscure any difference in the success rates between the three treatments.*

Table 6: Success Rates (Complete Clearance at Visit 6/Day 112/EOT) by Treatment Group

Population (n)	Diclofenac Sodium	Solaraze	Vehicle
Subjects with AKs located on back of hands or arms in mITT population (n=85)	3/33= 9.1%	4/31=12.9%	0/21= 0%
All subjects in mITT population (n=605)	53/241=22.0%	70/244=28.7%	12/120=10.0%
Subjects with AKs located on back of hands or arms in PP population (n=69)	3/28=10.7%	4/24=16.7%	0/17=0%
All subjects in PP population (n=460)	43/187=23.0%	57/180=31.7%	11/93=11.8%

3) *To avoid the increased variability associated with a wide range of the number of AKs in the treatment area, the decreased efficacy associated with a large number of AKs in the treatment area and the decreased efficacy for AKs located in certain anatomic areas, the OGD recommends in the posted Draft Guidance on Diclofenac Sodium Gel/Topical, 3% to enroll "Immunocompetent male or nonpregnant female at least 18 years of age with at least five (5) and no more than ten (10) clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AK lesions, each at least 4 mm in diameter, contained within a 25-cm^2 treatment area located on the face or bald scalp." However, this Draft Guidance was not posted until 1/25/11 and the study under review was conducted from 2/5/09 to 8/25/09.*

<u>Exclusion Criteria</u>

Subjects who met any of the following criteria were to be excluded from entry:

1. Subjects who are pregnant, nursing, or planning a pregnancy within the study participation period;

2. Subjects with a diagnosis of basal cell carcinoma, squamous cell carcinoma or any other confounding skin condition in the designated treatment area within the last six months;
3. Subjects with sunburn in the designated treatment area;
4. Subjects with clinically significant systemic disease (i.e., immunological deficiencies), unstable medical disorders, life-threatening disease, or current malignancies;
5. Subjects who have a known hypersensitivity to any of the following (in any dosage form): diclofenac sodium or to any component of the study drugs, aspirin, or other NSAIDS;
6. Subjects with active gastrointestinal ulceration or bleeding or severe renal or hepatic impairment;
7. Subjects who have been treated with any topical corticosteroid medications to the forehead, central face, scalp, back of hands, or forearms within 4 weeks prior to study entry;
8. Subjects who have been treated with the following within 60 days prior to study entry: prescribed topical retinoids, 5-fluorouracil (Efudex®), masoprocol (Actinex®), Acitretin (Soriatane), Imiquimod (Aldara®), diclofenac (Solaraze®), cryodestruction, chemodestruction, surgical excision, photodynamic therapy (blue light, aminolevulinic acid [Levulen, Kerastick]), or curettage anywhere on the face, scalp, back of hands or forearms; interferon/interferon inducers, cytotoxic drugs, drugs with major organ toxicity, immunomodulators, immunosuppressive therapies, or hyaluronan-containing cosmetics such as Visible Youth™;
9. Subjects treated with oral isotretinoin during the six months prior to study entry;
10. Subjects who are currently taking or have been treated with oral/systemic corticosteroids within eight weeks prior to the study entry (intranasal or inhaled corticosteroids are acceptable if kept constant throughout the study);
11. Subjects who have been treated with systemic cancer chemotherapy medications within six months of study entry;
12. Subjects who have had the following treatments to the designated treatment area within six months prior to study entry: psoralen plus ultraviolet A (PUVA), ultraviolet B (UVB), laser abrasion, or dermabrasion;
13. Subjects who had a trichloroacetic acid/lactic acid peel and or 50% glycolic acid peel within 60 days prior to study entry;
14. Subjects involved in activities requiring excessive or prolonged sun exposure;
15. Subjects who consume excessive amounts of alcohol, abuse drugs, or have any condition that would compromise compliance with this protocol;
16. Subjects who have participated in a clinical trial with an investigational drug or investigational device within a period of four weeks prior to study entry;
17. Subjects who have been previously enrolled in this study.

<u>Subjects could be discontinued from the study for any of the following reasons:</u>

a. The subject withdrew his or her consent for any reason;
b. The subject's condition worsened to the degree or lack of improvement after at least 28 days (treatment failure) that the Investigator felt it was unsafe for the subject to continue in the study;
c. The subject's drug code was unblinded;
d. There was a clinically meaningful finding that, in the opinion of the Investigator, prevented continuation;

e. An AE occurred for which the subject desired to discontinue treatment or the Investigator determined that it was in the subject's best interest to be discontinued;
f. There was a significant protocol violation, including subjects who missed more than 10 consecutive doses of study drug;
g. A concomitant therapy which may interfere with the results of the study was reported or required;
h. The subject was lost to follow-up. The Investigator documented efforts to attempt to reach the subject twice by telephone and sent a certified follow-up letter before concluding that the subject was lost to follow-up;
i. The subject became pregnant.

Subjects were instructed to take the following precautions during the study:[31]

1. Subjects were instructed to wash hands both before and after applying study drug.
2. Subjects were cautioned to never apply study drug to the eyes, nose, or mouth, or to skin wounds or infections.
3. Subjects were instructed that local skin reactions are common and should be expected with active treatment.
4. Subjects were instructed to avoid sun exposure and the use of sunlamps.
5. Subjects were instructed to not apply any other treatments (other creams, lotions, gels, ointments, etc.) or moisturizers, cosmetics containing hyaluron, over-the-counter retinol products or products containing alpha- or beta-hydroxy acids or aluminum acetate within the designated treatment area without their doctor's permission.
6. Sunscreen use in the designated treatment area was acceptable one hour after study drug application.
7. Use of hair care products (e.g., shampoo, conditioner, hair spray, gel) and shaving/shaving products in the designated treatment area was acceptable one hour after study drug application.

The following medications and procedures were prohibited during the study:

In addition to medications and procedures listed in the exclusion criteria, the following were prohibited during this study:

1. The use of any AK treatment, other than study drug, within the designated treatment area. However, surgical excision, cryodestruction and curettage are allowed on the face or scalp outside the designated treatment area.
2. Use of oral diclofenac during the study period.
3. Systemic corticosteroids (intranasal or inhaled corticosteroids are acceptable if kept constant throughout the study) or immunosuppressive agents.
4. Topical corticosteroids applied to the designated treatment area during the study period.
5. Moisturizers, cosmetics containing hyaluron, OTC retinol products and products containing alpha- or beta-hydroxy acids or aluminum acetate within the designated treatment area.

[31] Amended Protocol TOL-AK-2008-02 (Version 1.9) Section 5.4 Precautions (pg. 10) and Appendix III: Subject Instruction (pg. 39).

Procedures/Observations, and safety measures:

Table 7: Study TOL-AK-2008-02 Schedule of Events:

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	
Visit Day/Week	Day 1 (Baseline)	Day 14 (±3 days)	Day 28 (±3 days)	Day 56 (±5 days)	Day 84 End of Treatment (±5 days)	Day 112 Follow-up/Early Discontinuation (±5 days)	Unscheduled Visit
Screening/Consent	X						
Demographics	X						
Evaluate Inclusion/ Exclusion Criteria	X						
Medical History	X						
Record Concomitant Medication	X	X	X	X	X	X	X
Perform Abbreviated Physical Exam (including height, weight, vital signs)	X					X	
Urine Pregnancy Test (1)	X					X	
Perform Dermatological Assessment (Identify treatment area and complete anatomical diagram)	X						
Evaluate Treatment Area/Perform Lesion Count X2	X (2)	X	X	X	X	X	X
Dispense Study Drug, Review Subject Instructions, and Record Study Drug Accountability	X		X	X			
Dispense Subject Diary, Review Instructions	X		X	X			
Assess Adverse Events		X	X	X	X	X	X
Collect Subject Diary, Collect Study Drug and Document Study Drug Accountability			X	X	X	X (3)	X (3)
Review Subject Diary and Assess Compliance		X	X	X	X		X
Schedule/Confirm Next Visit	X	X	X	X	X		X
Complete electronic	X	X	X	X	X	X	X

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Unscheduled Visit
Visit Day/Week	Day 1 (Baseline)	Day 14 (±3 days)	Day 28 (±3 days)	Day 56 (±5 days)	Day 84 End of Treatment (±5 days)	Day 112 Follow-up/Early Discontinuation (±5 days)	
CRF (eCRF)							

(1) For women of child-bearing potential – – to be completed prior to enrollment and at the Follow-Up/Early Discontinuation Visit.
(2) To be done by the same trained lesion counter at Visit 1/Baseline, Visit 6/Day 112, and Early Discontinuation. However, in the rare circumstance that the Visit 1/Baseline lesion counter was not available, then the other trained lesion counter could perform the clinical assessment.
(3) Collect previously uncollected subject diary and assess compliance and/or study drug and record study drug accountability (if applicable).

The following procedures were scheduled in this study:

1. Subjects who met the entry criteria were examined to confirm the definite clinical diagnosis of 5 or more clinically typical visible, discrete, non-hyperkeratotic, non-hypertrophic AK lesions located within one 25-cm^2 treatment area (e.g., 5 cm x 5 cm or 3 cm x 8.3 cm or 2 cm x 12.5 cm) in one major body area (forehead, central face, scalp, back of hands, or forearms).
2. The location of each AK lesion and the designated treatment area was recorded on the anatomical diagram in the subject's source document. Plastic transparencies were provided to map the designated treatment area and to serve as a location guide at subsequent visits. A duplicate transparency was made for the subject to assist with locating the designated treatment area.
3. The same investigator, to the greatest extent possible, performed the dermatologic assessments for any given subject (i.e., at Visits 1 and 6, identified, counted, and located the target/baseline AK lesions). Complete (100%) clearance was defined as subjects who had no (zero) clinically visible AK lesions (including baseline lesions as well as new or subclinical AK lesions which appeared during treatment) in the designated treatment area at visit 6/day 112.
4. Subjects were instructed to apply the study medication only to the designated treatment area twice daily for 84 consecutive days (12 weeks).
5. The local skin reactions (see Table 8) were evaluated for intensity at each visit using the following four-point scale (0-3; see Table 9):

Table 8: Assessment of Local Skin Reactions

Sign	Description
Burning	Burning
Epidermal desquamation	Dryness/Flaking/Scaling
Edema	Swelling
Erosion/Ulceration	Absence of epidermis/dermis
Erythema	Redness
Pruritus	Itching
Pain	Pain

Sign	Description
Scabbing/Crusting	Crusted, dried pus, lymph or blood
Vesicles	Fluid containing structures
Weeping/Exudate	Fluids discharged in tissue or cavities

Table 9: Severity Scores for Local Skin Reactions

Score	Assessment	Description
0	None	Absent
1	Mild	Slight, barely perceptible
2	Moderate	Distinct presence
3	Severe	Marked, intense

Reviewer's comment: *The sponsor evaluated 10 different local skin reactions at the treatment site. In the posted Draft Guidance on Diclofenac Sodium Gel/Topical, 3%, the OGD recommends evaluating seven different local skin reactions, i.e., erythema, dryness, burning/stinging, erosion, edema, pain and itching. This minor difference is not considered to be an issue.*

6. The following visit window conventions were scheduled by the sponsor for the clinical evaluations and local skin reactions (see Table 10):

Table 10: Visit Window Conventions

Visit	Target day	Window
2	14	± 3 days
3	28	± 3 days
4	56	± 5 days
5	84	± 5 days
6	112	± 5 days

Reviewer's comment: *The sponsor permitted a slightly wider visit window (i.e., ± 5 days) for the primary endpoint evaluation at visit 6/day 112 than recommended by the OGD (i.e. ± 4 days) in the Draft Guidance on Diclofenac Sodium Gel/Topical, 3%. This guidance states:*

> *The PP population includes all randomized subjects who met all inclusion/exclusion criteria, applied a prespecified proportion of the scheduled applications (e.g., 75% to 125%) of the assigned product for the specified duration of the study, did not miss more than 10 consecutive scheduled applications, and completed the primary endpoint evaluation within the designated visit window (+/- 4 days) with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries, and the protocol violations that would affect the treatment evaluation.*

When Day 112 ± 4 days (i.e., Days 108 through 116) is used for Visit 6 to determine the Per Protocol (PP) population for the primary efficacy evaluation, the following additional 40 subjects would be deleted from the PP population:

(b) (6)

1)

2)

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22) (b) (6)

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34)

35)

36)

37)

38)

39)

It is the opinion of this reviewer that the deletion of an additional 40 subjects to comply with OGD recommendations that were not posted until after the study was completed is not reasonable. Thus, this reviewer accepts the proposal of the sponsor to include subjects with Visit 6 on Day 112 ± 5 days in the PP population.

7. All used and unused tubes of study drug will be collected at Visit 3/Day 28, Visit 4/Day 56, and Visit 5/Day 84 (End of Treatment).

Reviewer's comment: *The sponsor prematurely discontinued subjects from the study based upon non-compliance with treatment (based upon their definition of less than 80% or more than 120% of scheduled applications); however, the total number of doses applied per subject is not provided in the DC (Diary Compliance) or DA (Drug Accountability) datasets. The DC dataset and the Appendix Listing 1.6.2.5.1 only provides the number of doses applied by each subject per visit (and does not provide the total number during the study). The DA dataset and the Appendix Listing 16.2.5.1 only provides the "number of tubes dispensed" to each subject, the "number of tubes returned" by each subject, and the "date of last medication". Thus, the FDA statisticians have been asked to add the number of applications per visit per subject in the DC dataset and thus, determine the total number of study medication applications by subject. Then, subjects with less than 75% (i.e., 126 applications) or more than 125% (i.e., 210 applications) of the scheduled applications of study medication are to be excluded from the FDA PP population. Per the calculations of this reviewer, 168 applications of study medication were scheduled (i.e. twice daily dosing for 84 days) and 75% to 125% of the scheduled 168 applications is 126 to 210 applications.*

Treatment Compliance:
Subjects who missed more than 10 consecutive applications of study drug were considered non-compliant by the sponsor and were discontinued from the study.[32] It should be noted that the Statistical Analysis Plan for TOL-AK-2008-02 (pg. 6) also included "applied at least 80% and not more than 120% of doses" in their definition of treatment compliance.

Endpoints:
The primary endpoint of this study was the proportion of subjects achieving success [defined as achieving complete (100%) clearance of AK lesions in the designated treatment area(s) at Visit 6/day 112]. Complete clearance was defined as subjects who have no (zero) clinically visible AK lesions in the designated treatment area(s) at Visit 6/Day 112 (28 days post-last application visit). Complete (100%) clearance requires that all baseline lesions as well as new or subclinical AK lesions which appeared in the treatment area during therapy are no longer present. The primary endpoint was evaluated at the visit 6/day 112 (week 16; 28 days after last application) in the PP and mITT populations.

The test of superiority was based on the difference between each active treatment's success (i.e., complete clearance of AK in the treatment area) rate compared with that of the vehicle at visit 6/day 112.

Per the protocol, the proportion of subjects with partial clearance of AK lesions in the treatment area was a secondary endpoint analyzed in both the mITT and PP populations. Partial clearance was defined as having a 75% or greater reduction of AK lesions in the treatment area from Visit 1/Baseline to Visit 6/day 112.[33]

[32] Amended Protocol TOL-AK-2008-02 (Version 1.9) pg. 20.
[33] Amended Protocol TOL-AK-2008-02 (Version 1.9) pg. 24.

Reviewer's comments:

1) *The OGD recommends that the primary endpoint of the study is the proportion of subjects in the per protocol (PP) population with treatment success (100% clearance of all AK lesions within the treatment area) at study day 90 (30 days after completion of 60 days of treatment). All actinic keratoses (i.e., baseline actinic keratoses and any new actinic keratoses) within the treatment area are to be treated and included in the efficacy lesion count for each visit.*
2) *The sponsor's prespecified secondary endpoint is considered supportive information. It should be noted that the sponsor performed two additional secondary efficacy analyses that were not prespecified in the protocol, e.g., 1) complete clearance assessed at Visit 4/Day 56, and 2) complete clearance assessed at Visit 5/Day 84.*

Statistical analysis plan

Primary Endpoint: The primary endpoint of this study was complete clearance of AK lesions in the treatment area.

Sample Size: Per the Final Study Report (pg. 36 of 117), sample size was based on an assumed equivalent success rate (34%) for the Test Product and for the Reference Product and no greater than 18% for the Gel Vehicle. It was also assumed that nearly all of the subjects enrolled would qualify for the mITT population analyses and approximately 70% of the mITT group was expected to be qualified for the PP population analyses. Under these assumptions, 284 PP subjects (142 in each active treatment group) were anticipated to provide at least a 0.90 probability of showing therapeutic equivalence for the Test Product and Reference Product (using a 90% CI criterion). It was also anticipated that there would be an 0.80 probability of showing that each active treatment is statistically superior ($p<0.05$) to the vehicle control (204 mITT active treatment subjects compared to 102 mITT vehicle control subjects using independent, continuity-corrected, Z-tests). Thus, the total target number was 510 subjects (204 + 204 + 102). This number was later increased when it was determined that the active comparator had been provided in multiple batches. This was considered to have the potential to increase variability. Further, enrollment had proceeded so rapidly, that it was not possible to determine at the point of enrollment (based on information concerning withdrawal, protocol violations, etc.) if sufficient subjects had been enrolled for the evaluation of bioequivalence. Therefore the target number was increased to 590 subjects.

Analysis: For the bioequivalence analysis, the 90% confidence interval was constructed for the difference in the proportion of subjects with complete clearance of AK lesions between the test product and reference product at Visit 6/day 112 (week 16; 4 weeks post-last application). The confidence interval was calculated using Wald's method with Yates' continuity correction based on the data pooled from all clinical sites. Bioequivalence was to be established if this 90% confidence interval was contained within the interval of (–0.20 to +0.20). The analysis in the PP population was considered primary and that in the mITT population as supportive information.

According to the sponsor, the mITT population was the primary population for comparison of the difference in proportion of subjects with complete clearance of AK between the active treatment groups and the vehicle group.

Adverse events (AEs) were coded by the sponsor using the MedDRA dictionary. AEs were summarized by presenting the number and percentage of subjects who experienced any AE, death, SAE, or who withdrew from treatment by treatment group. Frequency and percent of subjects reporting AEs were tabulated by treatment group. Similar tables were summarized by severity and relationship to study drug. In summaries of severity and relationship, subjects who reported more than one event that mapped to the same preferred term were counted only once under the strongest severity and relationship, accordingly. Local skin reactions were summarized by treatment group, visit, frequency, and severity. The safety analyses were only conducted on the ITT population.

Study Conduct

Discussion of ITT and PP populations:
Three subject populations were defined by the sponsor per the protocol (pg. 22) as follows:

Intent-To-Treat (ITT)
1) enrolled into the study, AND
2) applied at least one dose of study treatment.

Modified Intent-To-Treat (mITT)
1) enrolled into the study,
2) met inclusion/exclusion criteria;
3) applied at least one dose of study treatment, AND
4) had at least one post-baseline efficacy evaluation.

Per-Protocol (PP)
1) enrolled into the study,
2) met inclusion/exclusion criteria,
3) maintained compliance with study drug applications (applied at least 80% (i.e., at least 134 doses) and not more than 120% (i.e., not more than 202 doses) of doses and did not miss 10 or more consecutive applications of study drug),
4) took no concomitant medications prohibited by the protocol,
5) had no other significant protocol violations, AND
6) returned for visit 6/day 112 within the visit window and had data on the primary efficacy variables for all clinical evaluations, OR
7) were discontinued early due to worsening disease or lack of improvement after at least 28 days with at least 80% treatment compliance rate treatment.

Reviewer's comments:
1) *Per the Final Study Report TOL-AK-2008-02 (pg. 32 of 217), the sponsor changed the definition of the mITT population from that in both the Original Protocol and Amendment #1 dated January 15, 2009 (see above) by replacing the requirement that subjects meet inclusion/exclusion criteria with the requirement that subjects had a baseline lesion count. The sponsor also changed the definition of the PP population from that in both the Original Protocol and Amendment #1 (see above) by adding that subjects had a baseline lesion count AND replacing "had data on the primary efficacy variables for all clinical evaluations" with*

"had a lesion count at Visit 6/day 112 AND changed the phrase "due to worsening disease or lack of improvement" to "insufficient therapeutic response". The sponsor did not include these changes in Section 9.8, entitled "Changes in the Conduct of the Study or Planned Analyses", of the Final Study Report TOL-AK-2008-02; however, these changes were made in the definitions of the mITT and PP populations listed in the Statistical Analysis Plan for TOL-AK-20089-02 dated January 29, 2009 on pg. 5-6.

2) *Per the Final Study Report (pg. 32 of 217), a last observation carried forward (LOCF) approach was used for missing efficacy data on the mITT population and missing efficacy data was not imputed in the PP population with the exception of subjects who discontinued early due to insufficient therapeutic response after completing at least 28 days of study drug use, had a compliance rate of at least 80%, and satisfied all other per protocol criteria. For these subjects, the missing efficacy data was imputed using an LOCF approach.*

3) *The OGD recommends in the posted Draft Guidance on Diclofenac Gel/Topical, 3% that the mITT population includes all randomized subjects who met all inclusion/exclusion criteria, received study treatment, and returned for at least one post-baseline visit and these criteria will be used to determine the FDA mITT population. The FDA mITT population will be used to compare both test and reference products to vehicle (placebo).*

4) *The OGD recommends in the posted Draft Guidance on Diclofenac Gel/Topical, 3% that the PP population include all randomized subjects who met all inclusion/exclusion criteria, applied a prespecified proportion of the scheduled applications (e.g., 75% to 125%) of the assigned product for the specified duration of the study, did not miss more than 10 consecutive scheduled applications, and completed the primary endpoint evaluation within the designated visit window (+/- **4** days) with no protocol violations that would affect the treatment evaluation and these criteria will be used to determine the FDA PP population. The FDA PP population will be used to compare the test and reference products, with the exception of increasing the designated visit window to (+/- **5** days), as proposed by the sponsor.*

5) *The OGD also recommends in the posted Draft Guidance on Diclofenac Gel/Topical, 3% that "Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of AK during the study should be discontinued, included in the PP population analysis as treatment failures, and provided with effective treatment. Subjects who are discontinued early from the study due to lack of treatment effect after completing at least four weeks of treatment should be included in the mITT and PP population as treatment failures. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF)." Thus, these additional criteria will be used to in the FDA efficacy analyses.*

Retention of Reserve Samples:
The sponsor stated that each investigational site where study drug was dispensed to at least one subject was required to randomly select and keep one block (five consecutively numbered subject boxes of study medication) of study drug at their facility as "retain samples", in accordance with 21 CFR 320.63 and 320.38.

Demographics and Baseline AK lesion count:
A total of 609 subjects, were enrolled into the study and randomized. Of these, 523 completed the study and 86 discontinued. The racial composition of the study population was overwhelmingly White (99.7%). Two subjects in the ITT population did not list their race as White. Baseline demographics, age, and race in the ITT and PP populations were similar in all treatment groups (see Tables 11 and 12). The mean age in the ITT population was 66.0 years (36-95), 65.3 years (32-92), and 63.8 years (21-84) in the test, reference, and vehicle groups, respectively. The mean AK lesion count at baseline for the ITT population was not statistically different among the treatment groups (p-value 0.9623).

Table 11: Demographic Characteristics for Intent to Treat Subjects (per Sponsor)

Characteristic	Category	Diclofenac Sodium Gel, 3% (N=187)	Solaraze™ Gel, 0.3% (N=180)	Vehicle (N=93)	Total (N=460)
Gender (n,%)	Female	50 (20.7%)	45 (18.3%)	23 (19.0%)	118 (19.4%)
	Male	191 (79.3%)	201 (81.7%)	98 (81.0%)	490 (80.6%)
Ethnicity (n,%)	Hispanic or Latino	12 (5.0%)	8 (3.3%)	5 (4.1%)	25 (4.1%)
	Not Hispanic or Latino	229 (95.0%)	238 (96.7%)	116 (95.9%)	583 (95.9%)
Race (n,%)	White	239 (99.2%)	246 (96.7%)	121 (100.0%)	606 (99.7%)
	Black or African American	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	American Indian or Alaska Native	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Native Hawaiian or Other Pacific Islander	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Age (years)	Mean ± SD	66.0 ± 10.3	65.3 ± 10.8	63.8 ± 10.6	65.6 ± 10.6
	Median	66.0	65.0	62.0	65.0
	Min, Max	36.0, 95.0	32.0, 92.0	21.0, 84.0	21.0, 95.0
Actinic Keratosis Lesion Count	Mean ± SD	6.5 ± 1.6	6.6 ± 2.1	6.6 ± 2.3	6.6 ± 2.0
	Median	6.0	6.0	6.0	6.0
	Min, Max	5.0, 14.0	5.0, 18.0	5.0, 24.0	5.0, 24.0

Source: Final Study Report TOL-AK-2008-02, Section 14, Table 14.1.3 (pg. 80-81 of 217)

Table 12: Demographic Characteristics for Per Protocol Subjects (per Sponsor)

Characteristic	Category	Diclofenac Sodium Gel, 3% (N=187)	Solaraze™ Gel, 0.3% (N=180)	Vehicle (N=93)	Total (N=460)
Gender (n,%)	Female	40 (21.4%)	34 (18.9%)	17 (18.3%)	91 (19.8%)
	Male	147 (78.6%)	146 (81.1%)	76 (81.7%)	369 (80.2%)
Ethnicity (n,%)	Hispanic or Latino	10 (5.3%)	7 (3.9%)	5 (5.4%)	22 (4.8%)
	Not Hispanic or Latino	177 (94.7%)	173 (96.1%)	88 (94.6%)	438 (95.2%)
Race (n,%)	White	185 (98.9%)	180 (100.0%)	93 (100.0%)	458 (99.6%)
	Black or African American	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	American Indian or Alaska Native	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Native Hawaiian or Other Pacific Islander	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Age (years)	Mean ± SD	66.2 ± 10.3	65.7 ± 11.1	64.5 ± 9.5	65.6 ± 10.5
	Median	66.0	65.5	62.0	65.0
	Min, Max	43.0, 89.0	32.0, 92.0	49.0, 84.0	32.0, 92.0
Actinic Keratosis Lesion Count	Mean ± SD	6.6 ± 1.6	6.6 ± 2.1	6.6 ± 2.3	6.6 ± 2.0
	Median	6.0	6.0	6.0	6.0
	Min, Max	5.0, 14.0	5.0, 18.0	5.0, 24.0	5.0, 24.0

Source: ANDA 200936 Module 2.7_Summary_Bioequivalence_Tables, Table 7.1 and ANDA 200936 Final Study Report TOL-AK-2008-02, Table 11-3, pg. 42.

Local Skin Reaction at baseline

According to the sponsor, local skin assessments observed at baseline for the ITT population revealed that the majority of subjects in each treatment group either did not have the specified skin reaction or had reactions that were categorized as mild.

Table 13: Local Skin Reactions at Baseline (per Sponsor)

Parameter	Category	Test n=241	Reference n=246	Vehicle n=121
Burning	None	235 (97.5%)	240 (97.6%)	117 (96.7%)
	Mild	5 (2.1%)	4 (1.6%)	4 (3.3%)
	Moderate	1 (0.4%)	2 (0.8%)	0
	Severe	0	0	0
Erythema (Redness)	None	125 (51.9%)	131 (53.3%)	68 (56.2%)
	Mild	97 (40.2%)	94 (38.2%)	46 (38.0%)
	Moderate	19 (7.9%)	21 (8.5%)	7 (5.8%)

Parameter	Category	Test n=241	Reference n=246	Vehicle n=121
	Severe	0	0	0
Epidermal Desquamation (Dryness/Flaking/Scaling)	None	143 (59.3%)	137 (55.7%)	72 (59.5%)
	Mild	87 (36.1%)	93 (37.8%)	40 (33.1%)
	Moderate	11 (4.6%)	16 (6.5%)	9 (7.4%)
	Severe	0	0	0
Pruritus (Itching)	None	207 (85.9%)	211 (85.8%)	106 (87.6%)
	Mild	28 (11.6%)	29 (11.8%)	12 (9.9%)
	Moderate	6 (2.5%)	6 (2.4%)	3 (2.5%)
	Severe	0	0	0
Pain	None	237 (98.3%)	245 (99.6%)	118 (97.5%)
	Mild	4 (1.7%)	1 (0.4%)	3 (2.5%)
	Moderate	0	0	0
	Severe	0	0	0
Edema (Swelling)	None	236 (97.9%)	241 (98.0%)	119 (98.3%)
	Mild	4 (1.7%)	5 (2.0%)	2 (1.7%)
	Moderate	1 (0.4%)	0	0
	Severe	0	0	0
Erosion/Ulceration	None	238 (98.8%)	244 (99.2%)	121 (100.0%)
	Mild	3 (1.2%)	2 (0.8%)	0
	Moderate	0	0	0
	Severe	0	0	0
Weeping/Exudate (Fluids discharge in tissue or cavities)	None	241 (100%)	246 (100%)	121 (100%)
	Mild	0	0	0
	Moderate	0	0	0
	Severe	0	0	0
Scabbing/Crusting/Crusted, dried pus, lymph or blood	None	232 (96.3%)	228 (92.7%)	117 (96.7%)
	Mild	8 (3.3%)	16 (6.5%)	3 (2.5%)
	Moderate	1 (0.4%)	2 (0.8%)	1 (0.8%)
	Severe	0	0	0
Vesicles (Fluid containing structures)	None	241 (100%)	246 (100%)	121 (100%)
	Mild	0	0	0
	Moderate	0	0	0
	Severe	0	0	0

Source: Final Study Report TOL-AK-2008-02, Tables 14.3.1.6.1 on pg. 151, 14.3.1.6.2 on pg. 153, 14.3.1.6.3 on pg. 155, 14.3.1.6.4 on pg. 157, 14.3.1.6.5 on pg. 159, 14.3.1.6.6 on pg. 161, 14.3.1.6.7 on pg. 163, 14.3.1.6.8 on pg. 165, 14.3.1.6.9 on pg. 167 and 14.3.1.6.10 on pg. 169.

Efficacy Results

Six hundred and nine (609) subjects were randomized to receive the study treatment; 242 in the test, 246 in the reference, and 121 in the vehicle group. One subject (b) (6) in the test group was excluded from the ITT (Safety) population due to not applying any study treatment. The most common reason for discontinuation from the study was due to withdrawal of consent (n=24 subjects), followed by adverse event (n=20 subjects), non-compliance with study treatment (n=20 subjects) and local skin reaction (n=15 subjects). Seven subjects, i.e., four in the test group (b) (6) two in the reference group (b) (6) and one in the vehicle group (b) (6)) took concomitant medication prohibited by the protocol, which excluded them from the PP population. Overall, more subject discontinuations occurred in the reference group compared to the test or vehicle group, i.e., reference: 16.7%, test: 13.2%, vehicle: 10.7%. The sponsor's disposition of subjects is shown in Table 14, the reason for discontinuation is listed in Table 15, and a summary of protocol deviations is provided in Table

16. Tables 17 and 18 show the summary of the sponsor's primary and secondary efficacy outcome analyses.

Per the sponsor, four subjects did not meet eligibility criteria and were excluded from the PP population[34]; however, the exact criteria not met were provided for only two subjects[35]:

1) Subject (b) (6) (test group) did not meet Exclusion criteria #10; exception was granted; subject was excluded from the PP Population.
2) Subject (b) (6) (reference group) did not meet Exclusion criteria #8; an exception was granted; subject was excluded from the PP Population.
3) Subject (b) (6) (reference group) "did not meet all entry criteria"; exception was not granted; subject was excluded from the PP Population..
4) Subject (b) (6) (reference group) "did not meet all entry criteria"; exception was not granted; subject was excluded from the PP Population.

Reviewer's comment: *This reviewer attempted to locate additional details regarding the specific violation of eligibility criteria for Subjects* (b) (6) *by searching through the submitted Case Report Forms (CRFs); however, no CRFs were submitted for the four subjects listed in Appendix Listing 16.2.3 as not meeting eligibility criteria. The sponsor submitted 29 Case Report Forms: 11 for subjects who had Serious Adverse Events (two of which also discontinued due to Adverse Event) and 20 for subjects who discontinued due to Adverse Event).*

Table 14: Disposition of Subjects; per Sponsor

Subject Disposition	Number (%) of Subjects			
	Diclofenac sodium n (%)	Solaraze® n (%)	Vehicle n (%)	Total n (%)
Number Enrolled and Randomized	242	246	121	609
Number Completed Study	210 (86.8)	205 (83.3)	108 (89.3)	523 (85.9)
Total Discontinued	32 (13.2)	41 (16.7)	13 (10.7)	86 (14.1)

Source: Final Study Report TOL-AK-2008-02 Table 10-1, pg. 38.

Table 15: Subject Discontinuation by Reason; per Sponsor

Subject Disposition	Number (%) of Subjects			
	Diclofenac sodium n (%)	Solaraze® n (%)	Vehicle n (%)	Total n (%)
Adverse event (1)	8 (3.3)	9 (3.7)	3 (2.5)	20 (3.3)
Insufficient Therapeutic Response (after at least 4 weeks of compliant treatment)	0	0	0	0
Non Compliant with Use of Study drug	7 (2.9)	10 (4.1)	3 (2.5)	20 (3.3)
Lost to Follow-Up	4 (1.7)	2 (0.8)	1 (0.8)	7 (1.1)

[34] Final Study Report TOL-AK-2008-02 Section 11.1 Data Sets Analyzed for Efficacy (pg. 39 of 217) and Appendix Listing 16.2.3 entitled "Listing of Subject Status" p. 5 of 42.
[35] Per Final Study Report TOL-AK-2008-02 Appendix Listing 16.2.2 entitled "Protocol Deviations", Appendix Listing 16.2.3 entitled "Subjects Excluded From the Efficacy Analysis" and dataset "EC" (Eligibility Criteria).

Subject Disposition	Number (%) of Subjects			
	Diclofenac sodium n (%)	Solaraze® n (%)	Vehicle n (%)	Total n (%)
Subject Decision/Withdrawal of Consent	10 (4.1)	9 (3.7)	5 (4.1)	24 (3.9)
Death	0	0	0	0
Other	3 (1.2)	11 (4.5)	1 (0.8)	15 (2.5)
Local skin reaction and withdrawal of consent	0	1 (0.4)	1 (0.8)	2 (0.3)
Local skin reaction and use of excluded medication	0	1 (0.4)	0	1 (0.2)
Local skin reaction	1 (0.4)	7 (2.8)	0	8 (1.3)
Severe skin reaction (primary), withdrew consent (secondary)	1 (0.4)	0	0	1 (0.2)
Severe skin reaction (primary), non compliance (secondary)	1 (0.4)	0	0	1 (0.2)
Severe skin reaction, protocol violation with study treatment	0	1 (0.4)	0	1 (0.2)
Severe skin reaction	0	1 (0.4)	0	1 (0.2)

Source: Final Study Report TOL-AK-2008-02, Table 10-1, pg. 38.
(1) includes intercurrent illness reported as AEs and leading to discontinuation; does not include local skin reactions included in the "Other" category.

Table 16: Protocol Deviations*; per Sponsor

Type	Number (%) of Subjects		
	Test (N=242)	Reference (N=246)	Vehicle (N=121)
Violated inclusion/exclusion criteria	1 (0.4%)	3 (1.2%)	0 (0.0%)
Took prohibited medication or other significant protocol violation	8 (3.3%)	2 (0.8%)	2 (1.7%)
Noncompliant treatment applications	2 (0.8%)	3 (1.2%)	5 (4.1%)
No lesion count data at visit 6	0 (0.0%)	3 (1.2%)	1 (0.8%)
Visit 6 out of window	13 (5.4%)	18 (7.3%)	8 (6.6%)
Non-Efficacy Related Discontinuation	31 (12.8%)	37 (15.0%)	12 (9.9%)

Source: ANDA 200936 Module 2.7_Summary_Bioequivalence_Tables, Table 13
*Protocol deviations included in the table are those that led to exclusion of subjects from per-protocol efficacy analyses.

Table 17: Primary Efficacy Analysis: Complete Clearance of AK lesions at visit 6/week 16 (4 weeks follow-up); per Sponsor

Parameter	Test	Reference	Vehicle	90% C.I. for Bioequivalence of Test to Reference	p-values	
					Test vs. Vehicle	Reference vs. Vehicle
Per-Protocol Subjects (n, %)						
	n=187	n=180	n=93			
Success	43 (23.0%)	57 (31.7%)	11 (11.8%)	(-16.8%, -0.5%)	NA	NA
Failure	144 (77.0%)	123 (68.3%)	82 (88.2%)			
Modified Intent-to-Treat Subjects (n, %)						
	n=241	n=244	n=120			
Success	53 (22.0%)	70 (28.7%)	12 (10.0%)	NA	0.0081	0.0001
Failure	188 (78.0%)	174 (71.3%)	108 (90.0%)			

Source: Final Study Report TOL-AK-2008-02, Table 14.2.1, pg. 87.

Table 18: Prespecified Secondary Efficacy Analysis; per Sponsor: At Least 75% Clearance of AK Lesions at visit 6/week 16 (4 weeks follow-up)

Parameter	Test	Reference	Vehicle	90% C.I. for Bioequivalence of Test to Reference	p-values	
					Test vs. Vehicle	Reference vs. Vehicle
Per-Protocol Subjects (n, %)						
	n=187	n=180	n=93			
Success	77 (41.2%)	89 (49.4%)	22 (23.7%)	(-17.3%, 0.8%)	NA	NA
Failure	110 (58.8%)	91 (50.6%)	71 (76.3%)			
Modified Intent-to-Treat Subjects (n, %)						
	n=241	n=244	n=120			
Success	98 (40.7%)	107 (43.9%)	24 (20.0%)	NA	0.0001	<0.0001
Failure	143 (59.3%)	137 (56.1%)	96 (80.0%)			

Source: Final Study Report TOL-AK-2008-02, Table 14.2.2, pg. 88.

Reviewer's comment: *The sponsor performed an assessment of treatment compliance by diary entries per visit. In their Listing 16.2.5.2 entitled "Listing of Diary Compliance", the sponsor provided the number of applications of study medication recorded in the subject's diary since their previous visit for each subject; however, they failed to provide the total number of applications of study medication during the study per subject, which would have permitted an assessment of those subjects with less than 80% (i.e., 134 application) or more than 120% (i.e., 202 applications) per the protocol and of those subjects with less than 75% (i.e., less than 126 applications) or more than 125% (i.e., 210 applications) per the FDA recommendations in the posted Draft Guidance on Diclofenac Sodium Gel/Topical, 3%.*

D. Bioequivalence Conclusion

The DCR concurred with the recommendations of the DSI and included all subjects from Dr. Miller's site in the listing of excluded subjects sent to the statisticians, i.e., the listing of subjects to be excluded from the FDA per-protocol and intent-to-treat subject populations when

performing the FDA bioequivalence evaluation of Study TOL-AK-2008-02. On June 6, 2013, the statistical review of the BE study with clinical endpoint, i.e., Study TOL-AK-2008-02, was finalized with the conclusion that the equivalence test passed for the success rate in the FDA's per-protocol (FPP) population and the two active treatment were statistically significantly better than the vehicle for the success rate in the FDA's intent-to-treat (FITT) population.[36]

The Division of Clinical Review (DCR) concurs with the FDA statisticians that when using data from the FDA-determined study populations for Study TOL-AK-2008-02, data submitted to ANDA 200936 confirms the sponsor's results. Thus, the DCR concludes that this study is adequate to support approval of the application. However, the formulation differences between the test and reference products are substantial and may negatively impact the performance of the test product. This deficiency is being addressed by the Division of Bioequivalence II.[37, 38]

V. Comparative Review of Safety

A. Brief Statement of Conclusions

The sponsor concluded that the safety profile of the test product was not statistically or clinically different than that of the reference product in the treatment of actinic keratoses.[39]

B. Description of Adverse Events

Safety was evaluated through a review of adverse events (AEs). Adverse events were recorded at each visit after Visit 1/Baseline. The greatest intensity or severity of each adverse event was reported as mild (i.e., AE that is easily tolerated), moderate (i.e., AE sufficiently discomforting to interfere with daily activity), and severe (i.e., AE that prevents normal daily activities). Tolerance was evaluated by assessing treated areas for local skin reactions. Local skin reactions were recorded at each visit after Visit 1/Baseline during the assessment of treated areas and were not recorded as AEs, unless, in the opinion of the Investigator, the event qualified as an AE.

A total of 158 subjects [69 (28.6%) in the test, 58 (23.6%) in the reference, and 31 (25.6%) in the vehicle group) experienced one or more treatment-emergent adverse events. Twenty (3.3%) subjects (8 test, 9 reference, 3 vehicle) discontinued the study due to "withdrawal due to adverse event". An additional 15 subjects (11 test, 3 reference, 1 vehicle) withdrew due to a local skin reaction, which the sponsor coded as "Other". This suggests that the test product may cause more skin reactions than the RLD.

Seventeen (17) subjects had at least one adverse event that was considered to be severe (7 test, 7 reference, 3 vehicle). Two of these severe adverse events were "hypersensitivity" (one test, one reference). Of note, the test group had 4 subjects who experienced a severe AE in the MedDRA system organ class "Skin and subcutaneous tissue disorders" (dermatitis contact=2; rash=1; skin

[36] ANDA 200936 Office of Biostatistics Statistical Review and Evaluation by Huaxixiang Li, Ph.D. finalized in DARRTS on 6/6/13.
[37] ANDA 200936 OGD Bioequivalence Deficiencies Letter finalized in DARRTS on 4/19/12.
[38] ANDA 200936 Division of Bioequivalence Review Diclofenac Sodium Topical Gel, 3% by Josephine Aimiuwu, Ph.D. finalized in DARRTS on 4/3/13.
[39] ANDA 200936 Section 5.3.1.2 (pg. 1 of 1).

irritation=1) compared to only 1 subject in the reference group (skin erosion=1) and no subject in the vehicle group.

Skin-related adverse events listed in the "Skin and subcutaneous tissue disorders" MedDRA system organ class, regardless of relationship to the study medication, occurred in 22 subjects (12 test, 8 reference, 2 vehicle). Skin-related adverse events probably or definitely related to study medication occurred in 17 subjects (9 test, 6 reference, 2 vehicle). Additionally, skin-related adverse events listed in the "General disorders and administration site conditions" MedDRA system organ class occurred in 3 subjects (2 test, 1 reference) and all were considered to be related: the AE "application site erythema" was reported by 1 test subject, the AE "application site irritation" was reported by 1 reference subject and the AE "application site rash" was reported by 1 test subject. Severe "Skin and subcutaneous tissue disorders" AEs occurred in five subjects (4 test, 1 reference): severe contact dermatitis was reported in 2 test subjects; severe rash was reported in 1 test subject; severe skin erosion was reported in 1 reference subject; severe skin irritation was reported in 1 test subject.[40] According to the sponsor's analysis, there were no notable differences between the treatment groups in the percentage of subjects with skin reactions reported as AEs related to study drug, with the exception of hypersensitivity reactions related to study drug being more common in the reference group (n=5).[41]

No deaths occurred in the study. Thirteen serious adverse events were experienced by 13 subjects (5 test, 5 reference, 3 vehicle) and none were considered by the sponsor to be related to the study drug. One of these SAEs (prostate cancer in test group) occurred in the 30-day follow-up period and was not reported until after data base lock.

The sponsor's summary of adverse events is listed in Tables 19 and 20 below. The list of serious adverse events by subject is shown in Table 21.

Reviewer's comment: *The frequency of any treatment-emergent adverse event (both "regardless of relationship to study medication" and "related to the study treatment") and the frequency of treatment-emergent skin-related AEs (both "regardless of relationship to study medication" and "related to the study treatment") were all numerically higher in the test group. Both the withdrawals due to a local skin reactions and the reported skin-related adverse events suggest that the test product may cause more skin reactions than the RLD.*

Table 19: Treatment-Emergent Adverse Events by Relationship (per Sponsor; ITT Population)

Type	Parameter	Test n=241	Reference n=246	Vehicle n=121
Overall	Subjects with any adverse event regardless of relationship to study medication	69 (28.6%)	58 (23.6%)	31 (25.6%)

[40] Final Study Report TOL-AK-2008-02 (pg. 60 of 217).
[41] Final Study Report TOL-AK-2008-02 (pg. 70 of 217).

Type	Parameter	Test n=241	Reference n=246	Vehicle n=121
	Subjects with any adverse events related to study medication	20 (8.3%)	14 (5.7%)	3 (2.5%)
Skin-Related	Subjects with skin-related adverse events regardless of relationship to study medication	12 (5.0%)	8 (3.3%)	2 (1.7%)
	Subjects with skin-related adverse events related to study medication	9 (3.7%)	6 (2.4%)	2 (1.7%)

Source: ANDA 200936 Final Study Report Table 14.3.1.1 pg. 103, Table 12-2 pg. 56, and Table 12-3 pg. 58.

Table 20: Incidence of Adverse Events in TOL-AK-2008-02 (per Sponsor; ITT Population)

MedDRA System Organ Class Preferred Term	**Diclofenac Sodium Gel, 3% (N=242)**	**Solaraze™ Gel, 3% (N=246)**	**Vehicle (N=121)**
Total Number of subjects reporting one or more Adverse Event (AE)	69 (28.5%)	58 (23.6%)	31 (25.6%)
Total Number of subjects reporting an Individual AE (i.e., total of numbers in column)	101	85	52
Blood and lymphatic system disorders			
Anemia	--	--	1 (0.8%)
Lymphoid tissue hyperplasia	--	1 (0.4%)	--
Cardiac disorders			
Arteriosclerosis coronary artery	--	--	1 (0.8%)
Bradycardia	1 (0.4%)	--	--
Myocardial infarction	--	1 (0.4%)	--
Ear and labyrinth disorders			
Cerumen impaction	1 (0.4%)	--	--
Ear pain	--	1 (0.4%)	--
Vertigo	--	1 (0.4%)	1 (0.8%)
Eye disorders			
Conjunctivitis	--	1 (0.4%)	1 (0.8%)
Eye irritation	1 (0.4%)	--	--
Eyelid exfoliation	1 (0.4%)	--	--
Ocular hyperemia	1 (0.4%)	--	--
Gastrointestinal disorders			
Abdominal pain upper	--	1 (0.4%)	--
Colitis ulcerative	--	1 (0.4%)	--
Diarrhea	1 (0.4%)	2 (0.8%)	1 (0.8%)
Diverticulum	--	--	1 (0.8%)
Dyspepsia	1 (0.4%)	1 (0.4%)	--
Gastritis	1 (0.4%)	1 (0.4%)	--
Gastroesophageal reflux disease	--	1 (0.4%)	--
Gingival pain	1 (0.4%)	--	--

MedDRA System Organ Class Preferred Term	**Diclofenac Sodium Gel, 3% (N=242)**	**Solaraze™ Gel, 3% (N=246)**	**Vehicle (N=121)**
Nausea	1 (0.4%)	1 (0.4%)	2 (1.7%)
Oral pain	1 (0.4%)	--	--
Toothache	1 (0.4%)	2 (0.8%)	1 (0.8%)
Vomiting	--	2 (0.8%)	1 (0.8%)
General disorders and administration site conditions			
Application site erythema	1 (0.4%)	--	--
Application site irritation	--	1 (0.4%)	--
Application site rash	1 (0.4%)	--	--
Application site scar	1 (0.4%)	--	--
Chest pain	1 (0.4%)	--	1 (0.8%)
Edema peripheral	1 (0.4%)	1 (0.4%)	1 (0.8%)
Immune system disorders			
Hypersensitivity	1 (0.4%)	5 (2.0%)	--
Infections and infestations			
Adenoviral upper respiratory infection	--	--	1 (0.8%)
Bronchitis	1 (0.4%)	2 (0.8%)	--
Cellulitis	1 (0.4%)	--	--
Gastroenteritis viral	--	--	1 (0.8%)
Herpes zoster	1 (0.4%)	1 (0.4%)	1 (0.8%)
Influenza	1 (0.4%)	--	--
Localized infection	--	1 (0.4%)	--
Lower respiratory tract infection	--	1 (0.4%)	--
Lyme disease	--	--	1 (0.8%)
Nasopharyngitis	4 (1.7%)	2 (0.8%)	2 (1.7%)
Otitis media	1 (0.4%)	--	--
Pneumonia	1 (0.4%)	1 (0.4%)	--
Respiratory tract infection	--	1 (0.4%)	--
Rhinitis	1 (0.4%)	--	1 (0.8%)
Sinusitis	2 (0.8%)	2 (0.8%)	--
Skin infection	--	2 (0.8%)	--
Tooth abscess	4 (1.7%)	--	--
Upper respiratory tract infection	3 (1.2%)	3 (1.2%)	5 (4.1%)
Urinary tract infection	2 (0.8%)	--	1 (0.8%)
Injury, poisoning and procedural complications			
Arthropod bite	1 (0.4%)	--	1 (0.8%)
Conjunctival abrasion	--	--	1 (0.8%)
Contusion	--	--	1 (0.8%)
Excoriation	3 (1.2%)	--	--
Foot fracture	--	1 (0.4%)	--
Meniscus lesion	1 (0.4%)	--	--
Muscle strain	1 (0.4%)	--	--

MedDRA System Organ Class Preferred Term	Diclofenac Sodium Gel, 3% (N=242)	Solaraze™ Gel, 3% (N=246)	Vehicle (N=121)
Postoperative constipation	1 (0.4%)	--	--
Procedural nausea	1 (0.4%)	--	--
Procedural pain	1 (0.4%)	--	--
Sunburn	--	1 (0.4%)	--
Tendon rupture	--	1 (0.4%)	--
Investigations			
Biopsy skin	--	--	1 (0.8%)
Blood cholesterol increased	--	1 (0.4%)	1 (0.8%)
Blood pressure increased	1 (0.4%)	--	--
Cardiac murmur	--	1 (0.4%)	--
Heart rate irregular	--	1 (0.4%)	--
Prostatic specific antigen increased	--	1 (0.4%)	--
Metabolism and nutrition disorders			
Decreased appetite	--	1 (0.4%)	--
Gout	--	1 (0.4%)	1 (0.8%)
Hyperlipidemia	--	1 (0.4%)	--
Musculoskeletal and connective tissue disorders			
Arthralgia	--	2 (0.8%)	--
Back pain	4 (1.7%)	1 (0.4%)	1 (0.8%)
Bursitis	1 (0.4%)	--	1 (0.8%)
Intervertebral disc protrusion	--	1 (0.4%)	--
Joint swelling	1 (0.4%)	--	--
Neck pain	1 (0.4%)	--	--
Osteoarthritis	--	1 (0.4%)	2 (1.7%)
Osteoporosis	--	1 (0.4%)	--
Pain in extremity	2 (0.8%)	2 (0.8%)	--
Neoplasms benign malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma	3 (1.2%)	--	1 (0.8%)
Benign neoplasm of spinal cord	--	1 (0.4%)	--
Malignant melanoma	--	--	1 (0.8%)
Neoplasm	2 (0.8%)	--	--
Prostate cancer	1 (0.4%)	--	--
Seborrheic keratoses	--	3 (1.2%)	--
Skin papilloma	1 (0.4%)	--	--
Squamous cell carcinoma	1 (0.4%)	--	--
Squamous cell carcinoma of skin	1 (0.4%)	--	1 (0.8%)
Nervous system disorders			
Amnesia	--	1 (0.4%)	--
Burning sensation	1 (0.4%)	--	--
Dizziness	1 (0.4%)	--	--
Dysgeusia	--	--	1 (0.8%)

MedDRA System Organ Class Preferred Term	Diclofenac Sodium Gel, 3% (N=242)	Solaraze™ Gel, 3% (N=246)	Vehicle (N=121)
Headache	7 (2.9%)	2 (0.8%)	3 (2.5%)
Hyperesthesia	1 (0.4%)	--	--
Syncope	--	--	1 (0.8%)
Psychiatric disorders			
Abnormal dreams	--	1 (0.4%)	--
Anxiety	--	--	1 (0.8%)
Depression	--	1 (0.4%)	--
Insomnia	1 (0.4%)	--	--
Renal and urinary disorders			
Nephrolithiasis	1 (0.4%)	--	--
Reproductive system and breast disorders			
Prostatitis	1 (0.4%)	--	--
Respiratory, thoracic and mediastinal disorders			
Asthma	--	1 (0.4%)	--
Cough	1 (0.4%)	1 (0.4%)	1 (0.8%)
Nasal congestion	1 (0.4%)	--	--
Pharyngolaryngeal pain	1 (0.4%)	--	1 (0.8%)
Post procedural pulmonary embolism	--	--	1 (0.8%)
Pulmonary embolism	--	--	1 (0.8%)
Rhinitis allergic	1 (0.4%)	--	--
Sinus congestion	1 (0.4%)	1 (0.4%)	--
Sneezing	--	--	1 (0.8%)
Skin and subcutaneous tissue disorders			
Actinic keratoses	--	1 (0.4%)	--
Dermatitis contact	4 (1.7%)	1 (0.4%)	--
Erythema	1 (0.4%)	--	--
Periorbital edema	--	1 (0.4%)	--
Rash	1 (0.4%)	2 (0.8%)	1 (0.8%)
Seborrheic dermatitis	1 (0.4%)	--	--
Skin discoloration	1 (0.4%)	--	--
Skin erosion	--	1 (0.4%)	--
Skin hypopigmentation	1 (0.4%)	1 (0.4%)	--
Skin irritation	1 (0.4%)	1 (0.4%)	--
Skin lesion	1 (0.4%)	1 (0.4%)	--
Skin plaque	1 (0.4%)	--	--
Skin reaction	1 (0.4%)	--	--
Skin swelling	--	1 (0.4%)	--
Swelling face	--	--	1 (0.8%)
Surgical and medical procedures			
Hip arthroplasty	1 (0.4%)	--	--
Knee arthroplasty	--	--	1 (0.8%)

MedDRA System Organ Class Preferred Term	Diclofenac Sodium Gel, 3% (N=242)	Solaraze™ Gel, 3% (N=246)	Vehicle (N=121)
Micrographic skin surgery	1 (0.4%)	--	--
Vascular disorders			
Aortic aneurysm	--	1 (0.4%)	--
Cerebrovascular accident	--	1 (0.4%)	--
Hypertension	--	2 (0.8%)	--
Intermittent claudication	--	1 (0.4%)	--

Source: ANDA 20936 Summary Table 8; Counts reflect number of subjects reporting one or more adverse events. Subjects reporting more than one adverse event in a category are only counted once.

Table 21: Serious Adverse Events (per Sponsor; ITT Population) n=13

	Number (%) of Subjects		
	Test n=241	Reference n=246	Vehicle n=121
SAE	SAEs n=5 (2.0%)	SAEs n=5 (2.0%)	SAEs n=3 (2.5%)
Cerebrovascular accident		1 (Subject (b) (6)	
Basal cell carcinoma	1 (Subject (b) (6)		
Lymphoid tissue hyperplasia		1 (Subject	
Myocardial infarction		1 (Subject	
Prostate cancer	2 (Subjects (b) (6) (b) (6))		
Osteoarthritis			1 (Subject (b) (6)
Hip arthroplasty	1 (Subject (b) (6))		
Pneumonia	1 (Subject)	1 (Subject (b) (6))	
Malignant melanoma			1 (Subject
Foot fracture		1 (Subject)	
Pulmonary embolism: Post procedural pulmonary embolism Post-operative: knee arthroplasty			1 (Subject

Source: ANDA 200936 Final Study Report Appendix 14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events p. 172-216.

Table 22: Summary of Serious Adverse Events by Subject (per Reviewer)

Site-Subject number	Treatment	Serious Adverse Event Listed on SAE Narrative; details
(b) (6)	Reference	**Cerebral vascular accident**; 65 year old male; began treatment (b) (6); 2 weeks later subject opted to withdraw consent due to skin reactions and he experienced loss of memory and disorientation during early termination visit on (b) (6); hospitalized (b) (6) for transient ischemic attack workup; Investigator considered event to be unrelated to study drug.
	Test	**Left temple basal cell carcinoma, nodular and infiltrative subtype to deep margin**; 68 year old male; narrative did not provide treatment start date; pathology report for skin biopsy of left temple performed on (b) (6) revealed Basal Cell Carcinoma, Nodular and Infiltrative Subtype to Deep Margin; underwent MOHS surgery with A-T plasty with length of repair 7 cm^2; continued in study; Investigator considered event to be unrelated to study drug.
	Reference	**Right superior postural area cutaneous lymphoid hyperplasia OR possibly a low-grade B-cell lymphoma**; 83 year old male; narrative did not provide treatment start date; pathology report for two skin biopsies from behind right ear performed on

Site-Subject number	Treatment	Serious Adverse Event Listed on SAE Narrative; details
(b) (6)		(b) (6) revealed "Lesion 1 is atypical lymphoid infiltrated with differential diagnosis including cutaneous lymphoid hyperplasia OR possibly a low-grade B cell lymphoma; Lesion 2 is an inflamed seborrheic keratoses"; subject referred for additional treatment, missed appointment and during End of Study visit on (b) (6), refused any follow-up; Investigator considered event to be unrelated to study drug.
	Reference	**Myocardial infarction**; 69 year old male; narrative did not provide treatment start date; presented to ER with chest pain on (b) (6) and admitted; underwent selective coronary angiography with stent placement in proximal RCA; complete Visit 6/Day 112 visit on (b) (6) Investigator considered event to be unrelated to study drug.
	Test	**Prostate cancer**; 73 year old male; narrative did not provide treatment start date; PSA elevated on (b) (6) underwent ultrasound and prostate biopsy on (b) (6) with diagnosis prostate cancer; plan was to have subject see urologist on (b) (6) continued in study; Investigator considered event to be unrelated to study drug.
	Test	**Prostate cancer**; 62 year old male; completed study (b) (6) and diagnosed with prostate cancer on (b) (6); underwent radical prostatectomy on (b) (6) Investigator considered event to be unrelated to study drug.
	Vehicle	**Right knee arthroplasty surgery**; 76 year old male; narrative did not provide treatment start date; underwent total knee arthroplasty (replacement) surgery due to osteoarthritis on (b) (6); continued in study; Investigator considered event to be unrelated to study drug.
	Test	**Total hip arthroplasty to right hip due to degenerative joint disease**; 64 year old male; randomized to treatment on (b) (6); hospitalized on (b) (6) for total hip replacement; continued in study; Investigator considered event to be unrelated to study drug.
	Reference	**Pneumonia**; 81 year old male; randomized to treatment on (b) (6); on (b) (6) hospitalized for pneumonia; discontinued from the study as a result of this event; Investigator considered event to be unrelated to study drug.
	Vehicle	**Malignant melanoma**; 81 year old male; narrative did not provide treatment start date; reported lesion on right forearm to Investigator during Visit 3/day 28 and biopsy revealed melanoma, nodular growth patter with ulceration; on (b) (6) underwent wide local excision with sentinel lymph node biopsy right axilla and full thickness skin graft; discontinued from the study as a result of this event; Investigator considered event to be unrelated to study drug.
	Reference	**Left type 1 open calcaneal fracture**; 59 year old male; randomized to treatment on (b) (6) or (b) (6) fell from a step ladder, broke his foot, hospitalized and underwent irrigation and debridement; on (b) (6) underwent open reduction and internal fixation; continued in study; Investigator considered event to be unrelated to study drug.
	Vehicle	**Partial left knee replacement for left knee medial osteoarthritis, pulmonary embolus, pulmonary embolus post-operative**; 75 year old male; narrative did not provide treatment start date; underwent left knee replacement on (b) (6); became unresponsive on (b) (6) and CT chest revealed bilateral pulmonary emboli; discontinued from the study as a result of this event; Investigator considered event to be unrelated to study drug.
	Test	**Pneumonia**; 95 year old male; on (b) (6) found confused and unresponsive at home; hospitalized for extensive right lower lobe pneumonia and intubated; discontinued from the study as a result of this event and completed early discharge visit on (b) (6); Investigator considered event to be unrelated to study drug.

Source: ANDA 200936 Final Study Report Appendix 14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events p. 172-216.

Evaluation of Local Skin Reactions

According to the sponsor's analysis:

1) The majority of subjects in each treatment group at both Baseline and End of Treatment (EOT) either did not have the specified skin reaction or had reactions that were categorized as mild.
2) In both active treatment groups, the percentage of subjects with moderate or severe local reactions increased between Baseline and Visit 6/Day 112.
3) Changes in severity were generally similar in the Diclofenac sodium Gel and Solaraze® Gel treatment groups.

The frequency and severity of local skin reactions were tabulated by the sponsor in Tables 23 and 24.

Table 23: Evaluation of Local Skin Reaction for Intent to Treat Subjects at visit 5 (end of therapy; week 12), per Sponsor

Parameter	Category	Test n=241	Reference n=246	Vehicle n=121
Burning	None	179 (74.3%)	165 (67.1%)	99 (81.8%)
	Mild	18 (7.5%)	31 (12.6%)	9 (7.4%)
	Moderate	11 (4.6%)	10 (4.1%)	0
	Severe	3 (1.2%)	1 (0.4%)	0
Erythema (Redness)	None	94 (39.0%)	79 (32.1%)	52 (43.0%)
	Mild	84 (34.9%)	86 (35.0%)	46 (38.0%)
	Moderate	30 (12.4%)	35 (14.2%)	10 (8.3%)
	Severe	3 (1.2%)	7 (2.8%)	0
Epidermal Desquamation (Dryness/Flaking/Scaling)	None	143 (59.3%)	137 (55.7%)	72 (59.5%)
	Mild	87 (36.1%)	93 (37.8%)	40 (33.1%)
	Moderate	11 (4.6%)	16 (6.5%)	9 (7.4%)
	Severe	0	0	0
Pruritus (Itching)	None	166 (68.9%)	144 (58.5%)	86 (71.1%)
	Mild	26 (10.8%)	44 (17.9%)	21 (17.4%)
	Moderate	15 (6.2%)	16 (6.5%)	1 (0.8%)
	Severe	4 (1.7%)	3 (1.2%)	0
Pain	None	199 (82.6%)	198 (80.5%)	105 (86.8%)
	Mild	7 (2.9%)	8 (3.3%)	3 (2.5%)
	Moderate	4 (1.7%)	1 (0.4%)	0
	Severe	1 (0.4%)	0	0
Edema (Swelling)	None	196 (81.3%)	187 (76.0%)	106 (87.6%)
	Mild	14 (5.8%)	14 (5.7%)	2 (1.7%)
	Moderate	1 (0.4%)	5 (2.0%)	0
	Severe	0	1 (0.4%)	0
Erosion/Ulceration	None	197 (81.7%)	185 (75.2%)	106 (87.6%)
	Mild	11 (4.6%)	16 (6.5%)	1 (0.8%)
	Moderate	3 (1.2%)	5 (2.0%)	1 (0.8%)
	Severe	0	1 (0.4%)	0
Weeping/Exudate (Fluids discharge in tissue or cavities)	None	206 (85.5%)	200 (81.3%)	107 (88.4%)
	Mild	5 (2.1%)	4 (1.6%)	1 (0.8%)
	Moderate	0	2 (0.8%)	0
	Severe	0	1 (0.4%)	0
Scabbing/Crusting/Crusted, dried pus, lymph or blood	None	190 (78.8%)	170 (69.1%)	102 (84.3%)
	Mild	11 (4.6%)	25 (10.2%)	4 (3.3%)

Parameter	Category	Test n=241	Reference n=246	Vehicle n=121
	Moderate	10 (4.1%)	10 (4.1%)	2 (1.7%)
	Severe	0	2 (0.8%)	0
Vesicles (Fluid containing structures)	None	211 (87.6%)	203 (82.5%)	108 (89.3%)
	Mild	0	1 (0.4%)	0
	Moderate	0	2 (0.8%)	0
	Severe	0	1 (0.4%)	0

Source: ANDA 200936 Final Study Report Tables 14.3.1.6.1 on pg. 152, 14.3.1.6.2 on pg. 154, 14.3.1.6.3 on pg. 156, 14.3.1.6.4 on pg. 158, 14.3.1.6.5 on pg. 160, 14.3.1.6.6 on pg. 162, 14.3.1.6.7 on pg. 164, 14.3.1.6.8 on pg. 166, 14.3.1.6.9 on pg. 168 and 14.3.1.6.10 on pg. 170.

Table 24: Evaluation of Local Skin Reaction for Intent to Treat Subjects at visit 6/week 16 (4 weeks follow-up), per Sponsor

Parameter	Category	Test n=241	Reference n=246	Vehicle n=121
Burning	None	223 (92.5%)	224 (91.1%)	115 (95.0%)
	Mild	3 (1.2%)	6 (2.4%)	0
	Moderate	4 (1.7%)	8 (3.3%)	1 (0.8%)
	Severe	4 (1.7%)	4 (1.6%)	1 (0.8%)
Erythema (Redness)	None	155 (64.3%)	153 (62.2%)	68 (56.2%)
	Mild	62 (25.7%)	66 (26.8%)	45 (37.2%)
	Moderate	12 (5.0%)	19 (7.7%)	4 (3.3%)
	Severe	5 (2.1%)	4 (1.6%)	0
Epidermal Desquamation (Dryness/Flaking/Scaling)	None	173 (71.8%)	171 (69.5%)	86 (71.1%)
	Mild	51 (21.2%)	57 (23.2%)	26 (21.5%)
	Moderate	6 (2.5%)	12 (4.9%)	5 (4.1%)
	Severe	4 (1.7%)	2 (0.8%)	0
Pruritus (Itching)	None	215 (89.2%)	214 (87.0%)	108 (89.3%)
	Mild	9 (3.7%)	11 (4.5%)	8 (6.6%)
	Moderate	6 (2.5%)	12 (4.9%)	0
	Severe	4 (1.7%)	5 (2.0%)	1 (0.8%)
Pain	None	225 (93.4%)	228 (92.7%)	117 (96.7%)
	Mild	4 (1.7%)	6 (2.4%)	0
	Moderate	2 (0.8%)	5 (2.0%)	0
	Severe	3 (1.2%)	3 (1.2%)	0
Edema (Swelling)	None	222 (92.1%)	223 (90.7%)	116 (95.9%)
	Mild	9 (3.7%)	11 (4.5%)	0
	Moderate	3 (1.2%)	5 (2.0%)	1(0.8%)
	Severe	0	3 (1.2%)	0
Erosion/Ulceration	None	223 (92.5%)	228 (92.7%)	117 (96.7%)
	Mild	10 (4.1%)	6 (2.4%)	0
	Moderate	1 (0.4%)	3 (1.2%)	0
	Severe	0	5 (2.0%)	0
Weeping/Exudate (Fluids discharge in tissue or cavities)	None	228 (94.6%)	234 (95.1%)	117 (96.7%)
	Mild	5 (2.1%)	5 (2.0%)	0
	Moderate	0	2 (0.8%)	0
	Severe	1 (0.4%)	1 (0.4%)	0
Scabbing/Crusting/Crusted, dried pus, lymph or blood	None	220 (91.3%)	220 (89.4%)	114 (94.2%)
	Mild	8 (3.3%)	9 (3.7%)	3 (2.5%)
	Moderate	3 (1.2%)	9 (3.7%)	0
	Severe	3 (1.2%)	4 (1.6%)	0
Vesicles (Fluid containing	None	232 (96.3%)	237 (96.3%)	117 (96.7%)

Parameter	Category	Test n=241	Reference n=246	Vehicle n=121
structures)	Mild	1 (0.4%)	2 (0.8%)	0
	Moderate	1 (0.4%)	1 (0.4%)	0
	Severe	0	2 (0.8%)	0

Source: ANDA 200936 Final Study Report Tables 14.3.1.6.1 on pg. 152, 14.3.1.6.2 on pg. 154, 14.3.1.6.3 on pg. 156, 14.3.1.6.4 on pg. 158, 14.3.1.6.5 on pg. 160, 14.3.1.6.6 on pg. 162, 14.3.1.6.7 on pg. 164, 14.3.1.6.8 on pg. 166, 14.3.1.6.9 on pg. 168 and 14.3.1.6.10 on pg. 170.

Reviewer's comment: *A more intense degree of local skin reaction occurred with the active treatments compared to the vehicle. Compared to baseline (see Table 13) when not a single subject had a severe local skin reaction, subjects in the active treatment groups at visit 6 had severe burning (n=8: 4 test, 4 reference), severe erythema (n=9: 5 test, 4 reference),* ***severe*** *epidermal desquamation (n=6: 4 test, 2 reference), severe pruritus (n=9: 4 test, 5 reference), severe pain (n=6: 3 test, 3 reference), severe edema (n=3 reference), severe erosion/ulceration (n=5 reference), severe weeping/exudate (n=2: 1 test, 1 reference), severe scabbing/crusting/crusted dried pus, lymph or blood (n=7: 3 test, 4 reference) and severe vesicles (n=2 reference). Overall, subjects dosed with the reference product reported more severe local skin reactions than subjects dosed with the test product (n=57 severe local skin reactions: 24 by test subjects, 33 by reference subjects).*

VI. Relevant Findings From Division of Scientific Investigations, Statistics and/or Other Consultant Reviews

A. Review of Bioequivalence Establishment Inspection Report

On 12/15/11, the OGD Division of Clinical Review (DCR) sent a Request for Inspection to the Office of Scientific Investigations (OSI), Division of Bioequivalence and GLP Compliance (DBGLPC) regarding ANDA 200936 with a due date of 3/15/12. The DCR requested that the following three new clinical sites be inspected:

Site # 1	Center for Dermatology Clinical Research (Study Site 1)
Address	2557 Mowry Avenue, Suite 34 Fremont, CA 94538
Phone	510-797-4111
Investigator (Name/Contact Info)	Sunil S. Dhawan, MD
# of subjects	12 (in Per Protocol Population; 19 enrolled)
Site # 2	Marina I. Peredo, MD (Study Site 2)
Address	260 Middle County Road, Suite 208 Smithtown, NY 11787
Phone	631-863-3223
Investigator (Name/Contact Info)	Marina I. Peredo, MD
# of subjects	16 (in Per Protocol Population; 19 enrolled)
Site # 3	Stephen Miller, MD (Study Site 5)
Address	8431 Fredericksburg Rd., Suite 100 San Antonio, TX 78229
Phone	210-614-2662
Investigator (Name/Contact Info)	Stephen Miller, MD
# of subjects	15 (in Per Protocol Population; 20 enrolled)

Due to other conflicting priorities, the inspection report was not finalized until a year after the requested due date., i.e., on 3/4/13. Per the report, ORA staff conducted inspections at all three requested sites:

- Site #1 Sunil S. Dhawan, MD on 8/10-23/12
- Site #2 Marina I. Peredo, MD on 12/10-18/12
- Site #3 Stephen Miller, MD on 10/02-10/12

Per the report, the inspections included a thorough examination of study records, facilities and equipment, and interviews and discussions with the firm's management and staff.

Forms FDA-483 were issued at Sites #1 and #3. The response from Dr. Dhawan at Site #1 (dated 8/30/12; received by OSI on 2/19/13) and the response from Dr. Miller at Site #3 (dated 10/29/12; received by OSI on 2/20/13) was included in the report. The report made the following observations re: Site #1 (Study Site 1) Sunil S. Dhawan, MD:

- Subject (b) (6) received treatment for actinic keratoses with liquid nitrogen on the upper and lower extremities on (b) (6) and was enrolled in the study on (b) (6). The Exclusion Criteria #8 excluded any subject who had been treated within 60 days prior to study entry with cryodestruction anywhere on the face, scalp, back of hands or forearms. While Dr. Shawan's response to his Form FDA-483 stated that this patient was treated with liquid nitrogen in an area outside the product treatment area, he did not provide any documentation supporting this statement.
- Subject (b) (6) had a history of peptic ulcer (b) (6) with concomitant medications including cimetidine. The Exclusion Criteria #6 excluded subjects with active gastrointestinal ulceration or bleeding. Dr. Shawan's response to his Form FDA-483 stated that this subject did not have active gastrointestinal ulceration and was taking cimetidine on a prn basis.
- The DNGLPC reviewer recommended that Subjects (b) (6) be excluded from the study if they met the exclusion criteria.
- Persons other than enrolled subjects wrote on different subject diaries; however, the DNGLPC reviewer recommended that this did not impact study outcome.
- Subject (b) (6) was noncompliant on Visits 3, 4, and 5, specifically the subject never returned the study medication tubes (which should have occurred on Visits 3 and 4) and never brought in the diaries after (b) (6) (Visit 3). The DNGLPC reviewer recommended that this subject be excluded from the BE evaluation.
- Dr. Dhawan signed the informed consent for subject (b) (6) two days after the subject and person explaining the consent to the subject signed the informed consent.
- Samples were not stored in accordance with labeled storage conditions, i.e., they were stored in a location without climate control or temperature recording equipment. Thus, the uncontrolled storage in Freemont, CA, where summer temperatures could have resulted in degradation of reserves, such as gel separation, thus, compromising their testing by DPA.

Reviewer's comments:

1) *It would have been a simple matter for Dr. Dhawan to have provided the "Dermatological Assessment" form page from the Case Report Form for Subject (b) (6), which would have confirmed the treatment area(s). However, no documentation of the treatment area was*

provided by Dr. Dhawan. It also appears from his response that Dr. Dhawan is not able to confirm the location of the cryodestruction on the upper extremities of Subject (b) (6) *and specifically, whether or not it occurred on the potential treatment areas of the forearm or back of hand. A Case Report Form was not submitted for this subject. However, Subject* (b) (6) (b) (6) *has already been excluded from the PP population by both the sponsor and the FDA due to Visit 6 being outside of the Window (per the "SUBJECT" dataset). Thus, recommend deleting subject* (b) (6) *(also known as* (b) (6)*) from the mITT population This subject had been treated with Solaraze.*

2) *Per the CMC (concomitant medication) dataset, subject* (b) (6) *was taking Cimetidine 400 mg orally for "peptic ulcer" on a "**prn**" frequency"; thus, this reviewer concurs with Dr. Shawan that taking this concomitant medication on a "prn" basis would not have excluded this subject from enrolling into the study. In addition, Subject* (b) (6) *has already been excluded from the mITT and the PP populations because there was no post-baseline lesion count (per the "SUBJECT" dataset); thus, it would make no difference to the study results whether or not this subject should or should not have been enrolled. This subject had been treated with vehicle.*
3) *This reviewer concurs with the DNGLPC reviewer that the minor changes to the subject diaries are unlikely to have impacted the study outcome.*
4) *Per the 'SUBJECT" dataset, subject* (b) (6) *(also known as* (b) (6)*) was excluded by the sponsor from the PP population due to lost diary cards from V4-V5 and was included by the sponsor in the mITT dataset. However, per Appendix 16.2.5.1, D1* (b) (6)*, date of last medication was Day 86* (b) (6)*, subject was dispensed 3 tubes of medication and returned 3 tubes of medication; per Appendix Listing 16.2.5.2, subject applied 76 doses from Visit 4 to Visit 5 with last study medication application on* (b) (6) *and total number of applications was 177 doses, which was within 75% to 125% (i.e., 126 to 210) of the scheduled 168 applications. Thus, Subject* (b) (6) *is included in the FDA PP population and this reviewer does not recommend deleting this subject from the PP population based upon the Inspection Report. Thus, this reviewer recommends no changes regarding subject* (b) (6) *based upon the Inspection Report, i.e., this subject should not be deleted from the mITT population because the posted Draft Guidance for this drug product recommends in Comment #9b that "(t)he mITT population includes all randomized subjects who met all inclusion/exclusion criteria, received study treatment, and returned for at least one post-baseline visit" and this subject met these recommendations. This subject had been treated with the test diclofenac sodium.*
5) *To this reviewer, Dr. Dhawan signing the informed consent for subject* (b) (6) *two days after the subject and person explaining the consent to the subject signed the informed consent is unlikely to have impacted the study outcome.*
6) *The DNGLPC reviewer sent samples from each of the three inspection sites to the DPA for testing.. On 3/18/13, this reviewer was sent an e-mail from the he DNGLPC reviewer which stated that the DPA was able to positively identify test and reference products coming from all the three sites. Thus, this is no longer an issue.*

The report made the following observations re: Site #3 Steven Miller, MD:

- A sealed randomization code was not available to the inspector. Dr. Miller responded that a sealed copy of randomization was never provided to him by the sponsor. Per the DNGLPC reviewer, in the absence of randomization codes or the original drug product

labels preserved at the clinical site, there is no assurance that subjects received their assigned treatments during the study.

- Investigational drug disposition records were not adequate with respect to dates, quantity, and use by subjects. Specifically, Protocol TOL-AK-2008-02 Investigational Product records showed Dr. Miller's receipt of Kits 4826-4830. The Investigational Product Return form does not account for Kits 4826-4830 as being used or returned. A Clincsys Clinical Research Note-To-File dated 3/15/10 documents "Study drug kits 4826-4830 were returned to (b) (4) however it cannot be determined if these kits were used or unused as it was not indicated on the site's paperwork and the drug has been destroyed. Per the DNGLPC reviewer, in the absence of complete drug accountability records for the use or disposition of study drugs provided to the clinical site by the sponsor, it cannot be confirmed if the subjects received their assigned treatments during the study as required by the protocol. In the opinion of the DNGLPC reviewer, integrity of the reported data cannot be assured.
- Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation, specifically:
  a. The CD-ROM received after completion of the study under study protocol TOP-AK-2008-02 does not include the capability to view details of audit trails.
  b. Protocol TOL-AK-2008-02, Protocol Section 5.3, Concomitant and Prohibited Medication, states in part that cryodestruction is allowed on the face or scalp outside the designated treatment area. Subjects (b) (6) received cryodestruction treatment during their participation in the study ; however, source records do not document whether cryodestruction occurred outside the designated treatment area. In his response, Dr. Miller stated that he did not document the location of the cryodestruction treatment but the treatment was outside the protocol treated areas.

Reviewer's comments:

1) *Due to the above serious concerns regarding the quality and integrity of the study data from Dr. Stephen Miller's site (site #5 in the study; 20 subjects enrolled), the DBGLPC reviewer recommends that all data from his site be excluded from the bioequivalence evaluation. This reviewer concurs that all data from the twenty Subjects* (b) (6) (b) (6) (b) (6) *should be deleted from both the mITT populations and the PP populations. This reviewer notes that per the "SUBJECT" dataset, all 20 subjects were in the mITT population and five Subjects* (b) (6) *had already been deleted by the sponsor from the PP population due to "Visit 6 out of window" for 3 subjects, "non-efficacy related discontinuation" for one subject and "took concomitant medication prohibited by protocol" for one subject*
2) *The FDA statistician has been asked to recalculate the bioequivalence endpoints in the mITT and PP populations after making the following adjustments based upon the Bioequivalence Establishment Inspection Report:*
   a. *ensuring that the following twenty-one Subjects* (b) (6) (b) (6) (b) (6) *are not included in the FDA mITT population*

b. ensuring that the following twenty Subjects (b) (6) (b) (6) (b) (6) *are not included in the FDA PP population.*

B. Review of the FDA Statistical Report

Questions for Statistician:

1) Please analysis the efficacy results for the primary endpoint, using the FDA Per Protocol (PP) and modified Intent-to-Treat (mITT) populations.

2) Per the posted Draft Guidance for this drug product, the FDA mITT population includes all randomized subjects who met all inclusion/exclusion criteria, received study treatment, and returned for at least one post-baseline visit and the FDA PP population includes all randomized subjects who met all inclusion/exclusion criteria, applied a prespecified proportion of the scheduled applications (e.g., 75% to 125%) of the assigned product for the specified duration of the study, did not miss more than 10 consecutive scheduled applications, and completed the primary endpoint evaluation within the designated visit window (+/- 4 days) with no protocol violations that would affect the treatment evaluation. It is the opinion of this reviewer that the deletion of an additional 40 subjects, in order to comply with OGD recommendations regarding the designated visit window ± **4** days for the primary endpoint evaluation (which were not posted until after this study was completed), is unreasonable. Thus, this reviewer accepts the sponsor's proposal to include subjects in the PP population if Visit 6 occurred on Day 112 ± **5** days.

   Please note that the sponsor prematurely discontinued subjects from the study based upon non-compliance with treatment (based upon their definition of less than 80% or more than 120% of scheduled applications); however, the total number of doses applied per subject is not provided in the DC (Diary Compliance) or DA (Drug Accountability) datasets. The DC dataset and the Appendix Listing 1.6.2.5.2 only provides the number of doses applied by each subject per visit (and does not provide the total number during the study). The DA dataset and the Appendix Listing 16.2.5.1 only provides the "number of tubes dispensed" to each subject, the "number of tubes returned" by each subject, and the "date of last medication". Please add the number of applications per visit per subject in the DC dataset and thus, determine the total number of study medication applications by subject. Then, subjects with less than 75% (i.e., 126 applications) or more than 125% (i.e., 210 applications) of the scheduled applications of study medication should be excluded from the FDA PP population. Per the calculations of this reviewer, 168 applications of study medication were scheduled (i.e. twice daily dosing for 84 days) and 75% to 125% of the scheduled 168 applications is 126 to 210 applications.

   In addition to the subjects deleted from the FDA PP and/or mITT population based upon the Inspection Report, this reviewer disagrees with the sponsor regarding the placement of 14 different subjects in the PP and/or mITT populations, as follows:

   1. The sponsor excluded Subject (b) (6) (test) from their PP population due to "lost diary card from V4-V5" and thus, being unable to confirm last 28 days of scheduled applications (i.e., from Day 56 to Day 84); however, per Appendix 16.2.5.1, D1 (b) (6)

date of last medication was Day 86 (b) (6), subject was dispensed 3 tubes of medication and returned 3 tubes of medication; per Appendix Listing 16.2.5.2, subject applied 76 doses from Visit 4 to Visit 5 with last study medication application on (b) (6) and total number of applications was 177 doses, which was within 75% to 125% (i.e., 126 to 210) of the scheduled 168 applications. Thus, Subject (b) (6) is included in the FDA PP population.

2. The sponsor excluded Subject (b) (6) (test) from their PP population due to "did not meet Exclusion Criteria #10 per Appendix Listing 16.2.2" (110 days on study; completed study); however, sponsor included this subject in their mITT population. This subject was excluded from both the FDA PP population and the FDA mITT population due to not meeting the Inclusion/Exclusion Criteria.
3. The sponsor excluded Subject (b) (6) (test) from their PP population due to "enrolled with a > 25 cm^2 treatment area"; however, this alone would be insufficient to exclude the subject, unless it was accompanied by an unusually large baseline lesion count. The treated body area was "back of hands" and only 5 lesions were counted at baseline. Thus, this subject was included in the FDA PP population.
4. The sponsor excluded Subject (b) (6) (test) from their PP population due to "took prohibited concomitant medication" [113 days on study; continued eight medications (all oral and all started prior to study), i.e., aspirin 160 mg qd for cardiac prophylaxis; one multivitamin tablet qd; niacin 1000 mg qd and simvastatin 20 mg qd for hypercholesterolemia; lisinopril 5 mg qd for hypertension; galantamine HBr 8 mg qd for mild dementia; calcium gluconate 600 mg qd for osteoarthritis; and etodolac acetic acid 300 mg qd for osteoarthritis; did not start any new drugs during study]; however, it appears that all concomitant medications were permitted for use during study. Thus, this subject was included in the FDA PP population.
5. The sponsor excluded Subject (b) (6) test) from their PP population due to "participating in another study for F/U; Tolmar requested withdraw" (112 days on study; her 14 concomitant medications were all approved drug products (Flonase, HCTZ, Zocor, aspirin, Nexium, Ex-lax, Dulcolax, Imodium A-D, allopurinol, levothyroxine, Tylenol XS, multivitamin/iron, vitamin E and Botox injection); however, all of her concomitant medications were approved drugs. Thus, subject does not appear to have taken an experimental drug product during the study and was included in the FDA PP population.
6. The sponsor excluded Subject (b) (6) (reference) from their PP population due to "not compliant with study medication applications. She was 84 days on study medication and 114 days on study (Day 1= (b) (6) and date of last medication Day 84= (b) (6)). Per Appendix Listing 16.2.5.1, 3 tubes of medication were dispensed to this subject and 3 tubes of medication were returned. Per Appendix Listing 16.2.5.2, subject applied a total of 132 doses of study medication, which was slightly less than the minimum 80% of scheduled doses per the protocol; however, it was within the 75% and 125% of scheduled doses recommended in the posted Draft Guidance. Thus, this subject was included in the FDA PP population.
7. The sponsor excluded Subject (b) (6) (reference) from their mITT population due to "no post-baseline lesion counts"; however, this subject had two post-baseline visits on Days 29 and 58, so this subject is included in the FDA mITT population.
8. The sponsor excluded Subject (b) (6) (reference) from their PP population due to "did not meet eligibility criteria per Appendix Listing 16.2.3; however, they included this

subject in their mITT population. This subject has been excluded from both the FDA PP and mITT populations due to not meeting eligibility criteria.

9. The sponsor excluded Subject (b) (6) (reference) from their PP population due to "did not meet eligibility criteria" per Appendix Listing 16.2.3; however, this subject was included in the sponsor's mITT population. Subject (b) (6) was excluded from both the FDA PP and mITT populations due to not meeting eligibility criteria.
10. The sponsor excluded Subject (b) (6) (reference) from their PP population due to "did not meet eligibility criteria" per Appendix Listing 16.2.3; however, this subject was included in the sponsor's mITT population. Subject (b) (6) was excluded from both the FDA PP and mITT populations due to not meeting eligibility criteria.
11. The sponsor excluded Subject (b) (6) (reference) from their mITT population due to "no post-baseline lesion counts"; however, this subject had one post-baseline visit on Day 148, so this subject is included in the FDA mITT population.
12. The sponsor excluded Subject (b) (6) (vehicle) from the PP population due to non-efficacy related premature discontinuation due to "lost to follow up" (17 days on study; missed the primary endpoint evaluation at Day 112) and the sponsor included this subject in the mITT population However, per Appendix Listing 16.2.5.1, this subject was seen on Day 1= (b) (6), was never seen again, and thus, was excluded from both the FDA PP and mITT populations due to not returning for at least one post-baseline visit.
13. The sponsor deleted Subject (b) (6) (vehicle) from their PP population due to "not compliant with study medication applications" (82 days on study medication; 112 days on study (Day 1= (b) (6) date of last medication Day 82= (b) (6); Visit 6= (b) (6)). Per Appendix Listing 16.2.5.1, the subject was dispensed 3 tubes and returned 3 tubes of medication. Per Appendix 16.2.5.2, subject applied a total of 206 doses of study medication, which was slightly more than the 120% of scheduled doses per the protocol; however, it was less than the 125% of scheduled doses recommended in the posted Draft Guidance. Thus, this subject was included in the FDA PP Population.
14. The sponsor excluded Subject (b) (6) (vehicle) from their PP population due to "not compliant with study medication application"; however, per Appendix Listing 16.2.5.2, subject applied 168 doses of medication, which is between 75% and 125% of scheduled applications and subject did not miss 10 or more consecutive doses (81 days on study medication; 116 days on study; per Appendix Listing 16.2.5.1, dispensed 3 tubes and returned 3 tubes of medication; Day 1= (b) (6); date of last medication Day 81= (b) (6); Visit 6= (b) (6).); thus, this subject is included in the FDA PP population.

Table 25: Subjects in Sponsor and FDA PP and mITT Populations by Treatment

Subject Disposition	Number (%) of Subjects			
	Diclofenac sodium n (%)	Solaraze® n (%)	Vehicle n (%)	Total n (%)
Number Enrolled and Randomized (a)	242	246	121	609
Number in Sponsor PP Population (a)	187 (excluded 55; 23%)	180 (excluded 66; 27%)	93 (excluded 28; 23%)	460 (excluded 149; 24%)

Subject Disposition	Number (%) of Subjects			
	Diclofenac sodium n (%)	Solaraze® n (%)	Vehicle n (%)	Total n (%)
Number in FDA PP Population (b)	176 (excluded 66; 27%)	164 (excluded 82; 33%)	87 (excluded 34; 28%)	427 (excluded 182; 30%)
Number in Sponsor mITT Population (a)	241 (excluded 1)	244 (excluded 2)	120 (excluded 1)	605 (excluded 4)
Number in FDA mITT Population (b)	232 (excluded 10)	234 (excluded 12)	115 (excluded 6)	581 (excluded 28)

Sources: (a) Final Study Report TOL-AK-2008-02 pg. 39, Table 10-1 pg. 38 and Table 14.1.1 pg. 78; (b) ANDA 200936 Statistical Review and Evaluation by Huaxiang Li, Ph.D. finalized 6/6/13 pg. 8 of 12.

Please exclude the following 157 subjects (56 test; 71 reference; 30 vehicle) from the FDA PP population:[42]

TEST: Diclofenac Sodium Gel 3%: n=56

1. (b) (6) non-efficacy related premature discontinuation and withdrawal of consent (85 days on study; missed the primary endpoint evaluation at Day 112; per Appendix Listing 16.2.5.1, date of last medication was unknown.)
2. (b) (6) non-efficacy related premature discontinuation (31 days on study medication; 40 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment". Per Appendix 16.2.5.1, subject was dispensed 2 tubes of medication, returned 2 tubes of medication, and date of last medication was Day 31 on (b) (6); per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 3 and 4.]
3. (b) (6) Visit 6 Out of Window [Day 1= (b) (6); Visit 6 (b) (6) =Day 102, instead of Day 112 (per sponsor's Appendix Listing 16.2.1.2, 102 days on study)]
4. (b) (6) Site Inspection
5. Site Inspection
6. Site Inspection
7. Visit 6 Out of Window [Day 1= (b) (6); Visit 6= (b) (6) =Day 120, instead of Day 112 (per sponsor, 120 days on study)]
8. (b) (6) Site Inspection
9. Site Inspection
10. Visit 6 Out of Window [Day 1= (b) (6); Visit 6= (b) (6) =Day 101, instead of Day 112 (per sponsor, 101 days on study)]
11. (b) (6) "took prohibited concomitant medication" [112 days on study; used the antifungal agent topical ciclopirox olamine (Loprox Shampoo 1%) for scalp folliculitis starting (b) (6) once every 4 days and ongoing; also took oral atorvastatin calcium (Lipitor) 40 mg for high cholesterol; treatment body area was central face (i.e., on the head), which was also the location of the application of the topical concomitant medication, Loprox

[42] It should be noted that FDA Statisticians deleted an additional 25 subjects from the final FDA PP population (i.e., 10 more test subjects, 11 more reference subjects and 4 more vehicle subjects) because their Visit 6 occurred outside Day 112 ± 5 days, per note α2 to Table 1 on pg. 8 of 12 of the ANDA 200936 Statistical Review and Evaluation by Huaxiang Li, Ph.D. finalized on 6/6/13.

Shampoo 1%); thus patient was excluded because this drug product was applied on or near treatment area.]

12. (b) (6) Visit 6 Out of Window [Day 1= (b) (6) Visit 6= (b) (6) =Day 119, instead of Day 112 (per sponsor, 119 days on study)]
13. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (last day of medication Day 57= (b) (6); 85 days on study; missed the primary endpoint evaluation at Day 112)
14. (b) (6) non-efficacy related premature discontinuation (58 days on medication; 72 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: per Appendix Listing 16/2/1/1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment"; per Appendix Listing 16/2/5/1, date of last medication Day 58= (b) (6)]
15. (b) (6) Visit 6 Out of Window [Day 1= (b) (6); Visit 6= (b) (6) =Day 100, instead of Day 112 (per sponsor, 100 days on study)]
16. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (20 days on medication; 29 days on study; missed the primary endpoint evaluation at Day 112)
17. (b) (6) did not meet Exclusion Criteria #10 per Appendix Listing 16.2.2 (110 days on study; completed study)
18. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (34 days on medication; 35 days on study; missed the primary endpoint evaluation at Day 112)
19. (b) (6) Visit 6 Out of Window [Day 1= (b) (6); Visit 6= (b) (6) =Day 118, instead of Day 112 (per sponsor, 118 days on study)]
20. (b) (6) non-efficacy related premature discontinuation (70 days on medication; 72 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment"; per Appendix Listing 16.2.5.1, date of last medication Day 70= (b) (6)]
21. (b) (6) non-efficacy related premature discontinuation due to lost to follow up (29 days ; missed the primary endpoint evaluation at Day 112)
22. (b) (6) non-efficacy related premature discontinuation due to adverse event (29 days on medication; 38 days on study; missed the primary endpoint evaluation at Day 112; last day of medication Day 29= (b) (6))
23. (b) (6) non-efficacy related premature discontinuation due to lost to follow up (30 days on study; missed the primary endpoint evaluation at Day 112)
24. (b) (6) not compliant with study medication applications (missed more than 10 consecutive doses between Visits 4 and 5; missed 12 applications between Visits 4 and 5; 82 days on study medication; 113 days on study); Per Appendix Listing 16.2.5.1, dispensed 3 tubes and returned 3 tubes of medication; Day 1= (b) (6); date of last medication Day 82= (b) (6); per Appendix Listing 16.2.5.2, Day 1= (b) (6); last date of study medication Day 82= (b) (6); total number of applications was 156, which is between 75% and 125% of expected application; however, missed 12 doses between Visits 4 and 5 with at least 10 being consecutive doses.
25. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) =Day 118, instead of Day 112)

26. (b) (6) non-efficacy related premature discontinuation due to adverse event "local skin reaction" (67 days on study medication; 70 days on study; missed the primary endpoint evaluation at Day 112)
27. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) =Day 121, instead of Day 112)
28. (b) (6) non-efficacy related premature discontinuation due to lost to follow up (37 days on study; missed the primary endpoint evaluation at Day 112)
29. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent on (b) (6) (seen at two visits: on Day 1= (b) (6) and on Day 112= (b) (6); 142 days on study; missed the primary endpoint evaluation at Day 112; did not return one tube of medication dispensed)
30. (b) (6) non-efficacy related premature discontinuation (85 days on medication; 86 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment"; per Appendix Listing 16.2.5.1 Day 1= (b) (6); date of last medication Day 85= (b) (6); per Appendix Listing 16.2.5.2, subjects missed 10 or more consecutive doses between Visits 4 and 5.]
31. (b) (6) non-efficacy related premature discontinuation due to adverse event "burning to face" (62 days on study; missed the primary endpoint evaluation at Day 112)
32. (b) (6) non-efficacy related premature discontinuation due to adverse event (57 days on study; missed the primary endpoint evaluation at Day 112; per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 3 and 4)
33. (b) (6) non-efficacy related premature discontinuation due to adverse event "local skin reaction" (54 days on study medication; 56 days on study; missed the primary endpoint evaluation at Day 112)
34. (b) (6) took prohibited concomitant medication (109 days on study; took oral prednisone ranging from 10 mg/day to 40 mg/day/glucocorticoids for contact dermatitis from (b) (6); systemic corticosteroids were prohibited during study by the protocol and by the posted Draft Guidance for the test product)
35. (b) (6) non-efficacy related premature discontinuation due to "a clinically meaningful finding that, in the opinion of the investigator, prevents continuation" (63 days on study medication; 64 days on study; missed the primary endpoint evaluation at; Day 112)
36. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) =Day 122, instead of Day 112)
37. (b) (6) non-efficacy related premature discontinuation due to lost to follow up (date of last medication not provided; 85 days on study; missed the primary endpoint evaluation at Day 112)
38. (b) (6) non-efficacy related premature discontinuation (59 days on study medication; 64 days on study; missed the primary endpoint evaluation at; Day 112) [**NOTE**: per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment"; Day 1= (b) (6); date of last medication Day 59= (b) (6)]
39. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) =Day 128, instead of Day 112)
40. (b) (6) non-efficacy related premature discontinuation (7 days on medication; 7 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: per Appendix Listing

16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment"; Day 1= (b) (6); date of last medication Day 7= (b) (6)]

41. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (9 days on study medication; 14 days on study; missed the primary endpoint evaluation at Day 112)
42. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (54 days on study medication; 56 days on study; missed the primary endpoint evaluation at Day 112)
43. (b) (6) non-efficacy related premature discontinuation due to adverse event (Day 1= (b) (6) 15 days on study; missed the primary endpoint evaluation at Day 112; per Appendix Listing 16.2.1.2, came for one post-baseline visit on Day 14= (b) (6))
44. (b) (6) took prohibited concomitant medication (112 days on study; took oral prednisone /glucocorticoids for sciatica from (b) (6); systemic corticosteroids are prohibited during study per the protocol and the posted Draft Guidance for the test drug)
45. (b) (6) non-efficacy related premature discontinuation due to severe skin reaction (62 days on study medication; 70 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: this premature discontinuation was incorrectly coded as primarily due to "other". It should have been coded to "adverse event: severe skin reaction". Per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 4 and 5.]
46. (b) (6) used moisturizer in treatment area, which is prohibited per the protocol; approved by Medical Monitor to remain in study (110 days in study; used moisturizer from (b) (6))
47. (b) (6) non-efficacy related premature discontinuation (36 days on study medication; 50 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: this premature discontinuation was incorrectly coded as primarily due to "other". It should have been coded to "adverse event: severe skin reaction". Per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 3 and 4.]
48. (b) (6) non-efficacy related premature discontinuation due to adverse event (50 days on study medication; 57 days on study; missed the primary endpoint evaluation at Day 112; per Appendix 16.2.5.1, Day 1= (b) (6); date of last medication Day 50= (b) (6))
49. (b) (6) non-efficacy related premature discontinuation due to adverse event (64 days on study; missed the primary endpoint evaluation at Day 112; per Appendix 16.2.5.1, Day 1= (b) (6); date of last medication Day 52= (b) (6))
50. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (76 days on study; missed the primary endpoint evaluation at Day 112; ; per Appendix 16.2.5.1, Day 1= (b) (6); date of last medication Day 75= (b) (6))
51. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) =Day 119, instead of Day 112)
52. (b) (6) non-efficacy related premature discontinuation (64 days on study medication; 88 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment"; per Appendix Listing 16.2.5.1, Day 1= (b) (6); date of last medication Day 64= (b) (6)]

53. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (76 days on study medication; 77 days on study; missed the primary endpoint evaluation at Day 112)
54. (b) (6) did not return for at least one post-baseline visit; non-efficacy related premature discontinuation due to withdrawal of consent (1 day on study; missed the primary endpoint evaluation at Day 112; seen only at Visit 1)
55. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) =Day 104, instead of 112)
56. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) =Day 103, instead of 112)

RLD: Solaraze® Gel 3%: n=71

1. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6 (b) (6) =Day 120, instead of Day 112)
2. (b) (6) non-efficacy related premature discontinuation (2 days on study medication; 8 days on study; missed the primary endpoint evaluation at Day 112) [per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment"; per Appendix Listing 16.2.5.1, Day 1= (b) (6), date of last medication (b) (6) and seen for one post-baseline visit on (b) (6)]
3. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) =Day 136, instead of Day 112)
4. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (15 days on study medication; 15 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6); seen for one post-baseline visit on (b) (6))
5. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (29 days on study; missed the primary endpoint evaluation at Day 112; per Appendix Listing 16.2.5.1, Day 1= (b) (6) and seen for one post-baseline visit on (b) (6); date of last medication not provided)
6. (b) (6) non-efficacy related premature discontinuation (37 days on study medication; 55 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: this premature discontinuation was incorrectly coded as primarily due to "other". It should have been coded to "adverse event: local skin reaction; per Appendix Listing 16.2.5.1, Day 1= (b) (6) and date of last medication Day 37= (b) (6)]
7. (b) (6) non-efficacy related premature discontinuation (25 days on study medication; 27 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: this premature discontinuation was incorrectly coded as primarily due to "other". It should have been coded to "adverse event: local skin reaction and withdrawal of consent"; Day 1= (b) (6); date of last medication Day 25= (b) (6).]
8. (b) (6) non-efficacy related premature discontinuation (63 days on study medication; 68 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: this premature discontinuation was incorrectly coded as primarily due to "other". It should have been coded to "adverse event: local skin reaction and use of prohibited concomitant medication". Day 1= (b) (6) and date of last medication Day 63= (b) (6). Per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 3 and 4.]
9. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) =Day 124, instead of Day 112)

10. (b) (6) Site Inspection
11. Site Inspection
12. Site Inspection
13. non-efficacy related premature discontinuation (55 days on study medication; 59 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: this premature discontinuation was incorrectly coded as primarily due to "other". It should have been coded to "adverse event: local skin reaction, itching and burning in treatment area". Day 1= (b) (6) and date of last medication Day 55= (b) (6)]
14. (b) (6) Site Inspection
15. Site Inspection
16. Site Inspection
17. Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) =Day 120, instead of Day 112)
18. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) = Day 120, instead of Day 112)
19 (b) (6) non-efficacy related premature discontinuation (52 days on study medication; 24 days on study due to withdrawal of consent; missed the primary endpoint evaluation at Day 112. Day 1= (b) (6) and date of last medication Day 52= (b) (6))
20. (b) (6) Visit 6 Out of Window (Day 1 (b) (6); Visit 6= (b) (6) =Day 106, instead of Day 112)
21. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (77 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6) and date of last medication Day 56= (b) (6))
22. (b) (6) non-efficacy related premature discontinuation due to adverse event: local skin reaction (27 days on study medication, 57 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6) and date of last medication Day 27= (b) (6))
23. (b) (6) non-efficacy related premature discontinuation due to lost to follow up (29 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6) and date of last medication not provided)
24. (b) (6) took prohibited concomitant medication (112 days in study; received dexamethasone 1cc injection/corticosteroids for inflammation/removal of neuroma left foot on (b) (6))
25. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (58 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6) and date of last medication was Day 50= (b) (6); per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 3 and 4)
26. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6 (b) (6) =Day 106, instead of Day 112)
27. (b) (6) non-efficacy related premature discontinuation due to adverse event (3 days on study medication; 18 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6), date of last medication was Day 3= (b) (6) and came for one post-baseline visit on (b) (6); per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 1 and 2.)
28. (b) (6) non-efficacy related premature discontinuation due to "other" (28 days on study medication; 32 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: this premature discontinuation was incorrectly coded as primarily due to

"other". It should have been coded to "adverse event: local skin reaction". Day 1= (b) (6), date of last medication Day 28= (b) (6)]

29. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6)=Day 120, instead of Day 112)
30. (b) (6) not meeting Exclusion Criteria #8 per Appendix Listing 16.2.2 (117 days on study)
31. (b) (6) not meeting all entry criteria per Appendix Listing 16.2.2 (2 days on study medication; 8 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6), date of last medication (b) (6) and made one post-baseline visit on (b) (6); per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment".)
32. (b) (6) not compliant with study medication applications (56 days on study medication; 112 days in study; Day 1= (b) (6) and date of last medication Day 56= (b) (6); per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 4 and 5.)
33. (b) (6) non-efficacy related premature discontinuation (39 days on study medication; 57 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment" Day 1= (b) (6) and date of last medication Day 39= (b) (6); per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 3 and 4.]
34. (b) (6) not meeting all entry criteria per Appendix Listing 16.2.2 (2 days on study medication; 4 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6) date of last medication Day 2= (b) (6) and made one post-baseline visit on (b) (6): per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment")
35. (b) (6) took prohibited concomitant medication (112 days on study; received oral methylprednisolone 4 mg/glucocorticoids on (b) (6) because of cataract surgery; systemic corticosteroids are prohibited during the study by both the protocol and the posted Draft Guidance for the test product)
36. (b) (6) non-efficacy related premature discontinuation due to adverse event (14 days on study medication; 14 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6); date of last medication Day 14= (b) (6) made one post-baseline visit on (b) (6))
37. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (77 days on study medication; 79 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6) and date of last medication Day 77= (b) (6))
38. (b) (6) missing Visit 5 ((b) (6)) lesion count due to local skin reaction and missing Visit 6 ((b) (6) lesion count due to "unable to assess" (Day 1= (b) (6); date of last medication Day 91= (b) (6) and seen at Visit 6 on Day 108= (b) (6))
39. (b) (6) Visit 6 Out of Window (Day 1= (b) (6) Visit 6= (b) (6) Day 121, instead of Day 112)
40. (b) (6) non-efficacy related premature discontinuation due to adverse event, i.e., "clinically meaningful finding that, in the opinion of the investigator, prevents continuation" (77 days on study medication; 85 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6) date of last medication Day 77= (b) (6)

41. (b) (6) non-efficacy related premature discontinuation due to adverse event "local skin reaction" (52 days on study medication; 61 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6) and date of last medication Day 52= (b) (6))
42. (b) (6) non-efficacy related premature discontinuation due to adverse event (35 days on study medication; 36 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6) and date of last medication Day 35= (b) (6))
43. (b) (6) non-efficacy related premature discontinuation (12 days on study medication; 21 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment", Day 1= (b) (6), date of last medication Day 12= (b) (6); made one post-baseline visit on (b) (6).]
44. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) Day 121, instead of Day 112)
45. (b) (6) non-efficacy related premature discontinuation due to adverse event (59 days on study medication; 96 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6) date of last medication Day 59= (b) (6) per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 4 and 5)
46. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6)=Day 126, instead of Day 112)
47. (b) (6) non-efficacy related premature discontinuation due to "other" (52 days on study medication; 57 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: this premature discontinuation was incorrectly coded as primarily due to "other". It should have been coded to "adverse event: local skin reaction". Day 1= (b) (6) and date of last medication Day 52= (b) (6)]
48. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6)=Day 120, instead of Day 112)
49. (b) (6) non-efficacy related premature discontinuation due to "other" (58 days on study medication; 58 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: this premature discontinuation was incorrectly coded as primarily due to "other". It should have been coded to "adverse event: local skin reaction". Day 1= (b) (6) and date of last medication Day 58= (b) (6).]
50. (b) (6) not compliant with study medication applications (78 days on study medication; 106 days on study; Day 1= (b) (6) and date of last medication Day 78= (b) (6); per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 4 and 5.)
51. (b) (6) non-efficacy related premature discontinuation due to lost to follow up (30 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6); date of last medication not provided; made one post-baseline visit)
52. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (47 days on study medication; 53 days on study; missed the primary endpoint evaluation at Day 112; Day1= (b) (6) and date of last medication Day 47= (b) (6))
53 (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6)=Day 102, instead of 112)
54. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6)=Day 120, instead of 112)

55. (b) (6) non-efficacy related premature discontinuation (36 days on study medication; 38 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment". Day 1= (b) (6) and date of last medication Day 36= (b) (6)
56. (b) (6) non-efficacy related premature discontinuation (56 days on study medication; 57 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment", Day 1= (b) (6) and date of last medication Day 56= (b) (6) per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 3 and 5.]
57. (b) (6) non-efficacy related premature discontinuation (66 days on study medication; 67 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment". Day 1= (b) (6) and date of last medication Day 66= (b) (6)
58. (b) (6) non-efficacy related premature discontinuation due to "other" (67 days on study medication; 78 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: this premature discontinuation was incorrectly coded as primarily due to "other". It should have been coded to "adverse event: severe skin reaction and protocol violation with study treatment". Day 1= (b) (6) and date of last medication Day 67= (b) (6); per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 4 and 5]
59. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) =Day 118, instead of Day 112)
60. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (88 days on study medication; 104 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6) and date of last medication Day 88= (b) (6))
61 (b) (6) non-efficacy related premature discontinuation due to adverse event (36 days on study medication; 45 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6) and date of last medication Day 36= (b) (6).)
62. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (23 days of study medication; 24 days on study; missed the primary endpoint evaluation at Day 112 Day 1= (b) (6) and date of last medication Day 23= (b) (6).)
63. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) =Day 106, instead of Day 112)
64. (b) (6) non-efficacy related premature discontinuation due to "other" (56 days on study medication; 57 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: this premature discontinuation was incorrectly coded as primarily due to "other". It should have been coded to "adverse event: local skin reaction". Day 1= (b) (6) and date of last medication Day 56= (b) (6); per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 3 and 4.]
65. (b) (6) non-efficacy related premature discontinuation due to "other" (70 days on study medication; 85 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: this premature discontinuation was incorrectly coded as primarily due to

"other". It should have been coded to "adverse event: local skin reaction". Day 1= (b) (6) and date of last medication Day 70= (b) (6)]

66. (b) (6) Visit 6 Out of Window (Day 1 (b) (6); Visit 6= (b) (6) =Day 120, instead of Day 112)
67. (b) (6) non-efficacy related premature discontinuation due to adverse event (56 days on study medication; 57 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6); date of last medication Day 56= (b) (6).)
68. (b) (6) non-efficacy related premature discontinuation (57 days on treatment; 58 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment". Day 1= (b) (6); date of last medication Day 57= (b) (6)]
69. (b) (6) non-efficacy related premature discontinuation due to "other" (47 days on study medication; 78 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: this premature discontinuation was incorrectly coded as primarily due to "other". It should have been coded to "adverse event: severe skin reaction. Day 1= (b) (6); date of last medication Day 47 = (b) (6).]
70. (b) (6) non-efficacy related premature discontinuation (99 days on study medication; 112 days on study; per Appendix Listing 16.2.1.1, prematurely discontinued on July 21, 2009 due to protocol violation; non-compliance with study treatment; however, per Appendix Listing 16.2.1.2, July 21, 2009 was study day 112; thus, subject completed study) [**NOTE**: per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment". Day 1= (b) (6); date of last medication Day 99= (b) (6); thus, subject was on study treatment significantly longer than planned due to staying on study medication until coming 2 weeks late to Visit 5.]
71. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) =Day 118, instead of Day 112)

Vehicle: n=30

1. (b) (6) took prohibited concomitant medication (113 days on study; Day 1= (b) (6); Visit 6= (b) (6); date of last medication (b) (6); received cortisone 50 mg/mL injection/glucocorticoids on 5/15/09 due to arthritis in shoulder; systemic corticosteroids are prohibited during the study by the protocol and the posted Draft Guidance for the test product)
2. (b) (6) did not return for at least one post-baseline visit; non-efficacy related premature discontinuation due to withdrawal of consent (1 day on study; missed the primary endpoint evaluation at Day 112)
3. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (1 day on study medication; 32 days on study; missed the primary endpoint evaluation at Day 112; Day 1 (b) (6); date of last medication Day 1= (b) (6); returned for one post-baseline visit on (b) (6)
4. (b) (6) non-efficacy related premature discontinuation due to adverse event (9 days on study medication; 15 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6); date of last medication Day 9= (b) (6) seen for one post-baseline visit on Day 15= (b) (6) per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 1 and 2.)

5. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) =Day 106, instead of Day 112)
6. (b) (6) Site Inspection
7. Site Inspection
8. Site Inspection
9. Site Inspection
10. Visit 6 Out of Window (Day 1 (b) (6); Visit 6= (b) (6) =Day 119, instead of Day 112)
11. (b) (6) non-efficacy related premature discontinuation due to lost to follow up (17 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6) never seen again; did not return for at least one post-baseline visit)
12. (b) (6) Visit 6 Out of Window [Day 1= (b) (6); Visit 6= (b) (6) =Day 106, instead of Day 112]
13. (b) (6) Visit 6 Out of Window [Day 1= (b) (6); Visit 6= (b) (6) =Day 120, instead of Day 112]
14. (b) (6) Visit 6 Out of Window [Day 1= (b) (6); Visit 6= (b) (6) =Day 118, instead of Day 112]
15. (b) (6) non-efficacy related premature discontinuation (61 days on study medication; 63 days on study; missed the primary endpoint evaluation at Day 112) **[NOTE**: per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment". Day 1= (b) (6); date of last medication Day 61= (b) (6)
16. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) =Day 119, instead of Day 112)
17. (b) (6) not compliant with study medication applications (83 days on study medication; 113 days on study; per Appendix Listing 16.2.5.1, dispensed 2 tubes and returned 2 tubes of medication; Day 1= (b) (6); date of last medication Day 83 (b) (6); missed Visit 4; Visit 6= (b) (6); per Appendix Listing 16.2.5.2, applied only 119 doses of medication, which is less than 75% of the scheduled applications)
18. (b) (6) not compliant with study medication applications (88 days on study medication; 115 days on study; per Appendix Listing 16.2.5.1, dispensed 3 tubes and returned 3 tubes of medication; Day 1= (b) (6); date of last medication Day 88= (b) (6); Visit 6= (b) (6); per Appendix Listing 16.2.5.2, applied only 13 doses of medication, which is less than 75% of the scheduled applications)
19. (b) (6) non-efficacy related premature discontinuation due to "other" (15 days on study medication; 16 days on study; missed the primary endpoint evaluation at Day 112) [**NOTE**: this premature discontinuation was incorrectly coded as primarily due to "other". It should have been coded to "adverse event: severe skin reaction. Day 1= (b) (6); date of last medication (b) (6); seen for one post-baseline visit; per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 1 and 2.]
20. (b) (6) non-efficacy related premature discontinuation (77 days on study medication; 79 days on study; missed the primary endpoint evaluation at Day 112) **[NOTE**: per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment". Day 1= (b) (6); date of last medication Day (b) (6).]

21. (b) (6) non-efficacy related premature discontinuation due to adverse event (37 days on study medication; 42 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6); date of last medication Day 37= (b) (6).)
22. (b) (6) Visit 6 Out of Window [Day 1= (b) (6); Visit 6= (b) (6) =Day 106, instead of Day 112]
23. (b) (6) not compliant with study medication applications (105 days on study medication; 118 days on study; per Appendix Listing 16.2.5.1, dispensed 3 tubes and returned 3 tubes of medication; Day 1= (b) (6); date of last medication Day 105= (b) (6); Visit 6= (b) (6); per Appendix Listing 16.2.5.2, total number of applications=211, which is higher than 125% of scheduled applications)
24. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (28 days on study medication; 29 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6); date of last medication Day 28= (b) (6))
25. (b) (6) non-efficacy related premature discontinuation due to adverse event (68 days on study medication; 56 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6); date of last medication Day 68= (b) (6))
26. (b) (6) used moisturizer in treatment area, reported at V6 (83 days on study medication; 113 days on study; Day 1= (b) (6); date of last study medication Day 83= (b) (6); Visit 6= (b) (6); used Aveeno moisturizer on treatment area starting on (b) (6) due to local skin reaction, dry skin; moisturizers on treatment area are prohibited during the study by the protocol and the Draft Guidance for the test product)
27. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (79 days on study medication; 80 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6); date of last medication Day 79= (b) (6))
28. (b) (6) non-efficacy related premature discontinuation (85 days on study medication; 85 days on study; missed the primary endpoint evaluation at Day 112) **[NOTE**: per Appendix Listing 16.2.1.1 primary reason for subject discontinuation was "Protocol Violation; Non-compliance with study treatment". Day 1= (b) (6); date of last medication Day 85= (b) (6); per Appendix Listing 16.2.5.2, subject missed 10 or more consecutive doses between Visits 4 and 5.]
29. (b) (6) non-efficacy related premature discontinuation due to withdrawal of consent (16 days on study medication; 16 days on study; missed the primary endpoint evaluation at Day 112; Day 1= (b) (6); date of last medication Day 16= (b) (6); made one post-baseline visit)
30. (b) (6) Visit 6 Out of Window (Day 1= (b) (6); Visit 6= (b) (6) =Day 118, instead of Day 112)

Please exclude the following 28 subjects (10 test; 12 reference; 6 vehicle) from the FDA mITT population:

TEST: Diclofenac Sodium Gel 3%: n=10

1. (b) (6) Site Inspection
2. Site Inspection
3. Site Inspection
4. Site Inspection
5. Site Inspection
6. Site Inspection

7. (b) (6) Site Inspection
8. Site Inspection
9. not meeting Exclusion Criteria #10 per Appendix Listing 16.2.2 (110 days on study; completed study)
10. (b) (6) did not return for at least one post-baseline visit; non-efficacy related premature discontinuation (1 day on study).

RLD: Solaraze® Gel 3%: n=12

1. (b) (6) Site Inspection
2. Site Inspection
3. Site Inspection
4. Site Inspection
5. Site Inspection
6. Site Inspection
7. Site Inspection
8. Site Inspection
9. Site Inspection
10. (b) (6) not meeting Exclusion Criteria #8 per Appendix Listing 16.2.2 (117 days on study; completed study)
11. (b) (6) not meeting all entry criteria (discontinued prematurely due to protocol violations; non-compliance with study treatment; 8 days on study)
12. (b) (6) not meeting all entry criteria (discontinued prematurely due to protocol violations; non-compliance with study treatment; 4 days on study)

Vehicle: n=6

1. (b) (6) did not return for at least one post-baseline visit; non-efficacy related premature discontinuation (discontinued prematurely due to withdrawal of consent; 1 day on study)
2. (b) (6) Site Inspection
3. Site Inspection
4. Site Inspection
5. Site Inspection
6. non-efficacy related premature discontinuation due to lost to follow up (17 days on study; missed the primary endpoint evaluation at Day 112; per Appendix Listing 16.2.5.1, seen on Day 1= (b) (6); never seen again; did not return for at least one post-baseline visit)

The FDA Statistical Review and Evaluation of ANDA 200936 was finalized on 6/6/13. Six hundred and nine (609) subjects were enrolled and randomized. The sponsor's Modified Intent-to-Treat (MITT) and Per-Protocol (PP) populations1 had 605 and 460 subjects respectively. The FDA's Intent-to-Treat (FITT) and Per-Protocol (FPP) populations had 581 and 427 subjects respectively. In the FITT and FPP populations, the test and reference treatments were statistically significantly better than vehicle for the success rate at Visit 6/Day 112 (see Tables 26 and 27).

Table 26: FDA Statistical Efficacy analyses for the success rate at visit 6/Day 112 per FDA's FITT population

			P-value*	
Test	**Reference**	**Vehicle**	**Test vs. Vehicle**	**Reference vs. Vehicle**
22.41% (52/232)	28.63% (67/234)	10.43% (12/115)	0.0078	<0.0001

* p-values were derived from the two-sided Fisher's exact test.
Source: ANDA 200936 Diclofenac Sodium Gel, 3% Statistical Review and Evaluation by Huaixiang Li, Ph.D. finalized on 6/6/13, p. 11.

Table 27: FDA Statistical Efficacy analyses for the success rate at visit 6/Day 112 per FDA's FPP population

Test	Reference	The 90% CI for the Test versus Reference	Is the 90% CI within [-20%, 20%
26.14% (46/176)	32.32% (53/164)	-14.88%, 2.52%	Yes

Source: ANDA 200936 Diclofenac Sodium Gel, 3% Statistical Review and Evaluation by Huaixiang Li, Ph.D. finalized on 6/6/13, p. 11-12.

The comments on the sponsor's analyses and the conclusions of the FDA Statistical Review and Evaluations of ANDA 200936 were:

> Sponsor and FDA use same definition for the same success rate. There are minor differences between our and the sponsor's analyses results due to the differences between the sponsor's and the FDA's intent-to-treat and per-protocol populations.
>
> Conclusions Efficacy: The test and reference treatments were statistically significantly better than vehicle for the success rates (100% clearance of all AK lesions within the treatment area) at Visit 6/Day 112 for the FDA's intent-to-treat (FITT) population.
>
> Conclusions Equivalence: The test and reference treatments were found to be clinically equivalent for the success rates (100% clearance of all AK lesions within the treatment area) at Visit 6/Day 112 for the FDA's per-protocol (FPP) population.

C. Review of DARRTS Supp. Document No. 4

On April 26, 2010, the OGD issued a "refuse to receive" letter for ANDA 200936 under CFR 314.101(d)(3) for the following reasons:

> Your clinical endpoint bioequivalence study did not meet statutory requirements. For optimum sensitivity to detect differences between the test and reference products, the OGD requests that the treatment be administered for only 60 days and the primary endpoint be evaluated at the study day 90, 30 days after the end of treatment. This is the earliest time at which a significant success proportion is expected and would be the most likely time to detect differences between test and reference products. Your study applied the study treatment for 84 days which is longer than the treatment duration recommended for demonstrating bioequivalence of this product. Your longer treatment duration is likely to obscure potential differences in formulation performance. You may submit a protocol for review and concurrence before conducting another study.

On June 3, 2010 (DARRTS received date June 4, 2010), the lawyer representing the sponsor (i.e., Robert C. Thies, Hyman, Phelps & McNamara, P.C.) submitted an 18-page letter appealing the OGD's "refuse to receive" decision (DARRTS Supp. Document No. 4). Their letter requested that the Agency immediately rescind its April 26, 2010 letter that revoked OGD's prior receipt of ANDA 200936. The letter also stated that "OGD's unilateral revocation of its prior decision is scientifically incorrect and contrary to law and agency precedent." To support this statement, the sponsor argued that their study design was acceptable because: 1) Tolmar had conducted a BE study with a clinical endpoint of the same duration and of a similar design as the Phase 3 efficacy and safety study conducted to support the approval of Solaraze® Gel; and 2) the inactive ingredients used by Tolmar are different than those used in the RLD formulation; thus, Tolmar needed to establish the safety of its formulation by conducting a BE with clinical endpoint study (i.e., by conducting a clinical study with a 90-day treatment duration). In the letter, Tolmar stated that they had not sought the advice of the Agency prior to conducting their study (i.e., by submitting to the OGD a Controlled Correspondence or Protocol) because they anticipated a lengthy time for OGD response.

The sponsor's argument that the study design of Tolmar's BE study with a clinical endpoint is acceptable because it "matches" the study design of the Phase 3 efficacy and safety study conducted to support the approval of Solaraze® Gel is irrelevant. A BE study with a clinical endpoint study has a completely different purpose (i.e., to determine bioequivalence) than a Phase 3 efficacy and safety study (i.e., to determine efficacy and safety). A BE study with a clinical endpoint must be designed to best reveal whether there is any significant difference between the test product and the RLD. Thus, the OGD carefully considered what factors would be most likely to mask any such difference for this specific drug product, including a prolonged treatment duration, enrolling subjects with a large number of AK lesions (likely to decrease the possibility of achieving complete clearance of all AK lesions in the treatment area) or enrolling subjects with AKs located in an anatomic area believed to be more difficult to treat (such as the forearm/arm and back of the hand). The posted Draft Guidance on Diclofenac Gel/Topical, 3% specifically addresses these various factors by recommending that subjects be treated for the shortest time period that demonstrated efficacy (i.e., 60 days) and enrolling subjects with a defined number of AK lesions (i.e., at least five and no more than ten) located on the face or bald scalp. The sponsor also argues that the 90-day treatment duration based upon dose-response curved provided as "Figure 1" on p. 8-9. This argument fails to support their position because they failed to connect all of the data points for the active treatment in the first graph for Innovatory Study 03 (90 days). When the three points for the active treatment are connected, it clearly demonstrated that 90 days is at the top of the response curve for the active treatment. In addition, the third graph for Innovator Study 07 (90 days) failed to provide the data point for the active treatment at 90 days, i.e., the only two data points provided for the active treatment were at 60 and 120 days. while data points for the vehicle treatment were provided for baseline and at 60, 90, and 120 days).

The sponsor argued that because the ingredients used by Tolmar are different than those used in the RLD formulation, Tolmar needed to establish the safety of its formulation in a longer clinical study. This is not appropriate for a BE study. If safety issues are such a significant concern that longer safety studies are needed, then Tolmar needs to submit their drug product as a 505(b)

NDA, instead of an ANDA. NDA studies must explore a longer duration of treatment to ensure maintenance of the maximal effect and to ensure safety over the maximum period of use. In contrast, an ANDA applicant relies on FDA's previous finding that the RLD is safe and effective. ANDA studies do not include safety and/or efficacy studies, only bioequivalence studies.

VII. Formulation

The active ingredient, route of administration, dosage form, and strength of Tolmar Inc.'s Diclofenac Sodium Gel, 3% is the same as the RLD. The inactive ingredients of Tolmar Inc.'s Diclofenac Sodium Gel, 3% are the same as the RLD with the following exceptions:

- Tolmar Inc. added (b) (4), PEG-60 Hydrogenated Castor Oil, and (b) (4), Hydroxyethyl Cellulose, NF that are not found in the RLD.
- The RLD contains Hyaluronate Sodium and the Tolmar Inc.'s formulation does not.

Table 28: Formulation Comparison

Tolmar Inc.'s formulation			RLD's formulation	
Ingredient	**Function**	**Amount % w/w**	**Ingredient**	**% (w/w)**
Diclofenac Sodium, USP	Active Pharmaceutical Ingredient	3.0	Diclofenac Sodium	3.0
--	--	--	Hyaluronate Sodium	(b) (4)
Methoxypolyethylene Glycol 350, NF	(b) (4)		Polyethylene Glycol Monomethyl Ether	
PEG-60 Hydrogenated Castor Oil, NF			--	
Benzyl Alcohol, NF			Benzyl Alcohol	
Hydroxyethyl Cellulose, NF			--	
Purified Water, USP			Purified Water	

Source: ANDA 200936 Section 2.7 Clinical Summary, Summary_Bioequivalence_Tables, Table 6 and Section 3.2.P.1 for Tolmar Inc.'s formulation; ANDA 200936 Section 3.2.P.2.1.2 and Approved Labeling for RLD's

(b) (4)

Reviewer's comments: *The test formulation is qualitatively and quantitatively different from the reference product. While the active pharmaceutical ingredient is the same, the test product was formulated with PEG-60 hydrogenated Castor Oil, NF as* (b) (4) *instead of the Hyaluronate Sodium in the RLD. The test formulation also differs from the reference by including Hydroxyethyl Cellulose, NF as* (b) (4). (b) (4) (b) (4)

However, there is limited in-vitro data in the scientific literature demonstrating in an in-vitro Franz

(b) (4)

cell model, that the diffusion of 14C-labeled diclofenac was sustained and controlled by hyaluronan as compared to a butter control, that a depot or reservoir of the drug was formed in the epidermis, and that it was probably this layer that determined the rate of release of diclofenac within the skin.[44] *Thus, decreased efficacy might result if a generic sponsor, such as Tolmar, deletes the hyaluronate sodium from the formulation of Diclofenac Sodium Gel/Topical, 3%.*

VIII. Conclusions and Recommendation

A. Conclusions

1) The Division of Clinical Review (DCR) concurs with the recommendations of the Division of Scientific Inspection (DSI) and included all subjects from Dr. Miller's site in the listing of excluded subjects sent to the statisticians, i.e., the listing of subjects to be excluded from the FDA per-protocol and intent-to-treat subject populations when performing the FDA bioequivalence evaluation of Study TOL-AK-2008-02.

2) The FDA statistical analysis concluded that:

   Efficacy: The test and reference treatments were statistically significantly better than vehicle for the success rates (100% clearance of all AK lesions within the treatment area) at Visit 6/Day 112 for the FDA's intent-to-treat (FITT) population.

   Equivalence: The test and reference treatments were found to be clinically equivalent for the success rates (100% clearance of all AK lesions within the treatment area) at Visit 6/Day 112 for the FDA's per-protocol (FPP) population.[45]

   Thus, the statistical review of the BE study with clinical endpoint, i.e., Study TOL-AK-2008-02, concluded that the equivalence test passed for the success rate in the FDA's per-protocol (FPP) population and the two active treatment were statistically significantly better than the vehicle for the success rate in the FDA's intent-to-treat (FITT) population.

3) The Division of Clinical Review (DCR) concurs with the FDA statisticians that when using data from the FDA-determined study populations for Study TOL-AK-2008-02, data submitted to ANDA 200936 confirms the sponsor's results. Thus, the DCR concludes that this study is adequate to support approval of the application. However, the formulation differences between the test and reference products are substantial and may negatively impact the performance of the test product. This deficiency is being addressed by the Division of Bioequivalence II.

[44] Brown MB et al. The effect of hyaluronan on the in vitro deposition of diclofenac within the skin. *International Journal of Tissue Reactions*. 1995; 17(4):133 -140.
[45] ANDA 200936 Diclofenac Sodium Gel, 3% Statistical Review and Evaluation by Huaixiang Li, Ph.D., finalized on 5/24/13; 13 pg.

4) The clinical reviewer was not able to verify that the study protocol was approved by the two IRBs, and therefore is not able to conclude that study TOL-AK-2008-02 was in compliance with accepted ethical standards.

5) A draft guidance providing individual product bioequivalence recommendations for Diclofenac Sodium Gel/Topical, 3% is available at the following website: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240969.pdf

B. Recommendation

Recommend issuing a "Bioequivalence. Comments to be Provided to the Applicant" letter to the sponsor stating that the Division of Clinical Review has completed its review and has no further questions at this time.

_____ _____
Brenda S. Gierhart, M.D. Date
Medical Officer, Division of Clinical Review
Office of Generic Drugs

_____ _____
John R. Peters, M.D. Date
Director, Division of Clinical Review
Office of Generic Drugs

_____ _____
Ethan Stier, Ph.D. Date
Acting Director, Division of Bioequivalence II
Office of Generic Drugs

OFFICE OF GENERIC DRUGS CLINICAL REVIEW

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:200936 APPLICANT: Tolmar Inc.

DRUG PRODUCT: Diclofenac Sodium Topical Gel, 3%

The Division of Clinical Review has completed its review of TOL-AK-2008-02 and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, bioequivalence, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

John R. Peters, M.D.
Director, Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research

{See appended electronic signature page}

Ethan Stier, Ph.D.
Acting Director, Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

VIV. Appendix

References:

1) Aithal GP et al. Hepatic adducts, circulating antibodies, and cytokine polymorphisms in patients with diclofenac hepatotoxicity. *Hepatology*. 2004 May; 39 (5): 1430-1440.
2) Banks AT et al. Diclofenac-associated hepatotoxicity: analysis of 180 cases reported to the Food and Drug Administration as adverse reactions. *Hepatology*. 1995 Sep; 22(3): 820-7.
3) Bhogaraju A et al. Diclofenac-associated hepatitis. *South Med J.* 1999 Jul; 92(7): 711-3.
4) Bjornsson E et al. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. *Scandinavian J Gastroenterology*. 2005; 40: 1095-1101.
5) Boelsterli UA. Diclofenac-induced liver injury: a paradigm of idiosyncratic drug toxicity. *Toxicology and Applied Pharmacology.* 2003; 192: 307-322.
6) Brown MB et al. The effect of hyaluronan on the in vitro deposition of diclofenac within the skin. *International Journal of Tissue Reactions*. 1995; 17(4):133 -140.
7) Brown MB et al. An in vitro investigation into the effect of glycosaminoglycans on the skin partitioning and deposition of NSAIDs. *Int J Pharm.* 2001 Aug 28; 225(1-2): 113-21.
8) Brown MB and Jones SA. Hyaluronic acid: a unique topical vehicle for the localized delivery of drugs to the skin. *J Eur Acad Dermatol Venereol.* 2005 May; 19(3): 308-18.
9) De Abajo FJ et al. Acute and clinically relevant drug-induced liver injury: a population based case-control study. *Br J Clin Pharmacol*. 2004: 58(1):71 -80.
10) Greaves RRS et al. Inadvertent diclofenac rechallenge from generic and non-generic prescribing, leading to liver transplantation for fulminant liver failure. *Eur J Gastroenterol Hepatol.* 2001; 13: 71-73.
11) Griffiths C. Drug treatment of photoaged skin. *Drugs & Aging*. 1999 Apr; 14(4): 289-301.
12) Helfgott SM et al. Diclofenac-associated hepatotoxicity. *JAMA*. 1990 Nov 28; 264(20): 2660-2.
13) Jarvis B and DP Figgitt. Topical 3% diclofenac in 2.5% hyaluronic acid gel: A review of its use in patients with actinic keratosis. *Am J Clin Dermatol*. 2003; 4(3): 203-213.
14) Jones AL et al. Fulminant hepatic failure due to diclofenac treated successfully by orthotopic liver transplantation. *Transplantation Proceedings.* 1998; 30: 192-194.
15) Liao YH et al. Hyaluronan: pharmaceutical characterization and drug delivery. *Drug Deliv.* 2005 Nov-Dec; 12(6): 327-42.
16) Merk HF. Topical diclofenac in the treatment of actinic keratoses. *International Journal of Dermatology*. 2007; 46: 12-18.
17) Peters DC and RH Foster. Diclofenac/hyaluronic acid. *Drugs & Aging*. 1999 Apr; 14(4): 313-9.
18) Rivers JK. Diclofenac/hyaluronic acid: A viewpoint by Jason K. Rivers. *Drugs & Aging*. 1999 Apr; 14(4): 320-1.
19) Rossi R et al. Actinic keratosis. *International Journal of Dermatology*. 2007; 46: 895-904.
20) Rostom A et al. Nonsteroidal anti-inflammatory drugs and hepatic toxicity: a systematic review of randomized controlled trials in arthritis patients. *Clinical Gastroenterology and Hepatology.* 2005; 3: 489-498.
21) Willoughby DA. Diclofenac/hyaluronic acid: A viewpoint by Derek A. Willoughby. *Drugs & Aging*. 1999 Apr; 14(4): 320-1.
22) Wolf JE et al. Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratosis. *International Journal of Dermatology*. 2001; 40: 709-713.

Table 29: Diclofenac Sodium Gel NDAs (n=4: (b) (4))

Active Ingredient; Form/Route; Strength	NDA Number; Approval Date; Sponsor; Marketing Status; IND	Approved Indication	OND Review Division
(b) (4)			
Diclofenac Sodium; Gel/Topical; 3% (a) (b)	NDA 021005 Solaraze®; Approved 10/16/00; Fougera Pharmaceuticals Inc. (formerly Nycomed US Inc); Prescription; Related IND 041931 for treatment of simple basal cell carcinoma was submitted by Hyal Pharmaceutical Corporation Inc (Canada) on 4/1/93 (stamp date), is regulated by DDDP, is active (latest submission received 3/13/08) and current sponsor is Nycomed US Inc.	"for the topical treatment of actinic keratoses"	DDDP [Drug Classification listed in DARRTS is non-steroidal anti-inflammatory skin agents (4020700)]
Diclofenac Sodium; Gel/Topical; 1%	NDA 022122 Voltaren® Gel; Approved 10/17/07; Novartis Consumer Health, Inc; Prescription; Related IND 064334 for treatment of osteoarthritis was submitted on 11/28/00 (stamp date), is regulated by DAARP, is active (latest submission received 1/25/10) and current sponsor is Novartis Consumer Health, Inc.	"for the relief of the pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands"	DAAAP [Drug Classification listed in DARRTS is non-narcotic analgesics (5030250)]
(b) (4)			

Source: Search by this reviewer of DARRTS, Orange Book, Daily Med and Drugs@ FDA conducted on 6/10/13.
DAAAP=Division of Anesthesia, Analgesia, and Addiction Products
DARRTS=Document Archiving, Reporting & Regulatory Tracking System
DDDP=Division of Dermatology and Dental Products

(a) Regarding the pivotal Phase 3 clinical trials supporting approval of NDA 012005, per the Medical Officer Review of Original NDA 021005 and the Solaraze® Gel, 3% approved product labeling, three pivotal Phase 3 clinical trials were conducted in a total of 427 subjects (213 were randomized to Hyal's 3% diclofenac gel and 214 to gel vehicle):
   1) Study **CT1101-03** (US) randomized 120 subjects [59 were treated with diclofenac (27 with one treatment "block", 25 with two treatment "blocks", 7 with 3 treatment "blocks") [**NOTE**: if all lesions completely resolved in any given treatment 30-day "block", the subject was considered to have successfully completed the trial and could stop study drug]; 59 treated with vehicle (32 with one treatment "block", 21 with two treatment "blocks" and 6 with three treatment "blocks"); 2 subjects were excluded after randomization without evidence of drug use) at 4 sites.

2) Study **CT1101-04** (Canada) randomized 195 subjects [97 treated with diclofenac (49 randomized to 30 days treatment with 1.2 "blocks" per subject; 48 for 60 days with 1.4 "blocks" per subject); 98 treated with vehicle (49 randomized to 30 days treatment with 1.3 "blocks" per subject; 49 for 60 days with 1.3 "blocks" per subject) at 6 sites.
3) Study **CT1101-07** (US) randomized 112 subjects [56 were treated with diclofenac (54 with one treatment "block"; 2 with 2 treatment "blocks"); 55 treated with vehicle (all with 1 treatment "block"); 1 did not apply treatment] at one site.

Each subject had no fewer than five AK lesions in a major body area, contained in one to three (i.e., up to three major body areas were studied in any subject) 5 cm x 5 cm areas in a defined body region (i.e., scalp, forehead, face, forearm and back of hand). All subjects were 18 years of age or older (male and female) with no clinically significant medical problems outside of the AK lesions and had undergone a 60-day washout period from disallowed medications (masoprocol, etretinate, 5-fluorouracil, cyclosporine, retinoids, trichloroacetic acid/lactic acid/peel, 50% glycolic acid peel) and hyaluronan-containing cosmetics. Subjects were excluded from participation for reasons of known or suspected hypersensitivity to any Hyal's diclofenac gel ingredient, pregnancy, allergies to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), or other dermatological conditions in the designated treatment site which might affect the absorption of the study medication. Application of dermatologic products such as sunscreens, cosmetics, and other drug products was not permitted. Subjects were instructed to avoid sun exposure.

Duration of treatment was 30 or 60 days in CT1101-04, and up to 90 days in the other two pivotal Phase 3 studies. Subjects were instructed to apply twice daily a small amount (i.e., approximately 0.5 g; however, some subjects used a plastic vaginal applicator adapted for use on the medication tubes and indicating when 0.5 gm of gel had been expressed into it, others were instructed to apply an amount of gel the "size of a pea or "one finger tip unit") of Hyal's 3% diclofenac gel or vehicle gel onto each "block" of affected skin using their fingers, followed by gently smoothing the gel into the affected skin. For subjects with 3 blocks of affected skin, the maximum daily dose was 3.0 grams. Every effort was to be made to apply the study medication at the same times during the day.

The primary efficacy variable was complete clearing of the AK lesions at the 30-day post-treatment visit in all treated major body sites (see Tables 30 and 31). No long term subject follow-up (i.e., after the 30-day post-treatment assessment) was performed for the detection of recurrence. Compliance was determined by both "actual weight of medication used/expected use x 100%" and by "actual number of applications/expected number x 100%".The sponsor also conducted studies assessing the primary skin irritation potential, contact sensitization potential and phototoxicity potential of Hyal's 3% diclofenac gel and subjects were assessed for the presence of serum antidiclofenac antibodies.

Table 30: Complete Clearance of Actinic Keratosis Lesions at 30 Days Post-Treatment (all locations)

		Solaraze® Gel	Vehicle	p-value
Study 1	90 days treatment	27/58 (47%)	11/59 (19%)	<0.001
Study 2	90 days treatment	18/53 (34%)	10/55 (18%)	0.061
Study 3	60 days treatment	15/48 (31%)	5/49 (10%)	0.021
	30 days treatment	7/49 (14%)	2/49 (4%)	0.221

Source: Solaraze® Approved Labeling dated 11/06 available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=2508

Table 31: Complete Clearance of Actinic Keratosis Lesions at 30 Days Post-Treatment (by location)

		Scalp	Forehead	Face	Arm/ Forearm	Back of Hand
Study 1	**90 days treatment**					
	Solaraze®	1/4 (25%)	17/30 (57%)	9/17 (53%)	4/12 (33%)	6/16 (38%)
	Vehicle	3/9 (33%)	8/24 (33%)	5/17 (29%)	4/12 (33%)	0/14 (0)
	p-value	0.7646	0.0908	0.1682	1.000	0.0650

		Scalp	Forehead	Face	Arm/ Forearm	Back of Hand
Study 2	**90 days treatment**					
	Solaraze®	2/6 (33%)	9/19 (47%)	4/5 (80%)	5/8 (63%)	1/17 (6%)
	Vehicle	0/4 (0)	6/22 (27%)	2/8 (25%)	0/5 (0)	3/16 (19%)
	p-value	0.4235	0.1870	0.0727	0.0888	0.2818
Study 3	**60 days treatment**					
	Solaraze®	3/7 (43%)	13/31 (42%)	10/19 (53%)	0/1 (0)	2/8 (25%)
	Vehicle	0/6 (0)	5/36 (14%)	2/13 (15%)	0/2 (0)	1/9 (11%)
	p-value	0.2271	0.0153	0.0433	–	0.4637
	30 days treatment					
	Solaraze®	2/5 (40%)	4/29 (14%)	3/14 (21%)	0/0 (0)	0/9 (0)
	Vehicle	0/5 (0)	2/29 (7%)	2/18 (11%)	0/1 (0)	1/9 (11%)
	p-value	0.2299	0.3748	0.4322	–	0.6521
All data combined						
	Solaraze®	8/22 (36%)	43/109 (39%)	26/55 (47%)	9/21 (43%)	9/50 (18%)
	Vehicle	3/24 (13%)	21/111 (19%)	11/56 (20%)	4/20 (20%)	5/48 (10%)
	p-value	0.0903	0.0013	0.0016	0.2043	0.3662

Source: Solaraze® Approved Labeling dated 11/06 available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=2508

(b) Regarding the systemic absorption of topical Diclofenac Sodium Gel, 3%, the **Pharmacokinetics**, Absorption section of the approved **Solaraze®** labeling states:

> When Solaraze® is applied topically, diclofenac is absorbed into the epidermis. In a study in subjects with compromised skin (mainly atopic dermatitis and other dermatitic conditions) of the hands, arms or face, approximately 10% of the applied dose (2 grams of 3% gel over 100 cm^2) of diclofenac was absorbed systemically in both normal and compromised epidermis after seven days, with four times daily applications.
>
> After topical application of 2 g Solaraze® three times daily for six days to the calf of the leg in healthy subjects, diclofenac could be detected in plasma. Mean bioavailability parameters were AUC^{0-t} 9±19 ng/hr/mL (mean±SD) with a C_{max} of 4±5 ng/mL and a T_{max} of 4.5±8 hours. In comparison, a single oral 75 mg dose of diclofenac (Voltaren®) produced an AUC of 1600 ng/hr/mL. Therefore, the systemic bioavailability after topical application of Solaraze® is lower than after oral dosing.
>
> Blood drawn at the end of treatment from 60 subjects with AK lesions treated with Solaraze® in three adequate and well-controlled clinical trials was assayed for diclofenac levels. Each subject was administered 0.5 g of Solaraze® Gel twice a day for up to 105 days. There were up to three 5 cm × 5 cm treatment sites per subject on the face, forehead, hands, forearm, and scalp. Serum concentrations of diclofenac were, on average, at or below 20 ng/mL. These data indicate that systemic absorption of diclofenac in subjects treated topically with Solaraze® is much lower than that occurring after oral daily dosing of diclofenac sodium.
>
> No information is available on the absorption of diclofenac when Solaraze® is used under occlusion.

Table 32: Diclofenac Sodium Gel ANDAs (b) (4)

ANDA Number	Submission Date (letter)	Product	Sponsor	Indications	Status
200936 (a)	12/14/09 (stamp date 12/16/09)	Diclofenac Sodium Gel, 3%	Tolmar Inc	Topical treatment of actinic keratoses	Pending (as of 9/28/12)
(b) (4)					

ANDA Number	Submission Date (letter)	Product	Sponsor	Indications	Status
					(b) (4)

Source: Search by reviewer of Agency Document Archiving, Reporting & Regulatory Tracking System (DARRTS) conducted on 6/10/13.

(a) **ANDA 200936** submitted by Tolmar Inc for Diclofenac Sodium Gel, 3% contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) (i.e., Paragraph IV Certification) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. The first filing review for this ANDA resulted in "Filing Acknowledgement" letter being issued on 3/18/10. After the OGD Clinical Team finalized their Filing Review on 4/12/10, a "Refuse to Receive" letter issued on 4/26/10. After receiving correspondence from Tolmar on 6/3/10, the "Refuse to Receive" letter was rescinded on 6/11/10. ANDA 200936 contains the results of the bioequivalence study with clinical endpoint #TOL-AK-2008-02, a double blind, 2:2:1 randomized, parallel-group, vehicle-controlled multicenter study conducted in 609 subjects with 5 or more clinically typical visible, discrete, nonhyperkeratotic, non-hypertrophic lesions contained in one 25 cm^2 treatment area in one major body area (as defined in this study: forehead, central face, scalp, back of hands, and forearms). The primary efficacy variable was the percentage of subjects in the Per Protocol (PP) achieving complete clearance (defined as achieving 100% clearance of AK lesions in the designated treatment area) at Visit 6/Day 112/End of Treatment after 84 days of treatment. Per the sponsor, complete clearance (i.e., "success") was achieved in the PP population at Day 112 by 43 subjects (23.0%) treated with Tolmar's Diclofenac Sodium Gel, 3% and by 57 subjects (31.7%) treated with Solaraze® (diclofenac sodium) Gel, 3% (Doak Dermatologics, a division of Nycomed US) with the 90% CI (-16.8%, -0.5%). The primary superiority comparisons between each active treatment and the vehicle control were evaluated in the mITT population. Per the sponsor, complete clearance (i.e., "success") was achieved in the mITT population at Day 112 by 53 subjects (22.0%) treated with Tolmar's Diclofenac Sodium Gel, 3%. by 70 subjects (28.7%) treated with Solaraze®, and by 12 subjects (10.0%) treated with vehicle and both p-values for the comparison of active versus vehicle were statistically significant (i.e., $p<0.05$). Based upon the results of this study, the sponsor also concluded that the safety profile of the test product was not statistically or clinically different than that of the reference product.

Table 33: Diclofenac Sodium Gel, 3% Protocols Submitted to the OGD (b) (4)

Protocol Number; Available Documents	Drug Name; Dosage Form	Firm	Rec'd Date	Date of FDA Letter
(b) (4)				

Source: Search by reviewer conducted on 6/10/13 of OGD Tracking Systems, DBE Tracking Systems, Protocol Database at: http://cdsogd1/seltrack/Protocols.ASP

(a) (b) (4)

On 8/27/09, a 4-page document entitled "Request for Consultation", the draft Clinical Team review of OGD (b) (4) and the Draft Guidance on Diclofenac (Gel, 3%) were consulted to the OND DDDP. The OGD Request for Consultation stated:

> The OGD is preparing to post individual product bioequivalence recommendations on the FDA Guidance for Industry Webpage for generic versions of diclofenac sodium gel, 3% (reference listed drug, Solaraze® Gel,

3%). Please review the attached Draft Guidance on Diclofenac, in particular the recommended study design and endpoints for the clinical endpoint bioequivalence study in the treatment of actinic keratosis, and provide any comments. (b) (4)

The DDDP then requested the advice of the Capt. E. Dennis Bashaw, Pharm. D., Director, Division of Clinical Pharmacology 3 (DCP3) in OND. The DDDP Request for Consultation to DCP3 included the three documents previously sent by OGD to DDDP (in their Request for Consultation) and it stated:

> OGD has consulted DDDP regarding a draft guidance that they will post regarding diclofenac as it concerns bioequivalence for generic products. Please advise if Biopharm has any concerns from a biopharmaceutics viewpoint. Please comment on the paragraph under "Systemic Exposure" in the "Request for Consultation" letter, where OGD will not ask for any pharmacokinetic bioequivalence studies. Do you agree with this in the light of the fact that Solaraze may be getting new warnings in the label consistent with clinically significant systemic exposure?

The DCP3 response finalized on 10/1/09 contained the following conclusion and recommendation:

> While it is analytically feasible to detect in vivo plasma levels of diclofenac following topical application, the levels detected do not rise to the regulatory standard of assessing bioavailability at the site of action (as the blood is neither the site of action or intimately linked). Nor are the levels associated in a predictive fashion with toxicity such that they can be used to assure safety for the product. The proposed use of a bioequivalency study with clinical endpoints for the assessment of equivalency between topically applied generic and reference product is appropriate from a clinical pharmacology standpoint and supported by the regulations (see 21 CFR 320.24 (b)(4)).[46]

The DDDP response received on 11/6/09 contained the following recommendations:

> 1. It is recommended that the BE trial follow the protocol of the innovator studies where subjects should have no fewer than 5 AK lesions in a major body area, which was defined as one of five 5cm x 5cm regions: scalp (doesn't need to be bald), forehead, face, forearm, and hand. Subjects should be limited to 3 body areas as defined in the innovator studies. This will allow for maximum use and reflect clinical practice, as the indication for Solaraze does not limit treatment of AKs to only the face and bald scalp. The reason for this may have been that when all areas were combined, clearance of AKs reached statistical significance.
>
> 2. It is recommended that 5 cm by 5 cm regions be allowed in the trial rather than one contiguous 25 cm area, as AKs are discreet lesions that may or may not be clustered in one area. Using a 25 cm^2 contiguous area will limit the number of AKs that may be treated and may also increase the amount of non-diseased skin that would be exposed. It also will decrease the amount of drug product that the subject will be exposed to, as subjects used 0.5 gms per body region treated twice a day (3 regions = 1.5 gms). Thus the maximum used in the trials was 3.0 grams a day.
>
> 3. It is recommended that the statement in the guidance under the heading **"Additional comments regarding the BE study with clinical endpoint"**, in item #1: …Normally 0.5 gram of gel is used to cover one contiguous 25-cm^2 treatment area" should be deleted, as it is a not an accurate statement for the reasons sited above.
>
> 4. It is recommended that the statement in the guidance under the heading **"Additional comments regarding the BE study with clinical endpoint"**, in item #2: ….a disease such as AK, in which spontaneous resolution may occur" be deleted, as AKs very seldom, if ever spontaneously resolve. Actinic keratoses are precancerous lesions in which a significant percentage (from 6% - 12%) will evolve to squamous cell carcinoma, which depending on the location, can be fatal.
>
> 5. Regarding systemic bioavailability, although the systemic absorption of Solaraze is less than that of the oral drug product, the systemic bioavailability of Solaraze is (b) (4) that of the oral product. In a recent consult from the Office of Clinical Pharmacology-3, when comparing the topical diclofenac products, under maximum usage plasma AUC values of Solaraze where (b) (4) than Voltaren gel, and (b) (4) than Flector patch and Solaraze shows some accumulation with multiple dosing.[47] These former two products have had reports of systemic toxicity, particularly hepatic toxicity. There has been one confounding

[46] NDA 021005 Memorandum by Capt. E. Dennis Bashaw, Pharm.D., Director, Division of Clinical Pharmacology-3, finalized on 10/1/09, pg. 9 of 10.

(b) (4)

report of interstitial nephritis associated with Solaraze use (Subject was also on prilosec) and in the clinical trials for this product, 2-3% of subjects treated with Solaraze had elevated LFTs compared to none in placebo.

The Office of Clinical Pharmacology states that although the topical diclofenac products have been associated with systemic toxicity, without a concentration effect relationship, the value of in vivo plasma level equivalence requirements in preventing or managing this risk is speculative. While it is analytically feasible to detect in vivo plasma levels of diclofenac following topical application, the levels detected do not rise to the regulatory standard of assessing bioavailability at the site of action (as the blood is neither the site of action or intimately linked). Nor are the levels associated in a predictive fashion with toxicity such that they can be used to assure safety for the product. The proposed use of a bioequivalency study with clinical endpoints for the assessment of equivalency between topically applied generic and reference product is appropriate from a clinical pharmacology standpoint and supported by the regulations (see 21 CFR 320.24 (b)(4)).2[48] Thus, while the Offices of DDDP and Clinical Pharmacology agree with OGD that a PK trial for bioequivalence is not necessary and that it will not inform for safety, the proposed BE trial design should evaluate subjects for possible systemic effects through clinical monitoring of adverse events and monitoring of laboratory parameters that include routine chemistries, hematology parameters, and urinalysis as markers of systemic effects.

This protocol was closed after posting the Draft Guidance on Diclofenac Sodium Gel/Topical, 3% on 1/25/11 and sending an OGD regulatory letter containing responses to the sponsor's questions on 2/1/11.

Table 34: Diclofenac Sodium Gel, 3% Controlled Correspondences Submitted to the OGD (n=7: (b) (4)

CTL No.	Title	Description	Status	Doc Date	From
02-592 (a)	Diclofenac Sodium Gel, 3%	(b) (4)		10/8/02	(b) (4)
06-0132 (b)	Inactive ingredients			1/27/06	
06-0174 (c)	Inactive ingredients			1/27/06	
06-1336 (d)	Diclofenac Sodium Gel, 3%			9/18/06	
09-0608 (e)	Diclofenac gel (b) (4)			10/27/09	
11-0632 (f)	Diclofenac Sodium Gel, 3%			9/7/11	
12-0467 (g)	Diclofenac Sodium Gel, 3%			5/1/12	

Source: Search by reviewer conducted on 6/10/13 of OGD-Controls (Correspondence) Document Tracking System at: http://cdsogd1/SelTrack/DOC.ASP

[48] Office of Clinical Pharmacology-3 Consult; Memo-to-file, NDA 021005, N000; Finalized in DARRTS on 10/1/09, pg. 8.

(a) (b) (4)

(b)

(c)

(d)

(e)

(f)

(g)

Table 35: Lesion Counts in Subjects with Lesions on Back of Hands or Arm/Forearm Locations in the Modified Intent-to-Treat (mITT) Population

Unique Subject Number	Treatment	Body Area	Lesion Count Visit 1	Lesion Count Visit 6
Diclofenac Sodium n=33 (Arms=9; Back of hands=24); Success 3/33=9.1%				
(b) (6)	Diclofenac Sodium	Back of hands	9	3
	Diclofenac Sodium	Back of hands	6	0
	Diclofenac Sodium	Back of hands	12	2
	Diclofenac Sodium	Back of hands	6	5
	Diclofenac Sodium	Back of hands	6	2
	Diclofenac Sodium	Arms	12	8
	Diclofenac Sodium	Back of hands	5	5
	Diclofenac Sodium	Back of hands	5	2

Unique Subject Number	Treatment	Body Area	Lesion Count Visit 1	Lesion Count Visit 6
(b) (6)	Diclofenac Sodium	Back of hands	5	1
	Diclofenac Sodium	Arms	6	0
	Diclofenac Sodium	Arms	7	0
	Diclofenac Sodium	Back of hands	9	2
	Diclofenac Sodium	Arms	5	6
	Diclofenac Sodium	Back of hands	6	6
	Diclofenac Sodium	Arms	6	1
	Diclofenac Sodium	Back of hands	8	3
	Diclofenac Sodium	Arms	6	1
	Diclofenac Sodium	Back of hands	5	5
	Diclofenac Sodium	Back of hands	5	2
	Diclofenac Sodium	Arms	6	6
	Diclofenac Sodium	Back of hands	6	2
	Diclofenac Sodium	Back of hands	7	5
	Diclofenac Sodium	Back of hands	6	6
	Diclofenac Sodium	Back of hands	9	9
	Diclofenac Sodium	Back of hands	6	6
	Diclofenac Sodium	Back of hands	6	2
	Diclofenac Sodium	Back of hands	7	6
	Diclofenac Sodium	Back of hands	9	4
	Diclofenac Sodium	Back of hands	5	1
	Diclofenac Sodium	Back of hands	5	4
	Diclofenac Sodium	Back of hands	7	5
	Diclofenac Sodium	Arms	7	3
	Diclofenac Sodium	Arms	6	1
Solaraze n=31 (Arms=15; Back of hands=16); Success 4/31=12.9%				
(b) (6)	Solaraze	Back of hands	7	1
	Solaraze	Back of hands	5	0
	Solaraze	Back of hands	5	7
	Solaraze	Arms	6	3
	Solaraze	Back of hands	7	1
	Solaraze	Arms	6	5
	Solaraze	Back of hands	10	7
	Solaraze	Arms	7	4
	Solaraze	Back of hands	12	12
	Solaraze	Arms	5	1
	Solaraze	Arms	5	3
	Solaraze	Back of hands	6	6
	Solaraze	Back of hands	6	1
	Solaraze	Back of hands	5	8
	Solaraze	Arms	7	7
	Solaraze	Arms	5	2
	Solaraze	Arms	6	6

Unique Subject Number	Treatment	Body Area	Lesion Count Visit 1	Lesion Count Visit 6
(b) (6)	Solaraze	Arms	11	5
	Solaraze	Arms	6	6
	Solaraze	Back of hands	5	5
	Solaraze	Back of hands	6	4
	Solaraze	Arms	5	5
	Solaraze	Back of hands	6	6
	Solaraze	Back of hands	6	6
	Solaraze	Back of hands	6	6
	Solaraze	Arms	5	4
	Solaraze	Back of hands	6	0
	Solaraze	Arms	8	7
	Solaraze	Back of hands	5	0
	Solaraze	Arms	7	4
	Solaraze	Arms	8	0
Vehicle n=21 (Arms=13; Back of hands=8); Success 0/21=0%				
(b) (6)	Vehicle	Back of hands	5	3
	Vehicle	Arms	7	6
	Vehicle	Back of hands	6	3
	Vehicle	Back of hands	6	3
	Vehicle	Arms	5	6
	Vehicle	Arms	7	14
	Vehicle	Arms	5	3
	Vehicle	Arms	10	8
	Vehicle	Back of hands	7	5
	Vehicle	Arms	6	2
	Vehicle	Arms	5	5
	Vehicle	Back of hands	6	6
	Vehicle	Arms	5	5
	Vehicle	Arms	6	6
	Vehicle	Back of hands	5	5
	Vehicle	Back of hands	7	7
	Vehicle	Arms	7	2
	Vehicle	Back of hands	7	2
	Vehicle	Arms	5	2
	Vehicle	Arms	24	7
	Vehicle	Arms	5	7

Source: Analysis by this reviewer of Appendix Listing 16.2.6.2 entitled "Listing of Lesion Counts in mITT (LOCF) Population": p.235-539.

(b) (4)

Table 36: Lesion Counts in Subjects with Lesions on Back of Hands or Arm/Forearm Locations in the Per Protocol (PP) Population

Unique Subject Number	Treatment	Body Area	Lesion Count Visit 1	Lesion Count Visit 6
Diclofenac Sodium n=28 (Arms=9; Back of hands=19); Success 3/28=10.7%				
(b) (6)	Diclofenac Sodium	Back of hands	9	3
	Diclofenac Sodium	Back of hands	6	0
	Diclofenac Sodium	Back of hands	6	2
	Diclofenac Sodium	Arms	12	8
	Diclofenac Sodium	Back of hands	5	5
	Diclofenac Sodium	Back of hands	5	2
	Diclofenac Sodium	Back of hands	5	1
	Diclofenac Sodium	Arms	6	0
	Diclofenac Sodium	Arms	7	0
	Diclofenac Sodium	Arms	5	6
	Diclofenac Sodium	Back of hands	6	6
	Diclofenac Sodium	Arms	6	1
	Diclofenac Sodium	Back of hands	8	3
	Diclofenac Sodium	Arms	6	1
	Diclofenac Sodium	Back of hands	5	5
	Diclofenac Sodium	Arms	6	6
	Diclofenac Sodium	Back of hands	6	2
	Diclofenac Sodium	Back of hands	7	5
	Diclofenac Sodium	Back of hands	6	6
	Diclofenac Sodium	Back of hands	9	9
	Diclofenac Sodium	Back of hands	6	2
	Diclofenac Sodium	Back of hands	7	6
	Diclofenac Sodium	Back of hands	9	4
	Diclofenac Sodium	Back of hands	5	1
	Diclofenac Sodium	Back of hands	5	4
	Diclofenac Sodium	Back of hands	7	5
	Diclofenac Sodium	Arms	7	3
	Diclofenac Sodium	Arms	6	1
Solaraze n=24 (Arms=12; Back of hands=12); Success 4/24=16.7%				
(b) (6)	Solaraze	Back of hands	7	1
	Solaraze	Back of hands	5	0
	Solaraze	Arms	6	3
	Solaraze	Back of hands	7	1
	Solaraze	Arms	6	5
	Solaraze	Back of hands	10	7
	Solaraze	Arms	7	4
	Solaraze	Arms	5	1
	Solaraze	Arms	5	3

Unique Subject Number	Treatment	Body Area	Lesion Count Visit 1	Lesion Count Visit 6
(b) (6)	Solaraze	Back of hands	6	1
	Solaraze	Arms	5	2
	Solaraze	Arms	6	6
	Solaraze	Arms	11	5
	Solaraze	Back of hands	5	5
	Solaraze	Back of hands	6	4
	Solaraze	Back of hands	6	6
	Solaraze	Back of hands	6	6
	Solaraze	Back of hands	6	6
	Solaraze	Arms	5	4
	Solaraze	Back of hands	6	0
	Solaraze	Arms	8	7
	Solaraze	Back of hands	5	0
	Solaraze	Arms	7	4
	Solaraze	Arms	8	0
Vehicle n=17 (Arms=12; Back of hands=5); Success 0/17=0%				
(b) (6)	Vehicle	Back of hands	5	3
	Vehicle	Back of hands	6	2
	Vehicle	Arms	5	6
	Vehicle	Arms	7	14
	Vehicle	Arms	5	3
	Vehicle	Arms	10	8
	Vehicle	Arms	6	2
	Vehicle	Arms	5	5
	Vehicle	Back of hands	6	6
	Vehicle	Arms	5	5
	Vehicle	Arms	6	6
	Vehicle	Back of hands	7	7
	Vehicle	Arms	7	2
	Vehicle	Back of hands	7	2
	Vehicle	Arms	5	2
	Vehicle	Arms	24	7
	Vehicle	Arms	5	7

Source: Analysis by this reviewer of Appendix Listing 16.2.6.1 entitled “Listing of Lesion Counts in PP Population”; p. 2-234.

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/s/

BRENDA S GIERHART
06/12/2013

JOHN R PETERS
06/12/2013

ETHAN M STIER
06/12/2013

Addendum to Clinical Review
of a Bioequivalence Study with a Clinical Endpoint

ANDA: 200936

Drug Product: Diclofenac Sodium Gel, 3%

Sponsor: Tolmar Inc.

Reference Listed Drug (RLD): Solaraze® (diclofenac sodium) Gel, 3% (NDA 021005) Nycomed US

Original Submission Date: 12/14/09

Original Primary Reviewer: Brenda S. Gierhart, M.D.

On 12/14/09, ANDA 200936 was submitted by Tolmar Inc. for Diclofenac Sodium Gel, 3% and it contained the results of the bioequivalence (BE) study with clinical endpoint **#TOL-AK-2008-02**, a double blind, 2:2:1 randomized, parallel-group, vehicle-controlled multicenter study conducted in 609 subjects with 5 or more clinically typical visible, discrete, nonhyperkeratotic, non-hypertrophic lesions contained in one 25 cm^2 treatment area in one major body area (as defined in this study: forehead, central face, scalp, back of hands, and forearms) treated twice daily for **84 days**. The primary efficacy variable was the percentage of subjects in the Per Protocol (PP) achieving complete clearance (defined as achieving 100% clearance of AK lesions in the designated treatment area) at **study day 112**/End of Treatment (i.e., 28 days after completion of treatment).

On 1/25/11, the Draft Guidance on Diclofenac Sodium Gel/Topical, 3% was posted.[1] Prior to the posting of this guidance, no advice regarding establishing BE for this drug product had been provided by the OGD to anyone. The BE study with clinical endpoint in this Draft Guidance recommended administering study drug twice daily for **60 days** and evaluating the primary endpoint on **study day 90** (30 days after completion of treatment). This treatment duration and time point for determining efficacy was recommended because it was the shortest of the three different treatment periods evaluated in the pivotal Phase 3 studies (i.e., 30 days, 60 days and 90 days) conducted to support approval of the RLD that demonstrated efficacy (see Table 1).

Table 1: Complete Clearance of Actinic Keratosis Lesions at 30 Days Post-Treatment (all locations)

		Solaraze® Gel	Vehicle	p-value
Study 1	90 days treatment	27/58 (47%)	11/59 (19%)	<0.001
Study 2	90 days treatment	18/53 (34%)	10/55 (18%)	0.061
Study 3	60 days treatment	15/48 (31%)	5/49 (10%)	0.021
	30 days treatment	7/49 (14%)	2/49 (4%)	0.221

[1] The document written to support posting the Draft Guidance on Diclofenac Sodium Gel/Topical, 3% was "Review of a [redacted] (b) (4) by Brenda S. Gierhart, MD finalized on 1/6/11 (44 pg).

Source: Solaraze® Approved Labeling dated 11/06 available at:
http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=2508

On 7/10/11, the OGD Clinical Review for ANDA 200936 was finalized and it stated that the longest treatment duration evaluated by the innovator in their Phase 3 studies (i.e., 90 days) was more likely to capture only the maximum effect and not the rate and extent of drug delivery to the site of action. Thus, it was concluded that the study design of TOL-AK-2008-02 with an 84-day treatment duration was not acceptable because the longer, 84-day treatment duration was likely to minimize any differences between the test and reference treatments with regard to rate and/or extent of drug delivery to the site of action.

On 7/10/11, a Complete Response-Fatal Flaw letter was issued for ANDA 200936 with the following section addressing the BE with clinical endpoint study:

> The FDA has determined that the bioequivalence study submitted for this application is unacceptable under 21 CFR 314.127(a)(6)(i), for the following reasons:
>
> > The design of TOL-AK-2008-02 is unacceptable because it may not be adequately sensitive to detect a difference in product performance. According to 21 CFR 320.24 (b)(4), well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for the purposes of demonstrating bioequivalence, are the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence. Clinical trials as an approach to demonstrate bioequivalence generally are considered insensitive.[2] To improve the sensitivity of comparative clinical trials, the dosing regimen and period of dosing must be carefully selected. If the doses chosen for both agents are too high then subjects may reach an upper threshold in response, leading to a false conclusion of equivalence.[3] We consider the same to be true of longer treatment durations.
> >
> > The primary difference between the 3 pivotal Phase 3 clinical studies supporting approval of the RLD was the duration of treatment (i.e., 30, 60 or 90 days). The shortest treatment duration demonstrating a statistically significant difference between active drug and placebo was 60 days of treatment. Increasing the treatment duration to 90 days resulted in an overall higher complete clearance rate only for the vehicle. Thus, the 90 day treatment duration is more likely to capture only the maximum effect and not the rate and extent of drug delivery to the site of action. The OGD recommends that Diclofenac Sodium Gel/Topical 3% be administered twice daily for <u>60 days</u> with the primary efficacy endpoint evaluation at the <u>30-day</u> post-treatment assessment in the bioequivalence study with clinical endpoint. Thus, the study design of TOL-AK-2008-02 with an 84-day treatment duration and the primary efficacy endpoint evaluation at the 28-day post-treatment assessment is not acceptable. The longer, 84-day treatment duration is likely to minimize any differences between the test and reference treatment effects.

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[2] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Bioavailability and bioequivalence studies for orally administered drug products-general considerations. March 2003; pg. 9.
[3] Jones B et al. Trials to assess equivalence: the importance of rigorous methods. *BMJ.* 1996; 313: 36-9.

In order to resolve these deficiencies, you will need to provide the following additional information:

…

4. Conduct a clinical endpoint study designed to have the maximum sensitivity for detecting differences in product performance between the test and reference products.

On 9/27/11, Tolmar's lawyers submitted a Request for Dispute Resolution re: Non-approval of ANDA 200936 to Helen Winkle and Janet Woodcock, MD and simultaneously submitted the Dispute Resolution document (with 9 attachments) as Supp. Document #13 to ANDA 200936 as a "Resubmission/After Action-Complete" and "Quality/Response to Information Request". The submission was reviewed in detail by the Division of Clinical Review and a reassessment of the acceptability of Tolmar's BE study with clinical endpoint was conducted by the Division of Clinical Review. After re-review of the innovator Phase 3 efficacy and safety studies, the DCR revised their previous evaluation of Tolmar's submitted bioequivalence (BE) study with clinical endpoint based upon a similar mean difference between Solaraze Gel and vehicle at both after 60 days of treatment (i.e., mean difference 21%) and after 90 days of treatment (i.e., mean difference 22%).

Table 2: Complete Clearance of Actinic Keratosis Lesions at 30 Days Post-Treatment (all locations)

	Treatment duration	Solaraze® Gel	Vehicle	Difference in %	Mean Difference in %	p-value
Study 1	90 days	27/58 (47%)	11/59 (19%)	28%	22%	<0.001
Study 2	90 days	18/53 (34%)	10/55 (18%)	16%		0.061
Study 3	60 days	15/48 (31%)	5/49 (10%)	21%	21%	0.021
	30 days	7/49 (14%)	2/49 (4%)	10%	10%	0.221

Sources: Calculation of Difference in % and Mean Difference in % by this reviewer; Solaraze® Approved Labeling dated 11/06 available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=2508

The DCR now concurs with Tolmar that their BE with clinical endpoint study is adequately sensitive to demonstrate whether their test drug product and the reference listed drug (RLD) are bioequivalent or not. Thus, Tolmar's BE with clinical endpoint study is now eligible for a full review. The DCR will be sending a Request for Consultation to the Division of Scientific Information pertaining to study site inspections and also sending a request for a formal statistical review of Tolmar's study.

_____ _____

Brenda S. Gierhart, M.D. Date
Acting Deputy Director, Division of Clinical Review
Office of Generic Drugs

_____ _____

John R. Peters, M.D. Date
Acting Director, Division of Clinical Review
Office of Generic Drugs

_____ _____

Barbara M. Davit, Ph.D., J.D. Date
Acting Director, Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: HFD-600 K. Webber/B. Davit/J. Peters/B. Gierhart/A. Sigler/N. Patel

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/s/

BRENDA S GIERHART
12/12/2011

JOHN R PETERS
12/12/2011

BARBARA M DAVIT
12/13/2011

Review of a Bioequivalence Study with a Clinical Endpoint

ANDA #200936
Tolmar Inc.

Diclofenac Sodium Gel, 3%

Brenda S. Gierhart, M.D.
Clinical Review Team

Submission dates reviewed:
12/14/09, 6/3/10, 7/8/10 & 4/19/11 (DARRTS letter dates)

Date of Review: 7/7/11

Table of Contents

Review of a Bioequivalence Study with a Clinical Endpoint for ANDA 200936

Executive Summary

ANDA 200936 was originally submitted on December 14, 2009 and the OGD issued a letter acknowledging receipt of the application on March 18, 2010. However, a filing review by the Clinical Review Team completed on April 12, 2010 found the study unacceptable because the study design was not adequately sensitive for detecting differences in formulation performance. Therefore, the OGD rescinded the acknowledgement letter of March 18 and issued a Refuse to Receive letter on April 26. The firm responded on June 3, 2010 with their justification for the study design, and the OGD reversed the prior decision and officially received the application for review on June 11, 2010, affirming the original date of receipt.

Tolmar's generic version of Diclofenac Sodium Gel, 3% has a markedly different formulation than that of the Reference Listed Drug (RLD). The RLD formulation contains (b) (4) odium hyaluronate, (b) (4) . The generic does not contain hyaluronate and instead contains hydroxyethyl cellulose as (b) (4) along with PEG-60 hydrogenated castor oil. The resulting viscosity is only (b) (4) of that of the RLD. This could result in a difference in efficacy that could be missed on a clinical endpoint study that is not adequately sensitive.

The sponsor conducted a double-blind, randomized, multi-center, parallel-group study in the treatment of actinic keratoses (AK) to demonstrate that Tolmar Inc.'s Diclofenac Sodium Gel, 3%, is bioequivalent to the RLD, Nycomed US's Solaraze® Gel, 3%. The protocol incorporated an 84-day treatment period, whereas the Agency recommends a treatment duration of 60 days. Subject evaluation for complete clearance of all AK lesions is to occur 30 days after the end of treatment. The draft Bioequivalence (BE) Recommendation for this specific product had not been posted at the time this application was submitted.

In the safety and efficacy studies conducted to support approval of the RLD, the Solaraze® Gel was statistically superior to vehicle (placebo) 30 days after completion of the 60-day treatment period. In separate studies of 90 days treatment duration, the treatment efficacy was somewhat higher, but the vehicle success rate was also higher, resulting in one study showing a non-significant difference between active treatment and vehicle. Based on these results, the OGD has concluded that the optimum duration of treatment for a bioequivalence study in the treatment of AK is 60 days.

It should be noted per 21 CFR 320.24 (b)(4), well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for the purposes of demonstrating bioequivalence, are the least accurate, sensitive, and reproducible of the general approaches for

measuring bioavailability or demonstrating bioequivalence. Clinical trials as an approach to demonstrate bioequivalence generally are considered insensitive.[1] To improve the sensitivity of comparative clinical trials, the dosing regimen and period of dosing must be carefully selected. If the doses chosen for both agents are too high then subjects may reach an upper threshold in response, leading to a false conclusion of equivalence.[2] The same may be true of a longer treatment duration. In all three of the Innovator's pivotal Phase 3 clinical studies supporting approval (see Tables 1 and 2), the primary efficacy variable was evaluated at the 30-day post-treatment visit and the dosing regimen was twice daily with approximately 0.5 gram of gel per "block" of affected skin. The primary difference between the three pivotal Phase 3 clinical studies supporting approval was the duration of treatment (i.e., 30, 60 or 90 days) and the shortest treatment duration demonstrating a statistically significant difference for the primary endpoint was 60 days of treatment. Increasing the treatment duration to 90 days resulted in an overall higher complete clearance rate for the vehicle. Thus, the 90 day treatment duration is more likely to capture only the maximum effect and not the rate and extent of drug delivery to the site of action. Diclofenac Sodium Gel/Topical 3% administered twice daily for 60 days with the primary efficacy endpoint evaluated at the 30-day post-treatment assessment is recommended by the OGD in the individual product guidance for a bioequivalence study with clinical endpoint. The study design of TOL-AK-2008-02 with an 84-day treatment duration is not acceptable. The longer, 84-day treatment duration is likely to minimize any differences between the test and reference treatments with regard to rate and/or extent of drug delivery to the site of action.

Table 1: Complete Clearance of Actinic Keratosis Lesions at 30 Days Post-Treatment (all locations)

		Solaraze® Gel	Vehicle	p-value
Study 1	90 days treatment	27/58 (47%)	11/59 (19%)	<0.001
Study 2	90 days treatment	18/53 (34%)	10/55 (18%)	0.061
Study 3	60 days treatment	15/48 (31%)	5/49 (10%)	0.021
	30 days treatment	7/49 (14%)	2/49 (4%)	0.221

Source: Solaraze® Approved Labeling dated 11/06 available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=2508

Table 2: Complete Clearance of Actinic Keratosis Lesions at 30 Days Post-Treatment (by location)

		Scalp	Forehead	Face	Arm/Forearm	Back of Hand
Study 1	**90 days treatment**					
	Solaraze®	1/4 (25%)	17/30 (57%)	9/17 (53%)	4/12 (33%)	6/16 (38%)
	Vehicle	3/9 (33%)	8/24 (33%)	5/17 (29%)	4/12 (33%)	0/14 (0)
	p-value	0.7646	0.0908	0.1682	1.000	0.0650

[1] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Bioavailability and bioequivalence studies for orally administered drug products-general considerations. March 2003; pg. 9.
[2] Jones B et al. Trials to assess equivalence: the importance of rigorous methods. *BMJ.* 1996; 313: 36-9.

		Scalp	Forehead	Face	Arm/Forearm	Back of Hand
Study 2	**90 days treatment**					
	Solaraze	2/6 (33%)	9/19 (47%)	4/5 (80%)	5/8 (63%)	1/17 (6%)
	Vehicle	0/4 (0)	6/22 (27%)	2/8 (25%)	0/5 (0)	3/16 (19%)
	p-value	0.4235	0.1870	0.0727	0.0888	0.2818
Study 3	**60 days treatment**					
	Solaraze	3/7 (43%)	13/31 (42%)	10/19 (53%)	0/1 (0)	2/8 (25%)
	Vehicle	0/6 (0)	5/36 (14%)	2/13 (15%)	0/2 (0)	1/9 (11%)
	p-value	0.2271	0.0153	0.0433	–	0.4637
	30 days treatment					
	Solaraze	2/5 (40%)	4/29 (14%)	3/14 (21%)	0/0 (0)	0/9 (0)
	Vehicle	0/5 (0)	2/29 (7%)	2/18 (11%)	0/1 (0)	1/9 (11%)
	p-value	0.2299	0.3748	0.4322	–	0.6521
All data combined	Solaraze	8/22 (36%)	43/109 (39%)	26/55 (47%)	9/21 (43%)	9/50 (18%)
	Vehicle	3/24 (13%)	21/111 (19%)	11/56 (20%)	4/20 (20%)	5/48 (10%)
	p-value	0.0903	0.0013	0.0016	0.2043	0.3662

Source: Solaraze® Approved Labeling dated 11/06 available at:
http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=2508

Tolmar's subject population is also not optimal for ensuring adequate sensitivity of the study to detect differences between the test and reference products. Although Tolmar specified an appropriate lower limit to baseline lesion count (at least 5 AK lesions), it did not specify a minimum size for the baseline lesions included in that count, and no upper limit was set. The data presented show that more subjects receiving the reference product had lesion counts above 10 compared to subjects receiving the test product. This could have lowered the reference product success rate, thereby making the test and reference results more similar.

Tolmar also enrolled subjects with AK lesions on different body areas instead of enrolling only subjects with AK lesions on the face or balding forehead as specified in the Draft BE guidance. Although in the NDA studies fewer subjects had AK lesions on the back of the hands or forearms/arms, the success rate appears to be different for lesions in those areas than for lesions on the face or forehead. Therefore enrollment of subjects with lesions on the back of the hands or forearms/arms may have increased the variability in treatment response and confounded the study results.

The Final Study Report for Study TOL-AK-2008-02 states that 609 subjects were enrolled and randomized, 608 subjects were in the Intent-to-Treat (ITT; Safety) population, 605 subjects were included in the modified Intent-to-Treat (mITT) population and 460 subjects were included in

the Per Protocol (PP) population.[3] Per the sponsor, complete clearance [defined as 100% clearance of AK lesion count in the designated treatment area(s)] was achieved in 43 subjects (23.0%) in the Diclofenac Sodium Gel treatment group and 57 subjects (31.7%) in the Solaraze® Gel treatment group in the PP population at visit 6/day 112 (i.e., week 16; 4 weeks after treatment ended).[4] The sponsor concluded that the 90% Confidence Interval (CI) of the difference in the success rate between the test and reference products at visit 6 in the PP population is (-0.168, -0.005), which is within the bioequivalence limits of (-0.20 to +0.20).[5] Per the sponsor, both test and reference products are shown to be statistically superior to vehicle (p=0.0081 and p=0.0001, respectively) at visit 6 in the mITT population, demonstrating that the study is sufficiently sensitive to discriminate differences between products.

Reviewer's comment: *Although the difference in success rates is within the established bioequivalence limits, a 90% confidence interval entirely below 0 suggests that the test and reference products may not be truly equivalent in performance. Furthermore, superiority over placebo (vehicle) only ensures study sensitivity at the lower end of the dose response curve and does not address the limitations of a study with a longer treatment duration that may reach an upper threshold in response and lead to a false conclusion of equivalence.*

I. Recommendation on Approval

The formulation differences between the test and reference products are substantial and may negatively impact the performance of the test product. Due to inadequate sensitivity of the study design, the Clinical Review Team concludes that the data submitted to ANDA 200936 are not adequate to demonstrate bioequivalence of Tolmar Inc.'s Diclofenac Sodium Gel, 3%, with the reference listed drug, Nycomed US's Solaraze® Gel, 3%. Therefore, the study is not adequate to support approval of the application.

II. Summary of Clinical Findings

Due to inadequate sensitivity of the study design, the data presented in this ANDA 200936 are not adequate to demonstrate that Tolmar Inc.'s Diclofenac Sodium Gel, 3%, is bioequivalent to the reference listed drug, Nycomed US's Solaraze® Gel, 3%, using the primary endpoint of complete clearance of AK lesions (zero clinically visible) in the treated area at visit 6/day 112 (i.e., week 16; 4 weeks after completion of 84 days of treatment).

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[3] Per Final Study Report TOL-AK-2008-02 (pg. 32 of 217), the following analysis populations contained subjects who:
ITT (Safety Population): 1) enrolled into the study, AND 2) applied at least one dose of study drug.
mITT: 1) enrolled into the study, 2) applied at least one dose of study drug, 3) had a baseline lesion count, AND 4) had at least one post-baseline lesion count.
PP: 1) enrolled into the study, 2) met inclusion/exclusion criteria, 3) maintained compliance with study drug applications (applied at least 80% and not more than 120% of doses and did not miss 10 or more consecutive applications of study drug), 4) took no concomitant medications prohibited by the protocol, 5) had no other significant protocol violations, AND 6) returned for visit 6/day 112 within the visit window and had a lesion count in this visit, OR 7) were discontinued early due to insufficient therapeutic response (after completing at least 28 days of study drug use, with a compliance rate of at least 80%).
[4] Final Study Report TOL-AK-2008-02 (pg. 43 of 217).
[5] Per Final Study Report TOL-AK-2008-02 (pg. 43 of 217), the sponsor calculated the confidence interval using Wald's method with Yates' continuity correction.

CLINICAL REVIEW

A. Brief Overview of Clinical Program

Study TOL-AK-2008-02 was a randomized, double-blind, comparative study of Tolmar Inc.'s Diclofenac Sodium Gel, 3%, versus the reference listed drug, Nycomed US's Solaraze® Gel, 3%, in the treatment of AK. Six hundred and nine (609) subjects with five or more clinically typical visible, discrete, non-hyperkeratotic, non-hypertrophic AK lesions contained in one 25 cm^2 treatment area in one major body area as defined in this study: forehead, central face, scalp, back of hands, and forearms were randomized in a 2:2:1 ratio to receive the test, reference, or vehicle (placebo) gel twice daily for 84 days (12 weeks).

B. Comparative Efficacy

The primary endpoint of this study evaluated by the sponsor was the percentage of subjects in the PP population achieving complete clearance of AK lesions in the treated area at the 4-week follow-up visit (i.e., visit 6/day 112/week 16) after completion of 12 weeks of treatment. According to the sponsor, the success rate in the PP population at visit 6 was 23.0% in the test group and 31.7% in the reference group. The 90% CI of the difference in success rate between the two active products is (-0.168, -0.005), which is within the established bioequivalence limits of (-0.20 to +0.20). However, this confidence interval is entirely below zero, suggesting a difference between products, despite meeting the established limits. Given the specific differences in product formulations and the study design factors that are expected to result in decreased sensitivity of the study to detect differences in product performance, this study cannot be considered adequate to support a finding of bioequivalence between the test and reference products.

C. Comparative Safety

The sponsor concluded that the safety profile of the test product was not statistically or clinically different than that of the reference product in the treatment of actinic keratoses.[6]

A total of 158 subjects [i.e., 69 (28.6%) in the test group, 58 (23.6%) in the reference group, and 31 (25.6%) in the vehicle group] experienced one or more treatment-emergent adverse events. Twenty (3.3%) subjects (8 test, 9 reference, 3 vehicle) discontinued the study due to "withdrawal due to adverse event". An additional 15 subjects (11 test, 3 reference, 1 vehicle) withdrew due to a local skin reaction, which the sponsor coded as "Other". Local skin reactions recorded during the assessment of the treated area were not reported as AEs, unless, in the opinion of the Investigator, the event qualified as an AE.

Reviewer's comment: *The more than three-fold higher number of test subjects withdrawing due to a local skin reaction suggests that the test formulation may be more irritating than the RLD.*

Skin-related adverse events listed in the "Skin and subcutaneous tissue disorders" MedDRA system organ class, regardless of relationship to the study medication, occurred in 22 subjects (12 test, 8 reference, 2 vehicle). Skin-related adverse events probably or definitely related to study medication occurred in 17 subjects (9 test, 6 reference, 2 vehicle). Additionally, 3 skin-related adverse events were listed in the "General disorders and administration site conditions", MedDRA system organ class and all were considered to be related: the AE "application site

[6] ANDA 200936 Section 5.3.1.2 (pg. 1 of 1).

erythema" was reported by 1 test subject, the AE "application site irritation" was reported by 1 reference subject and the AE "application site rash" was reported by 1 test subject. Severe "Skin and subcutaneous tissue disorders" AEs occurred in five subjects; severe contact dermatitis was reported in 2 test subjects and was not reported in the other treatment groups; severe rash was reported in 1 test subject and was not reported in the other treatment groups; severe skin erosion was reported in 1 reference subject and was not reported in the other treatment groups; severe skin irritation was reported in 1 test subject and was not reported in the other treatment groups.[7] According to the sponsor's analysis, there were no notable differences between the treatment groups in the percentage of subjects with skin reactions reported as AEs related to study drug, with the exception of hypersensitivity reactions related to study drug being more common in the reference group (n=5).[8]

No death occurred in the study. Thirteen serious adverse events were experienced by 13 subjects (5 test, 5 reference, 3 vehicle) and none were considered by the sponsor to be related to the study drug.

Clinical Review

I. Introduction and Background

Solaraze® (diclofenac sodium) Gel, 3% is a topical nonsteroidal anti-inflammatory drug (NSAID) approved under NDA 021005 for the treatment of actinic keratoses. The mechanism of action of diclofenac sodium for the treatment of actinic keratoses (AK) is unknown.[9]

According to the approved labeling, systemic absorption of diclofenac in subjects treated topically with Solaraze® is much lower than that occurring after oral daily dosing of diclofenac sodium. Blood was drawn at the end of treatment from 60 subjects with AK lesions treated with Solaraze® in three adequate and well-controlled clinical trials. Each subject was administered 0.5 g of Solaraze Gel twice a day for up to 105 days. There were up to three 5 cm x 5 cm treatment sites per subject on the face, forehead, hands, forearm and scalp. Serum concentrations of diclofenac were on average at, or below 20 ng/mL.

In clinical studies, localized dermal side effects such as contact dermatitis, exfoliation, dry skin, and rash were found in subjects treated with Solaraze® at a higher incidence than in those with vehicle (placebo).

A. Drug Established Name, Drug Class

Drug Established Name: Diclofenac Sodium Gel, 3%
Drug Class: Nonsteroidal anti-inflammatory drug (NSAID)

[7] Final Study Report TOL-AK-2008-02 (pg. 60 of 217).
[8] Final Study Report TOL-AK-2008-02 (pg. 70 of 217).
[9] **CLINICAL PHARMACOLOGY** section of the Solaraze® (diclofenac sodium) Gel, 3% Approved Labeling,

B. Trade Name of Reference Drug, NDA number, Date of approval, Approved Indication(s), Dose, Regimens

Reference Drug (NDA number): Solaraze® (diclofenac sodium) Gel, 3% (NDA 021005), Nycomed US (see Appendix, Table 25)
Date of approval: 10/16/00
Approved indication(s) based on label approved on 10/16/00: For the topical treatment of actinic keratoses (AK). Sun avoidance is indicated during therapy.
Recommended dosing regimens: Per the approved labeling, Solaraze® Gel, 3% should be applied to lesion areas twice daily. It is to be smoothed on the affected skin gently. The amount needed depends upon the size of the lesion site. Assure that enough Solaraze Gel is applied to adequately cover each lesion. Normally 0.5 g of gel is used on each 5 cm x 5 cm lesions site. The recommended duration of therapy is from 60 days to 90 days. Complete healing of the lesion(s) or optimal therapeutic effect may not be evident for up to 30 days following cessation of therapy.

C. Regulatory Background

Tolmar Inc has not submitted any INDs, Protocols, Controlled Correspondences, or additional ANDAs to the OGD for Diclofenac Sodium Gel, 3%. No INDs have been submitted to the OGD for Diclofenac Sodium Gel, 3%.

The following Protocols (designated by "P"; see Appendix, Table 29), and/or Controlled Correspondence (designated by "C"; see Appendix, Table 30) have been submitted to the OGD for Diclofenac Sodium Gel, 3% by other sponsors:

Submission	Submission date	Status	Sponsor
C02-592	(b) (4)	(b) (4)	
C06-0132			
C06-0174			
C06-1336			
(b) (4)			
C09-0608			

The current submission is the only ANDA submitted to the OGD for Diclofenac Sodium Gel, 3% (see Appendix, Table 28). (b) (4) (b) (4)

D. Other Relevant Information

The treatment of AK is the only approved indication for Solaraze Gel, 3%. The clinical presentation of AK is straightforward, and clinical assessment is appropriate and reliable without the need for diagnostic biopsies at baseline or end of treatment. The recommended treatment regimen allows for a duration of treatment from 60 to 90 days. The OGD recommends a single

bioequivalence study with a clinical endpoint in the treatment of AK for assessment of bioequivalence of generic Diclofenac Sodium Gel, 3% to the RLD. The recommended treatment duration is 60 days, the shortest labeled treatment duration.

II. Description of Clinical Data and Sources

Study Centers/Investigators: The study was conducted at the 37 sites that enrolled subjects. No subjects appear to have been enrolled at Sites #1, 2, 3 and 28. The sponsor certified that they did not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application. The sponsor also certified that neither they, nor any affiliated person responsible for the development or submission of the Diclofenac Sodium Gel, 3% ANDA, had sustained any convictions described under section 306(1) and 2306 (b) of the Act within the past 5 years.

Table 3: Study TOL-AK-2008-02 Sites, Principal Investigators and Number of Subjects per Site

Site Number *	Site Number **	Principal Investigator	Randomized n=609	Per-Protocol Analyses n=460	Modified Intent-to-Treat Analyses n=605	Intent-to-Treat Analyses n=608
1	4	Sunil S. Dhawan, MD	19	12	18	19
2	5	Marina I Peredo, MD	19	16	19	19
3	6	Elyse S Rafal, MD	15	13	15	15
4	7	Jonathan S Weiss, MD	13	8	13	13
5	8	Stephen Miller, MD	20	15	20	20
6	9	Krunal M Patel, MD	15	11	15	15
7	10	Dow B Stough, MD	14	10	14	14
8	11	Leonard Swinyer, MD	15	13	15	15
9	12	Stanley C Gilbert, MD	15	8	15	15
10	13	Robert S Haber, MD	4	3	4	4
11	14	David M Pariser, MD	15	13	15	15
12	15	Terry M Jones, MD	15	14	15	15
13	16	William B Harwell, MD	29	23	28	29
14	17	Joseph F Fowler, Jr, MD	15	12	15	15
15	18	Elizabeth A Arthur, MD	10	6	10	10
16	19	Keith H Loven, MD	6	5	6	6
17	20	Kenneth G Gross, MD	15	10	15	15
18	21	David L Kaplan, MD	11	5	10	11
19	22	Joel Schlessinger, MD	35	17	35	35
20	23	Michael Jarratt, MD	15	14	15	15
21	24	John H Tu, MD MS	25	21	25	25
22	25	Mark R Ling, MD PhD	15	6	15	15
23	26	Paul Yamauchi, MD, PhD	15	14	15	15
24	27	James M Swinehart, MD	15	11	15	15
26	29	Steven Kempers, MD	14	13	14	14

Site Number *	Site Number **	Principal Investigator	Randomized n=609	Per-Protocol Analyses n=460	Modified Intent-to-Treat Analyses n=605	Intent-to-Treat Analyses n=608
27	30	Eduardo Tschen, MD	18	14	18	18
28	31	Adnan Nasir, MD, PhD	20	15	20	20
29	32	Zoe Diana Draelos, MD	15	13	15	15
30	33	Linda Murray, DO	15	9	15	15
31	34	Frank E Dunlap, MD	15	10	15	15
32	35	Francisco Flores, MD	15	14	15	15
33	36	Hector Wiltz, MD	15	13	15	15
34	37	Robert T Matheson, MD	30	30	30	30
35	38	Linda Stein Gold, MD	15	11	15	15
36	39	J.. Michael Maloney, III, MD	15	11	15	15
37	40	David Kerr, MD	15	11	14	14
38	41	Phoebe Rich MD	22	16	22	22

*Site number per Subject2 dataset submitted in Original ANDA 200936
** Site number per Subject dataset submitted in Original ANDA 200936

Study Period: February 5, 2009 to August 25, 2009

Enrollment: A total of six hundred and nine (609) subjects were randomized into the study.

III. Clinical Review Methods

A. Overview of Materials Consulted in Review

Original Submission: Original ANDA 200936 electronic submission received on 12/16/09 (i.e., DARRTS Supp. Document No. 1; letter date 12/14/09) was reviewed.

ANDA Amendments:

1) DARRTS Supp. Document No. 4: On June 3, 2010 (DARRTS received date June 4, 2010), the lawyer representing the sponsor (i.e., Roger C. Thies, Hyman, Phelps & McNamara, P.C.) submitted an appeal of refusal to receive decision and it was reviewed.

2) DARRTS Supp. Document No. 5: On April 26, 2010, the OGD asked the sponsor to provide additional data regarding the submitted clinical endpoint study. In response, the sponsor submitted the additional data (cover letter dated June 30, 2010; DARRTS letter date July 8, 2010; DARRTS received date July 9, 2010) and it was reviewed.

3) DARRTS Supp. Document No. 8: On April 19, 2011, the OGD asked the sponsor to provide the total number of subjects enrolled at each site and the number of subjects in the Per Protocol Population at each site for the submitted BE with clinical endpoint study TOK-AK-2008-02. In response, the sponsor submitted a 3-page table containing the requested information (cover letter and DARRTS letter date April 19, 2010; DARRTS received date

April 20, 2011) and it was reviewed. The table confirmed the number of randomized subjects per site and Per Protocol subjects per site provided in Table 3.

B. Overview of Methods Used to Evaluate Data Quality and Integrity

Division of Scientific Investigations (DSI) Report:

A DSI inspection was not requested for this study because the study design was not adequate to support approval of the application.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

This reviewer was unable to locate any information regarding approval of the study protocol by any Investigational Review Board (IRB). The Original Protocol (Version 1.8) is dated November 12, 2008 and Amendment #1 (Version 1.9) is dated January 15, 2009. It appears that the sponsor failed to provide a listing of all changes made in Amendment #1 to the protocol.

The sponsor reported that the standard subject informed consent form (13 pg.) was approved on January 19, 2009 by the (b) (4) IRB located (b) (4) and an amended subject informed consent form (13 pg.) was approved by the same IRB on January 26, 2009. This reviewer was unable to locate any information provided by the sponsor delineating the changes made to the amended consent form approved by the (b) (4) IRB. Specifically for the Henry Ford Health System site, a different subject informed consent form (12 pg.) Version 2 was approved on January 27, 2009 by the Henry Ford Health System IRB located in Detroit, MI.

Reviewer's comment: *The sponsor stated that the study protocol was approved by an IRB*[10] *but did not submit verification from the IRB. A listing of the* (b) (4) *IRB* (b) (4) *Board Membership, a listing of the Henry Ford Health System IRB Membership and the informed consents approved by the two IRBs were located.*[11]

D. Evaluation of Financial Disclosure

The sponsor declared that they had not entered into any financial arrangement with the 37 listed clinical investigators (who enrolled all of the subjects for Study TOL-AK-2008-02), whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2 (a).

IV. Review of Bioequivalence Study with Clinical Endpoints

A. Brief Statement of Conclusions

[10] TOL-AK-2008-02 Final Study Report pg. 13 of 217.
[11] TOL-AK-2008-02 Final Study Report Appendix 16.1.3. entitled "Ethics Committee(s)/Institutional Review Boards and Sample Informed Consents pg. 1-54 of 54.

Due to the unacceptable study design, a FDA statistical analysis was not performed.

B. General Approach to Review of the Comparative Efficacy of the Drug

The sponsor's study (protocol #TOL-AK-2008-02) was reviewed to evaluate bioequivalence of the test product and the reference product. The primary endpoint of this study is the complete clearance of AK lesions (zero clinically visible actinic keratosis lesions in the treatment area) at 4-weeks post-treatment (week 16). The sponsor's proposed primary parameter was evaluated for bioequivalence and secondary parameters were considered as supportive information.

C. Detailed Review of Bioequivalence Studies with Clinical Endpoints

1. The sponsor's 52-page Original Protocol TOL-AK-2008-02 is dated November 12, 2008 (Version 1.8) and it was not reviewed by the OGD prior to the ANDA submission.

2. Protocol TOL-AK-2008-02 was amended (Amendment #1) on January 15, 2009 (Version 1.9). Per the sponsor, it revised the treatment area from one to two 5 cm x 5 cm treatment areas to one 25 cm^2 treatment area and made other changes. The sponsor submitted a copy of this amended 51-page protocol; however, it appears that the sponsor failed to provide a listing of all changes made in Amendment #1 to the protocol.

3. The sponsor's standard subject informed consent form (13 pg.) was approved on January 19, 2009 by the (b) (4) IRB located (b) (4) and an amended subject informed consent form (13 pg.) was approved by the same IRB on January 26, 2009. This reviewer was unable to locate any information provided by the sponsor delineating the changes made to the amended consent form approved by the (b) (4) IRB. Specifically for the Henry Ford Health System site, a different subject informed consent form (12 pg.) Version 2 was approved on January 27, 2009 by the Henry Ford Health System IRB located in Detroit, MI.

Protocol Review (TOL-AK-2008-02):

Title: A Double-Blind, Randomized, Parallel-Group, Vehicle-Controlled, Multicenter Study to Evaluate the Safety and Bioequivalence of Diclofenac Sodium Gel, 3% (TOLMAR Inc.) to Solaraze® (Diclofenac sodium) Gel, 3% and Compare Both Active Treatments to a Vehicle Control in the Treatment of Actinic Keratosis

Objective: The objectives of this study were to demonstrate comparable safety, tolerability, and efficacy of Diclofenac sodium Gel, 3% and Solaraze® (diclofenac sodium) Gel, 3% in the treatment of AK in order to demonstrate bioequivalence, and to demonstrate superiority of the two active gels over that of the vehicle control.

Study Design: This was a 16-week, 2:2:1 randomized, double-blind, parallel-group, vehicle-controlled, multicenter study design comparing the following three products (all supplied in 100 gram tubes) applied for 12 weeks (84 days):

1. Test: Diclofenac Sodium Gel, 3%, Tolmar Inc., Batch/Lot #3241A, manufactured 11/08.

2. Reference: Solaraze® (diclofenac sodium) Gel, 3%, Doak Dermatologics (current sponsor Nycomed US), Batch/Lot #8064201 expiration date 2/10; #8205201 expiration date 5/10; #8205301 expiration date 5/10; #8205401 expiration date 5/10; #8205101 expiration date 5/10; #8346401 expiration date 8/10; #8346301 expiration date 8/10; #8346601 expiration date 8/10.
3. Placebo (Vehicle): Tolmar Inc., Batch/Lot #3240.

The initial application of study drug was conducted under direct supervision of study drug dispenser. Subjects were instructed to wash treatment area with cold water and pat dry prior to applying study drug. Subjects were instructed to gently apply the assigned study medication twice daily to the designated area(s) for 84 days (12 weeks). The amount of study drug needed depended upon the size of the treatment area. Subjects were instructed to apply enough study drug to adequately cover each lesion. Normally, 0.5 gram (pea size) of gel was used on the 5 cm × 5 cm area. Subjects used a diary to record each date (i.e., mm/dd/yy) of treatment and whether or not study treatment as applied in the AM (i.e., AM: □ Yes □ No) and in the PM (i.e., PM: □ Yes □ No) on that specific date.[12] There were a total of six study visits Visit 1/Day 1: Baseline, Visit 2/Day 14 (±3 days), Visit 3/Day 28 (±3 days), Visit 4/Day 56 (±5 days), Visit 5/Day 84 (±5 days) (End of Treatment [EOT]), and Visit 6/Day 112 (±5days): (Follow-up/Early Discontinuation).

Reviewer's comment: *The issue at hand pertains to the design of the clinical endpoint study. It should be noted per 21 CFR 320.24 (b)(4), well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for the purposes of demonstrating bioequivalence, are the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence. It has been recommended that clinical trials as an approach to demonstrate bioequivalence generally are considered insensitive.[13] To improve the sensitivity of comparative clinical trials, the dosing regimen and period of dosing must be carefully selected. If the doses chosen for both agents are too high then subjects may reach an upper threshold in response, leading to a false conclusion of equivalence.[14] The same may be true of a longer treatment duration. In all 3 of the Innovator's pivotal Phase 3 clinical studies supporting approval (see Tables 1 and 2), the primary efficacy variable was evaluated at the 30-day post-treatment visit and the dosing regimen was twice daily with approximately 0.5 gram of gel per "block" of affected skin. The primary difference between the 3 pivotal Phase 3 clinical studies supporting approval was the duration of treatment (i.e., 30, 60 or 90 days) and the shortest treatment duration demonstrating a statistically significant difference for the primary endpoint was 60 days of treatment. Increasing the treatment duration to 90 days resulted in an overall higher complete clearance rate for the vehicle. Thus, the 90 day treatment duration is more likely to capture only the maximum effect and not the rate and extent of drug delivery to the site of action. The OGD recommends that Diclofenac Sodium Gel/Topical 3% be administered twice daily for 60 days with the primary efficacy endpoint evaluated at the*

[12] Amended Protocol TOL-AK-2008-02 (Version 1.9) pg. 44.
[13] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Bioavailability and bioequivalence studies for orally administered drug products-general considerations. March 2003; pg. 9.
[14] Jones B et al. Trials to assess equivalence: the importance of rigorous methods. *BMJ.* 1996; 313: 36-9.

30-day post-treatment assessment in the bioequivalence study with clinical endpoint. Thus, the study design of TOL-AK-2008-02 with an 84-day treatment duration with the primary efficacy endpoint evaluated at the 28-day post-treatment assessment is not acceptable. The longer, 84-day treatment duration is likely to minimize any differences between the test and reference treatments with regard to rate and/or extent of drug delivery to the site of action. The minor difference of the post-treatment assessment occurring at 30-days post-treatment (as recommended by the OGD) or at 28-days post-treatment (as in TOL-AK-2008-02) is not an issue.

Randomization:
Study personnel assigned a subject number to each enrolled subject. The subject number corresponded to a computer-generated randomization schedule assigning the number to one of the three treatment groups. The randomization scheme was generated so that Test Product, Reference Product, and Vehicle Gel were assigned in a 2:2:1 ratio, using a block of 5. The subject numbers were assigned sequentially in the order in which subjects were enrolled at each study center. Study drug was labeled and packaged so that neither the subject nor the Investigator could identify the treatment.

Blinding:
Per the sponsor, the study drug assigned to each subject number was determined by a computer-generated randomization schedule and the study drug was labeled and packaged, according to the random code, so that neither the subject nor the Investigator could identify the treatment. A three-part label was to be attached to each subject study kit box. The tear-off section of the label would be attached to the Study Drug Dispensing Log at the time the first tube was dispensed. The integrity of the randomization code-break tabs was checked periodically and at the conclusion of study, by the study monitor. The Investigator was not to open any code-break tabs unless absolutely necessary to provide medical treatment to a subject in an emergency and only with prior authorization from the Sponsor or designee. If the blind was broken for a subject, the subject was discontinued from the study and the reason recorded.

The study kit box contained three 100 gram tubes of study drug and one tube was dispensed at Visit 1/Baseline, Visit 2/day 28, and Visit 4/ day 56.[15] The test treatment and vehicle control were each described as being "transparent to translucent, colorless to light amber gel"; while the reference treatment was described as a "clear, transparent, colorless to slightly yellow gel".[16] Per the protocol, the study drug was blinded by covering the tubes of study drug with opaque material.[17] Per the protocol, each subject kit box was to bear a label showing the Sponsor's name, study protocol number, subject number, amount, date dispensed, dispensed by, directions for use and storage, and warnings: "For Dermatologic Use Only", "Not for Ophthalmic Use", "For External Use Only", "Keep Out of Reach of Children" and "Caution: New Drug - Limited by Federal (or United States) law to investigational use only."

Study Population:

[15] Final Study Report TOL-AK-2008-02 (pg. 22 of 217).
[16] Final Study Report TOL-AK-2008-02 (pg. 22 of 217).
[17] Amended Protocol TOL-AK-2008-02 (Version 1.9) pg. 18.

Inclusion Criteria

To be eligible for the study, subjects were to have fulfilled all of the following criteria:

1. Subjects with a definite clinical diagnosis of AK, i.e., five or more clinically typical visible, discrete, non-hyperkeratotic, non-hypertrophic lesions contained in one 25 cm^2 treatment area in one major body area as defined in this study: forehead, central face, scalp, back of hands, and forearms;
2. Subjects must be male or a non-pregnant, non-lactating female and at least 18 years of age;
3. Female subjects of childbearing potential (excluding subjects who are surgically sterilized or post menopausal for at least two years), in addition to having a negative urine pregnancy test, must be willing to use an acceptable form of birth control during the study. For the purpose of this study, the following are considered acceptable methods of birth control: oral contraceptives, contraceptive patches, Depo-Provera®, NuvaRing® (vaginal contraceptive) or Implanon™ (contraceptive implant); double barrier methods (e.g., condom and spermicide); intrauterine device (IUD); or abstinence with a documented second acceptable method of birth control if the subject were to become sexually active during the study;
4. Subjects 18 years of age or older must sign the IRB-approved written informed consent form (ICF) and HIPAA form;
5. Subjects must be willing and able to understand and comply with the requirements of the study, apply the study drug as instructed, return for the required treatment period visits, comply with therapy prohibitions, and be able to complete the study;
6. Subjects must be in good health and free from any clinically significant disease, other than AK, that might interfere with the study evaluations.

Reviewer's comments:

1) *The sponsor did not place an upper limit on the number of AKs contained in the treatment area and also did not prespecify a minimum size for the AKs counted in the treatment area, which will tend to increase the variability in study outcome. Subjects with >10 AKs may be less likely to achieve complete clearance. Per this reviewer's analysis of the baseline AK data submitted to ANDA 200936 in the DAS (lesion count) dataset, no subject was enrolled with less than 5 AKs within the treatment area; however, 23 subjects (7 test, 13 reference and 3 vehicle) in the mITT population[18][of which, 18 subjects (5 test, 11 reference and 2 vehicle) were in the PP population[19]) had 11-24 AKs within the treatment area at the baseline visit. The imbalance between the test and reference groups, with twice as many reference subjects than test subjects having >10 AKs within the treatment area at baseline, is likely to decrease the efficacy demonstrated by the reference group in achieving complete clearance of AKs. Per this reviewer's analysis (see Table 4), the success rates by treatment group for the 23 subjects with 11-24 baseline AKs in the mITT population were all lower than the success rates in the corresponding treatment groups for all subjects in the mITT population. In addition, the success rates by treatment group for the 18 subjects with 11-24 baseline AKs in*

(b) (6)

the PP population were all lower than the success rates in the corresponding treatment groups for all subjects in the PP population.

Table 4: Success Rates (Complete Clearance at Visit 6/Day 112/EOT) by Treatment Group

Population (n)	Diclofenac Sodium	Solaraze	Vehicle
Subjects with 11-24 baseline AKs in mITT population (n=23)	1/7=14.3%	2/13=15.4%	0/3=0%
All subjects in mITT population (n=605)	53/241=22.0%	70/244=28.7%	12/120=10.0%
Subjects with 11-24 baseline AKs in PP population (n=18)	1/5=20.0%	2/11=18.2%	0/2=0%
All subjects in PP population (n=460)	43/187=23.0%	57/180=31.7%	11/93=11.8%

2) *The sponsor also enrolled 85 subjects (33 test, 31 reference, and 21 vehicle) with treatment areas where AKs may be more difficult to eradicate, i.e., on the arms or back of the hands (see Appendix, Tables 27, 31, 32). Per this reviewer's analysis (see Table 5), the success rates by treatment group for the 85 subjects with AK treatment locations on the arms or back of the hands in the mITT population were all lower than the success rates in the corresponding treatment groups for all subjects in the mITT population. In addition, the success rates by treatment group for the 69 subjects with AK treatment locations on the arms or back of the hands in the PP population were all lower than the success rates in the corresponding treatment groups for all subjects in the PP population. The decreased efficacy of all three treatments for AKs located on the arms or back of the hands will tend to obscure any difference in the success rates between the three treatments.*

Table 5: Success Rates (Complete Clearance at Visit 6/Day 112/EOT) by Treatment Group

Population (n)	Diclofenac Sodium	Solaraze	Vehicle
Subjects with AKs located on back of hands or arms in mITT population (n=85)	3/33= 9.1%	4/31=12.9%	0/21= 0%
All subjects in mITT population (n=605)	53/241=22.0%	70/244=28.7%	12/120=10.0%
Subjects with AKs located on back of hands or arms in PP population (n=69)	3/28=10.7%	4/24=16.7%	0/17=0%
All subjects in PP population (n=460)	43/187=23.0%	57/180=31.7%	11/93=11.8%

3) *To avoid the increased variability associated with a wide range of the number of AKs in the treatment area, the decreased efficacy associated with a large number of AKs in the treatment area and the decreased efficacy for AKs located in certain anatomic areas, the OGD recommends in the posted Draft Guidance on Diclofenac Sodium Gel/Topical, 3% including "Immunocompetent male or nonpregnant female at least 18 years of age with at least five (5) and no more than ten (10) clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AK lesions, each at least 4 mm in diameter, contained within a 25-cm^2 treatment area located on the face or bald scalp."*

<u>Exclusion Criteria</u>
Subjects who met any of the following criteria were to be excluded from entry:

1. Subjects who are pregnant, nursing, or planning a pregnancy within the study participation period;
2. Subjects with a diagnosis of basal cell carcinoma, squamous cell carcinoma or any other confounding skin condition in the designated treatment area within the last six months;
3. Subjects with sunburn in the designated treatment area;
4. Subjects with clinically significant systemic disease (i.e., immunological deficiencies), unstable medical disorders, life-threatening disease, or current malignancies;
5. Subjects who have a known hypersensitivity to any of the following (in any dosage form): diclofenac sodium or to any component of the study drugs, aspirin, or other NSAIDS;
6. Subjects with active gastrointestinal ulceration or bleeding or severe renal or hepatic impairment;
7. Subjects who have been treated with any topical corticosteroid medications to the forehead, central face, scalp, back of hands, or forearms within 4 weeks prior to study entry;
8. Subjects who have been treated with the following within 60 days prior to study entry: prescribed topical retinoids, 5-fluorouracil (Efudex®), masoprocol (Actinex®), Acitretin (Soriatane), Imiquimod (Aldara®), diclofenac (Solaraze®), cryodestruction, chemodestruction, surgical excision, photodynamic therapy (blue light, aminolevulinic acid [Levulen, Kerastick]), or curettage anywhere on the face, scalp, back of hands or forearms; interferon/interferon inducers, cytotoxic drugs, drugs with major organ toxicity, immunomodulators, immunosuppressive therapies, or hyaluronan-containing cosmetics such as Visible Youth™;
9. Subjects treated with oral isotretinoin during the six months prior to study entry;
10. Subjects who are currently taking or have been treated with oral/systemic corticosteroids within eight weeks prior to the study entry (intranasal or inhaled corticosteroids are acceptable if kept constant throughout the study);
11. Subjects who have been treated with systemic cancer chemotherapy medications within six months of study entry;
12. Subjects who have had the following treatments to the designated treatment area within six months prior to study entry: psoralen plus ultraviolet A (PUVA), ultraviolet B (UVB), laser abrasion, or dermabrasion;
13. Subjects who had a trichloroacetic acid/lactic acid peel and or 50% glycolic acid peel within 60 days prior to study entry;
14. Subjects involved in activities requiring excessive or prolonged sun exposure;
15. Subjects who consume excessive amounts of alcohol, abuse drugs, or have any condition that would compromise compliance with this protocol;
16. Subjects who have participated in a clinical trial with an investigational drug or investigational device within a period of four weeks prior to study entry;
17. Subjects who have been previously enrolled in this study.

<u>Subjects could be discontinued from the study for any of the following reasons:</u>

1) The subject withdrew his or her consent for any reason;
2) The subject's condition worsened to the degree or lack of improvement after at least 28 days (treatment failure) that the Investigator felt it was unsafe for the subject to continue in the study;
3) The subject's drug code was unblinded;

4) There was a clinically meaningful finding that, in the opinion of the Investigator, prevented continuation;
5) An AE occurred for which the subject desired to discontinue treatment or the Investigator determined that it was in the subject's best interest to be discontinued;
6) There was a significant protocol violation, including subjects who missed more than 10 consecutive doses of study drug;
7) A concomitant therapy which may interfere with the results of the study was reported or required;
8) The subject was lost to follow-up. The Investigator documented efforts to attempt to reach the subject twice by telephone and sent a certified follow-up letter before concluding that the subject was lost to follow-up;
9) The subject became pregnant.

Subjects were instructed to take the following precautions during the study:[20]

1. Subjects were instructed to wash hands both before and after applying study drug.
2. Subjects were cautioned to never apply study drug to the eyes, nose, or mouth, or to skin wounds or infections.
3. Subjects were instructed that local skin reactions are common and should be expected with active treatment.
4. Subjects were instructed to avoid sun exposure and the use of sunlamps.
5. Subjects were instructed to not apply any other treatments (other creams, lotions, gels, ointments, etc.) or moisturizers, cosmetics containing hyaluron, over-the-counter retinol products or products containing alpha- or beta-hydroxy acids or aluminum acetate within the designated treatment
6. area without your doctor's permission
7. Sunscreen use in the designated treatment area was acceptable one hour after study drug application.
8. Use of hair care products (e.g., shampoo, conditioner, hair spray, gel) and shaving/shaving products in the designated treatment area was acceptable one hour after study drug application.

The following medications and procedures were prohibited during the study:

In addition to medications and procedures listed in the exclusion criteria, the following were prohibited during this study:

1. The use of any AK treatment, other than study drug, within the designated treatment area. However, surgical excision, cryodestruction and curettage are allowed on the face or scalp outside the designated treatment area.
2. Use of oral diclofenac during the study period.
3. Systemic corticosteroids (intranasal or inhaled corticosteroids are acceptable if kept constant throughout the study) or immunosuppressive agents.
4. Topical corticosteroids applied to the designated treatment area during the study period.
5. Moisturizers, cosmetics containing hyaluron, OTC retinol products and products containing alpha- or beta-hydroxy acids or aluminum acetate within the designated treatment area.

[20] Amended Protocol TOL-AK-2008-02 (Version 1.9) Section 5.4 Precautions (pg. 10) and Appendix III: Subject Instruction (pg. 39).

Procedures/Observations, and safety measures:

Table 6: Study TOL-AK-2008-02 Schedule of Events:

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Unscheduled Visit
Visit Day/Week	Day 1 (Baseline)	Day 14 (±3 days)	Day 28 (±3 days)	Day 56 (±5 days)	Day 84 End of Treatment (±5 days)	Day 112 Follow-up/Early Discontinuation (±5 days)	
Screening/Consent	X						
Demographics	X						
Evaluate Inclusion/ Exclusion Criteria	X						
Medical History	X						
Record Concomitant Medication	X	X	X	X	X	X	X
Perform Abbreviated Physical Exam (including height, weight, vital signs)	X					X	
Urine Pregnancy Test (1)	X					X	
Perform Dermatological Assessment (Identify treatment area and complete anatomical diagram)	X						
Evaluate Treatment Area/Perform Lesion Count X2	X (2)	X	X	X	X	X	X
Dispense Study Drug, Review Subject Instructions, and Record Study Drug Accountability	X		X	X			
Dispense Subject Diary, Review Instructions	X		X	X			
Assess Adverse Events		X	X	X	X	X	X
Collect Subject Diary, Collect Study Drug and Document Study Drug Accountability			X	X	X	X (3)	X (3)
Review Subject Diary and Assess Compliance		X	X	X	X		X
Schedule/Confirm Next Visit	X	X	X	X	X		X
Complete electronic CRF (eCRF)	X	X	X	X	X	X	X

(1) For women of child-bearing potential – – to be completed prior to enrollment and at the Follow-Up/Early Discontinuation Visit.
(2) To be done by the same trained lesion counter at Visit 1/Baseline, Visit 6/Day 112, and Early Discontinuation. However, in the rare circumstance that the Visit 1/Baseline lesion counter was not available, then the other trained lesion counter could perform the clinical assessment.
(3) Collect previously uncollected subject diary and assess compliance and/or study drug and record study drug accountability (if applicable).

The following procedures were scheduled in this study:

1. Subjects who met the entry criteria were examined to confirm the definite clinical diagnosis of 5 or more clinically typical visible, discrete, non-hyperkeratotic, non-hypertrophic AK lesions located within one 25-cm^2 treatment area (e.g., 5 cm x 5 cm or 3 cm x 8.3 cm or 2 cm x 12.5 cm) in one major body area (forehead, central face, scalp, back of hands, or forearms).
2. The location of each AK lesion and the designated treatment area was recorded on the anatomical diagram in the subject's source document. Plastic transparencies were provided to map the designated treatment area and to serve as a location guide at subsequent visits. A duplicate transparency was made for the subject to assist with locating the designated treatment area.
3. The same investigator, to the greatest extent possible, performed the dermatologic assessments for any given subject (i.e., at Visits 1 and 6, identified, counted, and located the target/baseline AK lesions). Complete (100%) clearance was defined as subjects who had no (zero) clinically visible AK lesions (including baseline lesions as well as new or subclinical AK lesions which appeared during treatment) in the designated treatment area at visit 6/day 112.
4. Subjects were instructed to apply the study medication only to the designated treatment area twice daily for 84 consecutive days (12 weeks).
5. The local skin reactions (see Table 7) were evaluated for intensity at each visit using the following four-point scale (0-3; see Table 8):

Table 7: Assessment of Local Skin Reactions

Sign	Description
Burning	Burning
Epidermal desquamation	Dryness/Flaking/Scaling
Edema	Swelling
Erosion/Ulceration	Absence of epidermis/dermis
Erythema	Redness
Pruritus	Itching
Pain	Pain
Scabbing/Crusting	Crusted, dried pus, lymph or blood
Vesicles	Fluid containing structures
Weeping/Exudate	Fluids discharged in tissue or cavities

Table 8: Severity Scores for Local Skin Reactions

Score	Assessment	Description
0	None	Absent
1	Mild	Slight, barely perceptible
2	Moderate	Distinct presence
3	Severe	Marked, intense

Reviewer's comment: *The sponsor evaluated 10 different local skin reactions at the treatment site. In the posted Draft Guidance on Diclofenac Sodium Gel/Topical, 3%, the OGD recommends evaluating seven different local skin reactions, i.e., erythema, dryness, burning/stinging, erosion, edema, pain and itching. This minor difference is not considered to be an issue.*

6. The following visit window conventions were scheduled by the sponsor for the clinical evaluations and local skin reactions (see Table 9):

Table 9: Visit Window Conventions

Visit	Target day	Window
2	14	± 3 days
3	28	± 3 days
4	56	± 5 days
5	84	± 5 days
6	112	± 5 days

Reviewer's comment: *While the sponsor permitted a slightly wider visit window (i.e., +/- 5 days) for the primary endpoint evaluation at visit 6/day 112 than recommended by the OGD (i.e. +/- 4 days), it was acceptable because of the prolonged treatment period of 60 days. In the Draft Guidance on Diclofenac Sodium Gel/Topical, 3%, the OGD recommends:*

> *The PP population includes all randomized subjects who met all inclusion/exclusion criteria, applied a prespecified proportion of the scheduled applications (e.g., 75% to 125%) of the assigned product for the specified duration of the study, did not miss more than 10 consecutive scheduled applications, and completed the primary endpoint evaluation within the designated visit window (+/- 4 days) with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries, and the protocol violations that would affect the treatment evaluation.*

7. All used and unused tubes of study drug will be collected at Visit 3/Day 28, Visit 4/Day 56, and Visit 5/Day 84 (End of Treatment).

Treatment Compliance:
Subjects who missed more than 10 consecutive applications of study drug were considered non-compliant by the sponsor and were discontinued from the study.[21] It should be noted that the Statistical Analysis Plan for TOL-AK-2008-02 (pg. 6) also included "applied at least 80% and not more than 120% of doses" in their definition of treatment compliance.

Endpoints:
The primary endpoint of this study was the proportion of subjects achieving success [defined as achieving complete (100%) clearance of AK lesions in the designated treatment area(s) at Visit 6/day 112]. Complete clearance was defined as subjects who have no (zero) clinically visible AK lesions in the designated treatment area(s) at Visit 6/Day 112 (28 days post-last application visit). Complete (100%) clearance requires that all baseline lesions as well as new or subclinical AK lesions which appeared in the treatment area during therapy are no longer present. The primary endpoint was evaluated at the visit 6/day 112 (week 16; 28 days after last application) in the PP and mITT populations.

The test of superiority was based on the difference between each active treatment's success (i.e., complete clearance of AK in the treatment area) rate compared with that of the vehicle at visit 6/day 112.

Per the protocol, the proportion of subjects with partial clearance of AK lesions in the treatment area was a secondary endpoint analyzed in both the mITT and PP populations. Partial clearance was defined as having a 75% or greater reduction of AK lesions in the treatment area from Visit 1/Baseline to Visit 6/day 112.[22]

Reviewer's comments:

1) *The OGD recommends that the primary endpoint of the study is the proportion of subjects in the per protocol (PP) population with treatment success (100% clearance of all AK lesions within the treatment area) at study day 90 (30 days after completion of 60 days of treatment). All actinic keratoses (i.e., baseline actinic keratoses and any new actinic keratoses) within the treatment area are to be treated and included in the efficacy lesion count for each visit.*

2) *The sponsor's prespecified secondary endpoint is considered supportive information. It should be noted that the sponsor performed two additional secondary efficacy analyses that were not prespecified in the protocol, e.g., 1) complete clearance assessed at Visit 4/Day 56, and 2) complete clearance assessed at Visit 5/Day 84.*

Statistical analysis plan
Primary Endpoint: The primary endpoint of this study was complete clearance of AK lesions in the treatment area.

Sample Size: Per the Final Study Report (pg. 36 of 117), sample size was based on an assumed equivalent success rate (34%) for the Test Product and for the Reference Product and no greater

[21] Amended Protocol TOL-AK-2008-02 (Version 1.9) pg. 20.
[22] Amended Protocol TOL-AK-2008-02 (Version 1.9) pg. 24.

than 18% for the Gel Vehicle. It was also assumed that nearly all of the subjects enrolled would qualify for the mITT population analyses and approximately 70% of the mITT group was expected to be qualified for the PP population analyses. Under these assumptions, 284 PP subjects (142 in each active treatment group) were anticipated to provide at least a 0.90 probability of showing therapeutic equivalence for the Test Product and Reference Product (using a 90% CI criterion). It was also anticipated that there would be an 0.80 probability of showing that each active treatment is statistically superior ($p<0.05$) to the vehicle control (204 mITT active treatment subjects compared to 102 mITT vehicle control subjects using independent, continuity-corrected, Z-tests). Thus, the total target number was 510 subjects (204 + 204 + 102). This number was later increased when it was determined that the active comparator had been provided in multiple batches. This was considered to have the potential to increase variability. Further, enrollment had proceeded so rapidly, that it was not possible to determine at the point of enrollment (based on information concerning withdrawal, protocol violations, etc.) if sufficient subjects had been enrolled for the evaluation of bioequivalence. Therefore the target number was increased to 590 subjects.

Analysis: For the bioequivalence analysis, the 90% confidence interval was constructed for the difference in the proportion of subjects with complete clearance of AK lesions between the test product and reference product at Visit 6/day 112 (week 16; 4 weeks post-last application). The confidence interval was calculated using Wald's method with Yates' continuity correction based on the data pooled from all clinical sites. Bioequivalence was to be established if this 90% confidence interval was contained within the interval of (–0.20 to +0.20). The analysis in the PP population was considered primary and that in the mITT population as supportive information.

According to the sponsor, the mITT population was the primary population for comparison of the difference in proportion of subjects with complete clearance of AK between the active treatment groups and the vehicle group.

Adverse events (AEs) were coded by the sponsor using the MedDRA dictionary. AEs were summarized by presenting the number and percentage of subjects who experienced any AE, death, SAE, or who withdrew from treatment by treatment group. Frequency and percent of subjects reporting AEs were tabulated by treatment group. Similar tables were summarized by severity and relationship to study drug. In summaries of severity and relationship, subjects who reported more than one event that mapped to the same preferred term were counted only once under the strongest severity and relationship, accordingly. Local skin reactions were summarized by treatment group, visit, frequency, and severity. The safety analyses were only conducted on the ITT population.

Study Conduct

Discussion of ITT and PP populations:
Three subject populations were defined by the sponsor per the protocol (pg. 22) as follows:

Intent-To-Treat (ITT)
1) enrolled into the study, AND
2) applied at least one dose of study treatment.

Modified Intent-To-Treat (mITT)
1) enrolled into the study,
2) met inclusion/exclusion criteria;
3) applied at least one dose of study treatment, AND
4) had at least one post-baseline efficacy evaluation.

Per-Protocol (PP)
1) enrolled into the study,
2) met inclusion/exclusion criteria,
3) maintained compliance with study drug applications (applied at least 80% (i.e., at least 134 doses) and not more than 120% (i.e., not more than 202 doses) of doses and did not miss 10 or more consecutive applications of study drug),
4) took no concomitant medications prohibited by the protocol,
5) had no other significant protocol violations, AND
6) returned for visit 6/day 112 within the visit window and had data on the primary efficacy variables for all clinical evaluations, OR
7) were discontinued early due to worsening disease or lack of improvement after at least 28 days with at least 80% treatment compliance rate treatment.

Reviewer's comments:

1) *Per the Final Study Report TOL-AK-2008-02 (pg. 32 of 217), the sponsor changed the definition of the mITT population from that in both the Original Protocol and Amendment #1 dated January 15, 2009 (see above) by replacing the requirement that subjects meet inclusion/exclusion criteria with the requirement that subjects had a baseline lesion count. The sponsor also changed the definition of the PP population from that in both the Original Protocol and Amendment #1 (see above) by adding that subjects had a baseline lesion count AND replacing "had data on the primary efficacy variables for all clinical evaluations" with "had a lesion count at Visit 6/day 112 AND changed the phrase "due to worsening disease or lack of improvement" to "insufficient therapeutic response". The sponsor did not include these changes in Section 9.8, entitled "Changes in the Conduct of the Study or Planned Analyses", of the Final Study Report TOL-AK-2008-02; however, these changes were made in the definition of the mITT population listed in the Statistical Analysis Plan for TOL-AK-20089-02 dated January 29, 2009 on pg. 5. The OGD recommends that the mITT population includes all randomized subjects who met all inclusion/exclusion criteria, received study treatment, and returned for at least one post-baseline visit. The mITT population should be used to compare both test and reference products to vehicle (placebo).*

2) *Per the Final Study Report (pg. 32 of 217), a last observation carried forward (LOCF) approach was used for missing efficacy data on the mITT population and missing efficacy data was <u>not</u> imputed in the PP population with the exception of subjects who discontinued early due to insufficient therapeutic response after completing at least 28 days of study drug use, had a compliance rate of at least 80%, and satisfied all other per protocol criteria. For these subjects, the missing efficacy data was imputed using an LOCF approach.*

Retention of Reserve Samples:
The sponsor stated that each investigational site where study drug was dispensed to at least one subject was required to randomly select and keep one block (five consecutively numbered subject boxes of study medication) of study drug at their facility as "retain samples", in accordance with 21 CFR 320.63 and 320.38.

Demographics and Baseline AK lesion count:
A total of 609 subjects, were enrolled into the study and randomized. Of these, 523 completed the study and 86 discontinued. The racial composition of the study population was overwhelmingly White (99.7%). Two subjects in the ITT population did not list their race as White. Baseline demographics, age, and race in the ITT and PP populations were similar in all treatment groups (see Tables 10 and 11). The mean age in the ITT population was 66.0 years (36-95), 65.3 years (32-92), and 63.8 years (21-84) in the test, reference, and vehicle groups, respectively. The mean AK lesion count at baseline for the ITT population was not statistically different among the treatment groups (p-value 0.9623).

Table 10: Demographic Characteristics for Intent to Treat Subjects (per Sponsor)

Characteristic	Category	Diclofenac Sodium Gel, 3% (N=187)	Solaraze™ Gel, 0.3% (N=180)	Vehicle (N=93)	Total (N=460)
Gender (n,%)	Female	50 (20.7%)	45 (18.3%)	23 (19.0%)	118 (19.4%)
	Male	191 (79.3%)	201 (81.7%)	98 (81.0%)	490 (80.6%)
Ethnicity (n,%)	Hispanic or Latino	12 (5.0%)	8 (3.3%)	5 (4.1%)	25 (4.1%)
	Not Hispanic or Latino	229 (95.0%)	238 (96.7%)	116 (95.9%)	583 (95.9%)
Race (n,%)	White	239 (99.2%)	246 (96.7%)	121 (100.0%)	606 (99.7%)
	Black or African American	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	American Indian or Alaska Native	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Native Hawaiian or Other Pacific Islander	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Age (years)	Mean ± SD	66.0 ± 10.3	65.3 ± 10.8	63.8 ± 10.6	65.6 ± 10.6
	Median	66.0	65.0	62.0	65.0
	Min, Max	36.0, 95.0	32.0, 92.0	21.0, 84.0	21.0, 95.0
Actinic Keratosis Lesion Count	Mean ± SD	6.5 ± 1.6	6.6 ± 2.1	6.6 ± 2.3	6.6 ± 2.0
	Median	6.0	6.0	6.0	6.0
	Min, Max	5.0, 14.0	5.0, 18.0	5.0, 24.0	5.0, 24.0

Source: Final Study Report TOL-AK-2008-02, Section 14, Table 14.1.3 (pg. 80-81 of 217)

Table 11: Demographic Characteristics for Per Protocol Subjects (per Sponsor)

Characteristic	Category	Diclofenac Sodium Gel, 3% (N=187)	Solaraze™ Gel, 0.3% (N=180)	Vehicle (N=93)	Total (N=460)
Gender (n,%)	Female	40 (21.4%)	34 (18.9%)	17 (18.3%)	91 (19.8%)
	Male	147 (78.6%)	146 (81.1%)	76 (81.7%)	369 (80.2%)
Ethnicity (n,%)	Hispanic or Latino	10 (5.3%)	7 (3.9%)	5 (5.4%)	22 (4.8%)
	Not Hispanic or Latino	177 (94.7%)	173 (96.1%)	88 (94.6%)	438 (95.2%)
Race (n,%)	White	185 (98.9%)	180 (100.0%)	93 (100.0%)	458 (99.6%)
	Black or African American	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	American Indian or Alaska Native	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Native Hawaiian or Other Pacific Islander	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Age (years)	Mean ± SD	66.2 ± 10.3	65.7 ± 11.1	64.5 ± 9.5	65.6 ± 10.5
	Median	66.0	65.5	62.0	65.0
	Min, Max	43.0, 89.0	32.0, 92.0	49.0, 84.0	32.0, 92.0
Actinic Keratosis Lesion Count	Mean ± SD	6.6 ± 1.6	6.6 ± 2.1	6.6 ± 2.3	6.6 ± 2.0
	Median	6.0	6.0	6.0	6.0
	Min, Max	5.0, 14.0	5.0, 18.0	5.0, 24.0	5.0, 24.0

Source: ANDA 200936 Module 2.7_Summary_Bioequivalence_Tables, Table 7.1 and ANDA 200936 Final Study Report TOL-AK-2008-02, Table 11-3, pg. 42.

Local Skin Reaction at baseline

According to the sponsor, local skin assessments observed at baseline for the ITT population revealed that the majority of subjects in each treatment group either did not have the specified skin reaction or had reactions that were categorized as mild.

Table 12: Local Skin Reactions at Baseline (per Sponsor)

Parameter	Category	Test n=241	Reference n=246	Vehicle n=121
Burning	None	235 (97.5%)	240 (97.6%)	117 (96.7%)
	Mild	5 (2.1%)	4 (1.6%)	4 (3.3%)
	Moderate	1 (0.4%)	2 (0.8%)	0
	Severe	0	0	0
Erythema (Redness)	None	125 (51.9%)	131 (53.3%)	68 (56.2%)
	Mild	97 (40.2%)	94 (38.2%)	46 (38.0%)
	Moderate	19 (7.9%)	21 (8.5%)	7 (5.8%)
	Severe	0	0	0
Epidermal Desquamation (Dryness/Flaking/Scaling)	None	143 (59.3%)	137 (55.7%)	72 (59.5%)
	Mild	87 (36.1%)	93 (37.8%)	40 (33.1%)

Parameter	Category	Test n=241	Reference n=246	Vehicle n=121
	Moderate	11 (4.6%)	16 (6.5%)	9 (7.4%)
	Severe	0	0	0
Pruritus (Itching)	None	207 (85.9%)	211 (85.8%)	106 (87.6%)
	Mild	28 (11.6%)	29 (11.8%)	12 (9.9%)
	Moderate	6 (2.5%)	6 (2.4%)	3 (2.5%)
	Severe	0	0	0
Pain	None	237 (98.3%)	245 (99.6%)	118 (97.5%)
	Mild	4 (1.7%)	1 (0.4%)	3 (2.5%)
	Moderate	0	0	0
	Severe	0	0	0
Edema (Swelling)	None	236 (97.9%)	241 (98.0%)	119 (98.3%)
	Mild	4 (1.7%)	5 (2.0%)	2 (1.7%)
	Moderate	1 (0.4%)	0	0
	Severe	0	0	0
Erosion/Ulceration	None	238 (98.8%)	244 (99.2%)	121 (100.0%)
	Mild	3 (1.2%)	2 (0.8%)	0
	Moderate	0	0	0
	Severe	0	0	0
Weeping/Exudate (Fluids discharge in tissue or cavities)	None	241 (100%)	246 (100%)	121 (100%)
	Mild	0	0	0
	Moderate	0	0	0
	Severe	0	0	0
Scabbing/Crusting/Crusted, dried pus, lymph or blood	None	232 (96.3%)	228 (92.7%)	117 (96.7%)
	Mild	8 (3.3%)	16 (6.5%)	3 (2.5%)
	Moderate	1 (0.4%)	2 (0.8%)	1 (0.8%)
	Severe	0	0	0
Vesicles (Fluid containing structures)	None	241 (100%)	246 (100%)	121 (100%)
	Mild	0	0	0
	Moderate	0	0	0
	Severe	0	0	0

Source: Final Study Report TOL-AK-2008-02, Tables 14.3.1.6.1 on pg. 151, 14.3.1.6.2 on pg. 153, 14.3.1.6.3 on pg. 155, 14.3.1.6.4 on pg. 157, 14.3.1.6.5 on pg. 159, 14.3.1.6.6 on pg. 161, 14.3.1.6.7 on pg. 163, 14.3.1.6.8 on pg. 165, 14.3.1.6.9 on pg. 167 and 14.3.1.6.10 on pg. 169.

Efficacy Results

Six hundred and nine (609) subjects were randomized to receive the study treatment; 242 in the test, 243 in the reference, and 121 in the vehicle group. One subject (b) (6) in the test group was excluded from the ITT (Safety) population due to not applying any study treatment. The most common reason for discontinuation from the study was due to withdrawal of consent (n=24 subjects), followed by adverse event (n=20 subjects), non-compliance with study treatment (n=20 subjects) and local skin reaction (n=15 subjects). Seven subjects, i.e., four in the test group (b) (6) two in the reference group (b) (6) and one in the vehicle group (b) (6) took concomitant medication prohibited by the protocol, which excluded them from the PP population. Overall, more subject discontinuations occurred in the reference group compared to the test or vehicle group, i.e., reference: 16.7%, test: 13.2%, vehicle: 10.7%. The sponsor's disposition of subjects is shown in Table 13, the reason for discontinuation is listed in Table 14, and a summary of protocol deviations is provided in Table 15. Tables 16 and 17 show the summary of the sponsor's primary and secondary efficacy outcome analyses.

Per the sponsor, four subjects did not meet eligibility criteria and were excluded from the PP population[23]; however, the exact criteria not met were provided for only two subjects[24]:

1) Subject (b) (6) (test group) did not meet Exclusion criteria #10; exception was granted; subject was excluded from the PP Population.
2) Subject (b) (6) (reference group) did not meet Exclusion criteria #8; an exception was granted; subject was excluded from the PP Population.
3) Subject (b) (6) (reference group) "did not meet all entry criteria"; exception was not granted; subject was excluded from the PP Population..
4) Subject (b) (6) (reference group) "did not meet all entry criteria"; exception was not granted; subject was excluded from the PP Population.

Reviewer's comment: *This reviewer attempted to locate additional details regarding the specific violation of eligibility criteria for Subjects (b) (6) by searching through the submitted Case Report Forms (CRFs); however, no CRFs were submitted for the four subjects listed in Appendix Listing 16.2.3 as not meeting eligibility criteria. The sponsor submitted 29 Case Report Forms: 11 for subjects who had Serious Adverse Events (two of which also discontinued due to Adverse Event) and 20 for subjects who discontinued due to Adverse Event).*

Table 13: Disposition of Subjects; per Sponsor

Subject Disposition	Number (%) of Subjects			
	Diclofenac sodium n (%)	Solaraze® n (%)	Vehicle n (%)	Total n (%)
Number Enrolled and Randomized	242	246	121	609
Number Completed Study	210 (86.8)	205 (83.3)	108 (89.3)	523 (85.9)
Total Discontinued	32 (13.2)	41 (16.7)	13 (10.7)	86 (14.1)

Source: Final Study Report TOL-AK-2008-02 Table 10-1, pg. 38.

Table 14: Subject Discontinuation by Reason; per Sponsor

Subject Disposition	Number (%) of Subjects			
	Diclofenac sodium n (%)	Solaraze® n (%)	Vehicle n (%)	Total n (%)
Adverse event (1)	8 (3.3)	9 (3.7)	3 (2.5)	20 (3.3)
Insufficient Therapeutic Response (after at least 4 weeks of compliant treatment)	0	0	0	0
Non Compliant with Use of Study drug	7 (2.9)	10 (4.1)	3 (2.5)	20 (3.3)
Lost to Follow-Up	4 (1.7)	2 (0.8)	1 (0.8)	7 (1.1)
Subject Decision/Withdrawal of Consent	10 (4.1)	9 (3.7)	5 (4.1)	24 (3.9)
Death	0	0	0	0
Other	3 (1.2)	11 (4.5)	1 (0.8)	15 (2.5)
Local skin reaction and withdrawal of consent	0	1 (0.4)	1 (0.8)	2 (0.3)

[23] Final Study Report TOL-AK-2008-02 Section 11.1 Data Sets Analyzed for Efficacy (pg. 39 of 217) and Appendix Listing 16.2.3 entitled "Listing of Subject Status" p. 5 of 42.
[24] Per Final Study Report TOL-AK-2008-02 Appendix Listing 16.2.2 entitled "Protocol Deviations", Appendix Listing 16.2.3 entitled "Subjects Excluded From the Efficacy Analysis" and dataset "EC" (Eligibility Criteria).

Subject Disposition	Number (%) of Subjects			
	Diclofenac sodium n (%)	Solaraze® n (%)	Vehicle n (%)	Total n (%)
Local skin reaction and use of excluded medication	0	1 (0.4)	0	1 (0.2)
Local skin reaction	1 (0.4)	7 (2.8)	0	8 (1.3)
Severe skin reaction (primary), withdrew consent (secondary)	1 (0.4)	0	0	1 (0.2)
Severe skin reaction (primary), non compliance (secondary)	1 (0.4)	0	0	1 (0.2)
Severe skin reaction, protocol violation with study treatment	0	1 (0.4)	0	1 (0.2)
Severe skin reaction	0	1 (0.4)	0	1 (0.2)

Source: Final Study Report TOL-AK-2008-02, Table 10-1, pg. 38.
(1) includes intercurrent illness reported as AEs and leading to discontinuation; does not include local skin reactions included in the "Other" category.

Table 15: Protocol Deviations*; per Sponsor

Type	Number (%) of Subjects		
	Test (N=242)	Reference (N=246)	Vehicle (N=121)
Violated inclusion/exclusion criteria	1 (0.4%)	3 (1.2%)	0 (0.0%)
Took prohibited medication or other significant protocol violation	8 (3.3%)	2 (0.8%)	2 (1.7%)
Noncompliant treatment applications	2 (0.8%)	3 (1.2%)	5 (4.1%)
No lesion count data at visit 6	0 (0.0%)	3 (1.2%)	1 (0.8%)
Visit 6 out of window 13	(5.4%)	18 (7.3%)	8 (6.6%)
Non-Efficacy Related Discontinuation	31 (12.8%)	37 (15.0%)	12 (9.9%)

Source: ANDA 200936 Module 2.7_Summary_Bioequivalence_Tables, Table 13
*Protocol deviations included in the table are those that led to exclusion of subjects from per-protocol efficacy analyses.

Table 16: Primary Efficacy Analysis: Complete Clearance of AK lesions at visit 6/week 16 (4 weeks follow-up); per Sponsor

Parameter	Test	Reference	Vehicle	90% C.I. for Bioequivalence of Test to Reference	p-values	
					Test vs. Vehicle	Reference vs. Vehicle
Per-Protocol Subjects (n, %)						
	n=187	n=180	n=93			
Success	43 (23.0%)	57 (31.7%)	11 (11.8%)	(-16.8%, -0.5%)	NA	NA

Parameter	Test	Reference	Vehicle	90% C.I. for Bioequivalence of Test to Reference	p-values	
					Test vs. Vehicle	Reference vs. Vehicle
Failure	144 (77.0%)	123 (68.3%)	82 (88.2%)			
Modified Intent-to-Treat Subjects (n, %)						
	n=241	n=244	n=120			
Success	53 (22.0%)	70 (28.7%)	12 (10.0%)	NA	0.0081	0.0001
Failure	188 (78.0%)	174 (71.3%)	108 (90.0%)			

Source: Final Study Report TOL-AK-2008-02, Table 14.2.1, pg. 87.

Table 17: Prespecified Secondary Efficacy Analysis; per Sponsor: At Least 75% Clearance of AK Lesions at visit 6/week 16 (4 weeks follow-up)

Parameter	Test	Reference	Vehicle	90% C.I. for Bioequivalence of Test to Reference	p-values	
					Test vs. Vehicle	Reference vs. Vehicle
Per-Protocol Subjects (n, %)						
	n=187	n=180	n=93			
Success	77 (41.2%)	89 (49.4%)	22 (23.7%)	(-17.3%, 0.8%)	NA	NA
Failure	110 (58.8%)	91 (50.6%)	71 (76.3%)			
Modified Intent-to-Treat Subjects (n, %)						
	n=241	n=244	n=120			
Success	98 (40.7%)	107 (43.9%)	24 (20.0%)	NA	0.0001	<0.0001
Failure	143 (59.3%)	137 (56.1%)	96 (80.0%)			

Source: Final Study Report TOL-AK-2008-02, Table 14.2.2, pg. 88.

Reviewer's comment: *The sponsor failed to perform any assessment of treatment compliance. In their Listing 16.2.5.2 entitled "Listing of Diary Compliance", the sponsor provided the number of applications recorded in the subject's diary since their previous visit for each subject; however, they failed to provide the total number of applications during the study per subject, which would have permitted an assessment of those subjects with less than 134 or more than 202 applications.*

D. Bioequivalence Conclusion

No conclusion can be made regarding whether the sponsor demonstrated bioequivalence in TOL-AK-2008-02, because the study was not designed to have optimum sensitivity to detect a difference in product performance. Given the difference in formulation, the lack of study sensitivity, and the study results having a 90% CI entirely below 0, this study suggests that the product is inferior in efficacy to the RLD. Given the characteristics of the excipients that were deleted and replaced in the test product compared to the RLD, there is also no assurance that the systemic diclofenac exposure of the test and reference products would be similar.

V. Comparative Review of Safety

A. Brief Statement of Conclusions

The sponsor concluded that the safety profile of the test product was not statistically or clinically different than that of the reference product in the treatment of actinic keratoses.[25]

B. Description of Adverse Events

Safety was evaluated through a review of adverse events (AEs). Adverse events were recorded at each visit after Visit 1/Baseline. The greatest intensity or severity of each adverse event was reported as mild (i.e., AE that is easily tolerated), moderate (i.e., AE sufficiently discomforting to interfere with daily activity), and severe (i.e., AE that prevents normal daily activities). Tolerance was evaluated by assessing treated areas for local skin reactions. Local skin reactions were recorded at each visit after Visit 1/Baseline during the assessment of treated areas and were not recorded as AEs, unless, in the opinion of the Investigator, the event qualified as an AE.

A total of 158 subjects [69 (28.6%) in the test, 58 (23.6%) in the reference, and 31 (25.6%) in the vehicle group) experienced one or more treatment-emergent adverse events. Twenty (3.3%) subjects (8 test, 9 reference, 3 vehicle) discontinued the study due to "withdrawal due to adverse event". An additional 15 subjects (11 test, 3 reference, 1 vehicle) withdrew due to a local skin reaction, which the sponsor coded as "Other". This suggests that the test product may cause more skin reactions than the RLD.

Seventeen (17) subjects had at least one adverse event that was considered to be severe (7 test, 7 reference, 3 vehicle). Two of these severe adverse events were "hypersensitivity" (one test, one reference). Of note, the test group had 4 subjects who experienced a severe AE in the MedDRA system organ class "Skin and subcutaneous tissue disorders" (dermatitis contact=2; rash=1; skin irritation=1) compared to only 1 subject in the reference group (skin erosion=1) and no subject in the vehicle group.

Skin-related adverse events listed in the "Skin and subcutaneous tissue disorders" MedDRA system organ class, regardless of relationship to the study medication, occurred in 22 subjects (12 test, 8 reference, 2 vehicle). Skin-related adverse events probably or definitely related to study medication occurred in 17 subjects (9 test, 6 reference, 2 vehicle). Additionally, 3 skin-related adverse events were listed in the "General disorders and administration site conditions", MedDRA system organ class and all were considered to be related: the AE "application site erythema" was reported by 1 test subject, the AE "application site irritation" was reported by 1 reference subject, and the AE "application site rash" was reported by 1 test subject. Severe "Skin and subcutaneous tissue disorders" AEs occurred in five subjects; severe contact dermatitis was reported in 2 test subjects and was not reported in the other treatment groups; severe rash was reported in 1 test subject and was not reported in the other treatment groups; severe skin erosion was reported in 1 reference subject and was not reported in the other treatment groups; severe skin irritation was reported in 1 test subject and was not reported in the other treatment groups.[26] According to the sponsor's analysis, there were no notable differences between the treatment

[25] ANDA 200936 Section 5.3.1.2 (pg. 1 of 1).
[26] Final Study Report (pg. 60 of 217).

groups in the percentage of subjects with skin reactions reported as AEs related to study drug, with the exception of hypersensitivity reactions related to study drug being more common in the reference group (n=5).[27]

No deaths occurred in the study. Thirteen serious adverse events were experienced by 13 subjects (5 test, 5 reference, 3 vehicle) and none were considered by the sponsor to be related to the study drug. One of these SAEs (prostate cancer in test group) occurred in the 30-day follow-up period and was not reported until after data base lock.

The sponsor's summary of adverse events is listed in Tables 18 and 19 below. The list of serious adverse events by subject is shown in Table 20.

Reviewer's comment: *The frequency of any treatment-emergent adverse event (both "regardless of relationship to study medication" and "related to the study treatment") and the frequency of treatment-emergent skin-related AEs (both "regardless of relationship to study medication" and "related to the study treatment") were all numerically higher in the test group. Both the withdrawals due to a local skin reactions and the reported skin-related adverse events suggest that the test product may cause more skin reactions than the RLD.*

Table 18: Treatment-Emergent Adverse Events by Relationship (per Sponsor; ITT Population)

Type	Parameter	Test n=241	Reference n=246	Vehicle n=121
Overall	Subjects with any adverse event regardless of relationship to study medication	69 (28.6%)	58 (23.6%)	31 (25.6%)
	Subjects with any adverse events related to study medication	20 (8.3%)	14 (5.7%)	3 (2.5%)
Skin-Related	Subjects with skin-related adverse events regardless of relationship to study medication	12 (5.0%)	8 (3.3%)	2 (1.7%)
	Subjects with skin-related adverse events related to study medication	9 (3.7%)	6 (2.4%)	2 (1.7%)

Source: ANDA 200936 Final Study Report Table 14.3.1.1 pg. 103, Table 12-2 pg. 56, and Table 12-3 pg. 58.

Table 19: Incidence of Adverse Events in TOL-AK-2008-02 (per Sponsor; ITT Population)

MedDRA System Organ Class Preferred Term	**Diclofenac Sodium Gel, 3% (N=242)**	**Solaraze™ Gel, 3% (N=246)**	**Vehicle (N=121)**
Total Number of subjects reporting one or more Adverse Event (AE)	69 (28.5%)	58 (23.6%)	31 (25.6%)
Total Number of subjects reporting an Individual AE (i.e., total of numbers in column)	101	85	52
Blood and lymphatic system disorders			

[27] Final Study Report (pg. 70 of 217).

MedDRA System Organ Class Preferred Term	Diclofenac Sodium Gel, 3% (N=242)	Solaraze™ Gel, 3% (N=246)	Vehicle (N=121)
Anemia	--	--	1 (0.8%)
Lymphoid tissue hyperplasia	--	1 (0.4%)	--
Cardiac disorders			
Arteriosclerosis coronary artery	--	--	1 (0.8%)
Bradycardia	1 (0.4%)	--	--
Myocardial infarction	--	1 (0.4%)	--
Ear and labyrinth disorders			
Cerumen impaction	1 (0.4%)	--	--
Ear pain	--	1 (0.4%)	--
Vertigo	--	1 (0.4%)	1 (0.8%)
Eye disorders			
Conjunctivitis	--	1 (0.4%)	1 (0.8%)
Eye irritation	1 (0.4%)	--	--
Eyelid exfoliation	1 (0.4%)	--	--
Ocular hyperemia	1 (0.4%)	--	--
Gastrointestinal disorders			
Abdominal pain upper	--	1 (0.4%)	--
Colitis ulcerative	--	1 (0.4%)	--
Diarrhea	1 (0.4%)	2 (0.8%)	1 (0.8%)
Diverticulum	--	--	1 (0.8%)
Dyspepsia	1 (0.4%)	1 (0.4%)	--
Gastritis	1 (0.4%)	1 (0.4%)	--
Gastroesophageal reflux disease	--	1 (0.4%)	--
Gingival pain	1 (0.4%)	--	--
Nausea	1 (0.4%)	1 (0.4%)	2 (1.7%)
Oral pain	1 (0.4%)	--	--
Toothache	1 (0.4%)	2 (0.8%)	1 (0.8%)
Vomiting	--	2 (0.8%)	1 (0.8%)
General disorders and administration site conditions			
Application site erythema	1 (0.4%)	--	--
Application site irritation	--	1 (0.4%)	--
Application site rash	1 (0.4%)	--	--
Application site scar	1 (0.4%)	--	--
Chest pain	1 (0.4%)	--	1 (0.8%)
Edema peripheral	1 (0.4%)	1 (0.4%)	1 (0.8%)
Immune system disorders			
Hypersensitivity	1 (0.4%)	5 (2.0%)	--
Infections and infestations			
Adenoviral upper respiratory infection	--	--	1 (0.8%)
Bronchitis	1 (0.4%)	2 (0.8%)	--
Cellulitis	1 (0.4%)	--	--

MedDRA System Organ Class Preferred Term	**Diclofenac Sodium Gel, 3% (N=242)**	**Solaraze™ Gel, 3% (N=246)**	**Vehicle (N=121)**
Gastroenteritis viral	--	--	1 (0.8%)
Herpes zoster	1 (0.4%)	1 (0.4%)	1 (0.8%)
Influenza	1 (0.4%)	--	--
Localized infection	--	1 (0.4%)	--
Lower respiratory tract infection	--	1 (0.4%)	--
Lyme disease	--	--	1 (0.8%)
Nasopharyngitis	4 (1.7%)	2 (0.8%)	2 (1.7%)
Otitis media	1 (0.4%)	--	--
Pneumonia	1 (0.4%)	1 (0.4%)	--
Respiratory tract infection	--	1 (0.4%)	--
Rhinitis	1 (0.4%)	--	1 (0.8%)
Sinusitis	2 (0.8%)	2 (0.8%)	--
Skin infection	--	2 (0.8%)	--
Tooth abscess	4 (1.7%)	--	--
Upper respiratory tract infection	3 (1.2%)	3 (1.2%)	5 (4.1%)
Urinary tract infection	2 (0.8%)	--	1 (0.8%)
Injury, poisoning and procedural complications			
Arthropod bite	1 (0.4%)	--	1 (0.8%)
Conjunctival abrasion	--	--	1 (0.8%)
Contusion	--	--	1 (0.8%)
Excoriation	3 (1.2%)	--	--
Foot fracture	--	1 (0.4%)	--
Meniscus lesion	1 (0.4%)	--	--
Muscle strain	1 (0.4%)	--	--
Postoperative constipation	1 (0.4%)	--	--
Procedural nausea	1 (0.4%)	--	--
Procedural pain	1 (0.4%)	--	--
Sunburn	--	1 (0.4%)	--
Tendon rupture	--	1 (0.4%)	--
Investigations			
Biopsy skin	--	--	1 (0.8%)
Blood cholesterol increased	--	1 (0.4%)	1 (0.8%)
Blood pressure increased	1 (0.4%)	--	--
Cardiac murmur	--	1 (0.4%)	--
Heart rate irregular	--	1 (0.4%)	--
Prostatic specific antigen increased	--	1 (0.4%)	--
Metabolism and nutrition disorders			
Decreased appetite	--	1 (0.4%)	--
Gout	--	1 (0.4%)	1 (0.8%)
Hyperlipidemia	--	1 (0.4%)	--
Musculoskeletal and connective tissue disorders			

MedDRA System Organ Class Preferred Term	Diclofenac Sodium Gel, 3% (N=242)	Solaraze™ Gel, 3% (N=246)	Vehicle (N=121)
Arthralgia	--	2 (0.8%)	--
Back pain	4 (1.7%)	1 (0.4%)	1 (0.8%)
Bursitis	1 (0.4%)	--	1 (0.8%)
Intervertebral disc protrusion	--	1 (0.4%)	--
Joint swelling	1 (0.4%)	--	--
Neck pain	1 (0.4%)	--	--
Osteoarthritis	--	1 (0.4%)	2 (1.7%)
Osteoporosis	--	1 (0.4%)	--
Pain in extremity	2 (0.8%)	2 (0.8%)	--
Neoplasms benign malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma	3 (1.2%)	--	1 (0.8%)
Benign neoplasm of spinal cord	--	1 (0.4%)	--
Malignant melanoma	--	--	1 (0.8%)
Neoplasm	2 (0.8%)	--	--
Prostate cancer	1 (0.4%)	--	--
Seborrheic keratoses	--	3 (1.2%)	--
Skin papilloma	1 (0.4%)	--	--
Squamous cell carcinoma	1 (0.4%)	--	--
Squamous cell carcinoma of skin	1 (0.4%)	--	1 (0.8%)
Nervous system disorders			
Amnesia	--	1 (0.4%)	--
Burning sensation	1 (0.4%)	--	--
Dizziness	1 (0.4%)	--	--
Dysgeusia	--	--	1 (0.8%)
Headache	7 (2.9%)	2 (0.8%)	3 (2.5%)
Hyperesthesia	1 (0.4%)	--	--
Syncope	--	--	1 (0.8%)
Psychiatric disorders			
Abnormal dreams	--	1 (0.4%)	--
Anxiety	--	--	1 (0.8%)
Depression	--	1 (0.4%)	--
Insomnia	1 (0.4%)	--	--
Renal and urinary disorders			
Nephrolithiasis	1 (0.4%)	--	--
Reproductive system and breast disorders			
Prostatitis	1 (0.4%)	--	--
Respiratory, thoracic and mediastinal disorders			
Asthma	--	1 (0.4%)	--
Cough	1 (0.4%)	1 (0.4%)	1 (0.8%)
Nasal congestion	1 (0.4%)	--	--
Pharyngolaryngeal pain	1 (0.4%)	--	1 (0.8%)

MedDRA System Organ Class Preferred Term	Diclofenac Sodium Gel, 3% (N=242)	Solaraze™ Gel, 3% (N=246)	Vehicle (N=121)
Post procedural pulmonary embolism	--	--	1 (0.8%)
Pulmonary embolism	--	--	1 (0.8%)
Rhinitis allergic	1 (0.4%)	--	--
Sinus congestion	1 (0.4%)	1 (0.4%)	--
Sneezing	--	--	1 (0.8%)
Skin and subcutaneous tissue disorders			
Actinic keratoses	--	1 (0.4%)	--
Dermatitis contact	4 (1.7%)	1 (0.4%)	--
Erythema	1 (0.4%)	--	--
Periorbital edema	--	1 (0.4%)	--
Rash	1 (0.4%)	2 (0.8%)	1 (0.8%)
Seborrheic dermatitis	1 (0.4%)	--	--
Skin discoloration	1 (0.4%)	--	--
Skin erosion	--	1 (0.4%)	--
Skin hypopigmentation	1 (0.4%)	1 (0.4%)	--
Skin irritation	1 (0.4%)	1 (0.4%)	--
Skin lesion	1 (0.4%)	1 (0.4%)	--
Skin plaque	1 (0.4%)	--	--
Skin reaction	1 (0.4%)	--	--
Skin swelling	--	1 (0.4%)	--
Swelling face	--	--	1 (0.8%)
Surgical and medical procedures			
Hip arthroplasty	1 (0.4%)	--	--
Knee arthroplasty	--	--	1 (0.8%)
Micrographic skin surgery	1 (0.4%)	--	--
Vascular disorders			
Aortic aneurysm	--	1 (0.4%)	--
Cerebrovascular accident	--	1 (0.4%)	--
Hypertension	--	2 (0.8%)	--
Intermittent claudication	--	1 (0.4%)	--

Source: ANDA 20936 Summary Table 8; Counts reflect number of subjects reporting one or more adverse events. Subjects reporting more than one adverse event in a category are only counted once.

Table 20: Serious Adverse Events (per Sponsor; ITT Population) n=13

SAE	Number (%) of Subjects		
	Test n=241	Reference n=246	Vehicle n=121
	SAEs n=5 (2.0%)	SAEs n=5 (2.0%)	SAEs n=3 (2.5%)
Cerebrovascular accident		1 (Subject (b) (6)	
Basal cell carcinoma	1 (Subject (b) (6)		
Lymphoid tissue hyperplasia		1 (Subject	
Myocardial infarction		1 (Subject	
Prostate cancer	2 (Subjects (b) (6)		

SAE	Number (%) of Subjects		
	Test n=241	Reference n=246	Vehicle n=121
	SAEs n=5 (2.0%)	SAEs n=5 (2.0%)	SAEs n=3 (2.5%)
Osteoarthritis			1 (Subject (b) (6)
Hip arthroplasty	1 (Subject (b) (6)		
Pneumonia	1 (Subject	1 (Subject (b) (6)	
Malignant melanoma			1 (Subject
Foot fracture		1 (Subject	
Pulmonary embolism: Post procedural pulmonary embolism Post-operative: knee arthroplasty			1 (Subject

Source: ANDA 200936 Final Study Report Appendix 14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events p. 172-216.

Table 21: Summary of Serious Adverse Events by Subject (per Reviewer)

Site-Subject number	Treatment	Serious Adverse Event Listed on SAE Narrative; details
(b) (6)	Reference	**Cerebral vascular accident**; 65 year old male; began treatment (b) (6); 2 weeks later subject opted to withdraw consent due to skin reactions and he experienced loss of memory and disorientation during early termination visit on (b) (6); hospitalized (b) (6) for transient ischemic attack workup; Investigator considered event to be unrelated to study drug.
	Test	**Left temple basal cell carcinoma, nodular and infiltrative subtype to deep margin**; 68 year old male; narrative did not provide treatment start date; pathology report for skin biopsy of left temple performed on (b) (6) revealed Basal Cell Carcinoma, Nodular and Infiltrative Subtype to Deep Margin; underwent MOHS surgery with A-T plasty with length of repair 7 cm^2; continued in study; Investigator considered event to be unrelated to study drug.
	Reference	**Right superior postural area cutaneous lymphoid hyperplasia OR possibly a low-grade B-cell lymphoma**; 83 year old male; narrative did not provide treatment start date; pathology report for two skin biopsies from behind right ear performed on (b) (6) revealed "Lesion 1 is atypical lymphoid infiltrated with differential diagnosis including cutaneous lymphoid hyperplasia OR possibly a low-grade B cell lymphoma; Lesion 2 is an inflamed seborrheic keratoses"; subject referred for additional treatment, missed appointment and during End of Study visit on (b) (6), refused any follow-up; Investigator considered event to be unrelated to study drug.
	Reference	**Myocardial infarction**; 69 year old male; narrative did not provide treatment start date; presented to ER with chest pain on (b) (6) and admitted; underwent selective coronary angiography with stent placement in proximal RCA; complete Visit 6/Day 112 visit on (b) (6) Investigator considered event to be unrelated to study drug.
	Test	**Prostate cancer**; 73 year old male; narrative did not provide treatment start date; PSA elevated on (b) (6); underwent ultrasound and prostate biopsy on (b) (6) with diagnosis prostate cancer; plan was to have subject see urologist on (b) (6) continued in study; Investigator considered event to be unrelated to study drug.
	Test	**Prostate cancer**; 62 year old male; completed study (b) (6) and diagnosed with prostate cancer on (b) (6) underwent radical prostatectomy on (b) (6) Investigator considered event to be unrelated to study drug.
	Vehicle	**Right knee arthroplasty surgery**; 76 year old male; narrative did not provide treatment start date; underwent total knee arthroplasty (replacement) surgery due to osteoarthritis on (b) (6) continued in study; Investigator considered event to be unrelated to study drug.
	Test	**Total hip arthroplasty to right hip due to degenerative joint disease**; 64 year old male; randomized to treatment on (b) (6); hospitalized on (b) (6) for total hip

Site-Subject number	Treatment	Serious Adverse Event Listed on SAE Narrative; details
(b) (6)		replacement; continued in study; Investigator considered event to be unrelated to study drug.
	Reference	**Pneumonia**; 81 year old male; randomized to treatment on (b) (6); on (b) (6) hospitalized for pneumonia; discontinued from the study as a result of this event; Investigator considered event to be unrelated to study drug.
	Vehicle	**Malignant melanoma**; 81 year old male; narrative did not provide treatment start date; reported lesion on right forearm to Investigator during Visit 3/day 28 and biopsy revealed melanoma, nodular growth patter with ulceration; on (b) (6) underwent wide local excision with sentinel lymph node biopsy right axilla and full thickness skin graft; discontinued from the study as a result of this event; Investigator considered event to be unrelated to study drug.
	Reference	**Left type 1 open calcaneal fracture**; 59 year old male; randomized to treatment on (b) (6); on (b) (6) fell from a step ladder, broke his foot, hospitalized and underwent irrigation and debridement; on (b) (6) underwent open reduction and internal fixation; continued in study; Investigator considered event to be unrelated to study drug.
	Vehicle	**Partial left knee replacement for left knee medial osteoarthritis, pulmonary embolus, pulmonary embolus post-operative**; 75 year old male; narrative did not provide treatment start date; underwent left knee replacement on (b) (6) became unresponsive on (b) (6) and CT chest revealed bilateral pulmonary emboli; discontinued from the study as a result of this event; Investigator considered event to be unrelated to study drug.
	Test	**Pneumonia**; 95 year old male; on (b) (6) found confused and unresponsive at home; hospitalized for extensive right lower lobe pneumonia and intubated; discontinued from the study as a result of this event and completed early discharge visit on (b) (6); Investigator considered event to be unrelated to study drug.

Source: ANDA 200936 Final Study Report Appendix 14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events p. 172-216.

Evaluation of Local Skin Reactions

According to the sponsor's analysis:

1) The majority of subjects in each treatment group at both Baseline and End of Treatment (EOT) either did not have the specified skin reaction or had reactions that were categorized as mild.
2) In both active treatment groups, the percentage of subjects with moderate or severe local reactions increased between Baseline and Visit 6/Day 112.
3) Changes in severity were generally similar in the Diclofenac sodium Gel and Solaraze® Gel treatment groups.

The frequency and severity of local skin reactions were tabulated by the sponsor in Tables 22 and 23.

Table 22: Evaluation of Local Skin Reaction for Intent to Treat Subjects at visit 5 (end of therapy; week 12), per Sponsor

Parameter	Category	Test n=241	Reference n=246	Vehicle n=121
Burning	None	179 (74.3%)	165 (67.1%)	99 (81.8%)
	Mild	18 (7.5%)	31 (12.6%)	9 (7.4%)
	Moderate	11 (4.6%)	10 (4.1%)	0
	Severe	3 (1.2%)	1 (0.4%)	0

Parameter	Category	Test n=241	Reference n=246	Vehicle n=121
Erythema (Redness)	None	94 (39.0%)	79 (32.1%)	52 (43.0%)
	Mild	84 (34.9%)	86 (35.0%)	46 (38.0%)
	Moderate	30 (12.4%)	35 (14.2%)	10 (8.3%)
	Severe	3 (1.2%)	7 (2.8%)	0
Epidermal Desquamation (Dryness/Flaking/Scaling)	None	143 (59.3%)	137 (55.7%)	72 (59.5%)
	Mild	87 (36.1%)	93 (37.8%)	40 (33.1%)
	Moderate	11 (4.6%)	16 (6.5%)	9 (7.4%)
	Severe	0	0	0
Pruritus (Itching)	None	166 (68.9%)	144 (58.5%)	86 (71.1%)
	Mild	26 (10.8%)	44 (17.9%)	21 (17.4%)
	Moderate	15 (6.2%)	16 (6.5%)	1 (0.8%)
	Severe	4 (1.7%)	3 (1.2%)	0
Pain	None	199 (82.6%)	198 (80.5%)	105 (86.8%)
	Mild	7 (2.9%)	8 (3.3%)	3 (2.5%)
	Moderate	4 (1.7%)	1 (0.4%)	0
	Severe	1 (0.4%)	0	0
Edema (Swelling)	None	196 (81.3%)	187 (76.0%)	106 (87.6%)
	Mild	14 (5.8%)	14 (5.7%)	2 (1.7%)
	Moderate	1 (0.4%)	5 (2.0%)	0
	Severe	0	1 (0.4%)	0
Erosion/Ulceration	None	197 (81.7%)	185 (75.2%)	106 (87.6%)
	Mild	11 (4.6%)	16 (6.5%)	1 (0.8%)
	Moderate	3 (1.2%)	5 (2.0%)	1 (0.8%)
	Severe	0	1 (0.4%)	0
Weeping/Exudate (Fluids discharge in tissue or cavities)	None	206 (85.5%)	200 (81.3%)	107 (88.4%)
	Mild	5 (2.1%)	4 (1.6%)	1 (0.8%)
	Moderate	0	2 (0.8%)	0
	Severe	0	1 (0.4%)	0
Scabbing/Crusting/Crusted, dried pus, lymph or blood	None	190 (78.8%)	170 (69.1%)	102 (84.3%)
	Mild	11 (4.6%)	25 (10.2%)	4 (3.3%)
	Moderate	10 (4.1%)	10 (4.1%)	2 (1.7%)
	Severe	0	2 (0.8%)	0
Vesicles (Fluid containing structures)	None	211 (87.6%)	203 (82.5%)	108 (89.3%)
	Mild	0	1 (0.4%)	0
	Moderate	0	2 (0.8%)	0
	Severe	0	1 (0.4%)	0

Source: ANDA 200936 Final Study Report Tables 14.3.1.6.1 on pg. 152, 14.3.1.6.2 on pg. 154, 14.3.1.6.3 on pg. 156, 14.3.1.6.4 on pg. 158, 14.3.1.6.5 on pg. 160, 14.3.1.6.6 on pg. 162, 14.3.1.6.7 on pg. 164, 14.3.1.6.8 on pg. 166, 14.3.1.6.9 on pg. 168 and 14.3.1.6.10 on pg. 170.

Table 23: Evaluation of Local Skin Reaction for Intent to Treat Subjects at visit 6/week 16 (4 weeks follow-up), per Sponsor

Parameter	Category	Test n=241	Reference n=246	Vehicle n=121
Burning	None	223 (92.5%)	224 (91.1%)	115 (95.0%)
	Mild	3 (1.2%)	6 (2.4%)	0
	Moderate	4 (1.7%)	8 (3.3%)	1 (0.8%)
	Severe	4 (1.7%)	4 (1.6%)	1 (0.8%)
Erythema (Redness)	None	155 (64.3%)	153 (62.2%)	68 (56.2%)
	Mild	62 (25.7%)	66 (26.8%)	45 (37.2%)
	Moderate	12 (5.0%)	19 (7.7%)	4 (3.3%)
	Severe	5 (2.1%)	4 (1.6%)	0

Parameter	Category	Test n=241	Reference n=246	Vehicle n=121
Epidermal Desquamation (Dryness/Flaking/Scaling)	None	173 (71.8%)	171 (69.5%)	86 (71.1%)
	Mild	51 (21.2%)	57 (23.2%)	26 (21.5%)
	Moderate	6 (2.5%)	12 (4.9%)	5 (4.1%)
	Severe	4 (1.7%)	2 (0.8%)	0
Pruritus (Itching)	None	215 (89.2%)	214 (87.0%)	108 (89.3%)
	Mild	9 (3.7%)	11 (4.5%)	8 (6.6%)
	Moderate	6 (2.5%)	12 (4.9%)	0
	Severe	4 (1.7%)	5 (2.0%)	1 (0.8%)
Pain	None	225 (93.4%)	228 (92.7%)	117 (96.7%)
	Mild	4 (1.7%)	6 (2.4%)	0
	Moderate	2 (0.8%)	5 (2.0%)	0
	Severe	3 (1.2%)	3 (1.2%)	0
Edema (Swelling)	None	222 (92.1%)	223 (90.7%)	116 (95.9%)
	Mild	9 (3.7%)	11 (4.5%)	0
	Moderate	3 (1.2%)	5 (2.0%)	1(0.8%)
	Severe	0	3 (1.2%)	0
Erosion/Ulceration	None	223 (92.5%)	228 (92.7%)	117 (96.7%)
	Mild	10 (4.1%)	6 (2.4%)	0
	Moderate	1 (0.4%)	3 (1.2%)	0
	Severe	0	5 (2.0%)	0
Weeping/Exudate (Fluids discharge in tissue or cavities)	None	228 (94.6%)	234 (95.1%)	117 (96.7%)
	Mild	5 (2.1%)	5 (2.0%)	0
	Moderate	0	2 (0.8%)	0
	Severe	1 (0.4%)	1 (0.4%)	0
Scabbing/Crusting/Crusted, dried pus, lymph or blood	None	220 (91.3%)	220 (89.4%)	114 (94.2%)
	Mild	8 (3.3%)	9 (3.7%)	3 (2.5%)
	Moderate	3 (1.2%)	9 (3.7%)	0
	Severe	3 (1.2%)	4 (1.6%)	0
Vesicles (Fluid containing structures)	None	232 (96.3%)	237 (96.3%)	117 (96.7%)
	Mild	1 (0.4%)	2 (0.8%)	0
	Moderate	1 (0.4%)	1 (0.4%)	0
	Severe	0	2 (0.8%)	0

Source: ANDA 200936 Final Study Report Tables 14.3.1.6.1 on pg. 152, 14.3.1.6.2 on pg. 154, 14.3.1.6.3 on pg. 156, 14.3.1.6.4 on pg. 158, 14.3.1.6.5 on pg. 160, 14.3.1.6.6 on pg. 162, 14.3.1.6.7 on pg. 164, 14.3.1.6.8 on pg. 166, 14.3.1.6.9 on pg. 168 and 14.3.1.6.10 on pg. 170.

Reviewer's comment: *As expected, a more intense degree of local skin reaction occurred with the active treatments compared to the vehicle. Compared to baseline (see Table 12) when no subject had any severe local skin reactions, subjects in the active treatment groups at visit 6 were found to have severe burning (n=8: 4 test, 4 reference), severe erythema (n=9: 5 test, 4 reference), severe epidermal desquamation (n=6: 4 test, 2 reference), severe pruritus (n=9: 4 test, 5 reference), severe pain (n=6: 3 test, 3 reference), severe edema (n=3 reference), severe erosion/ulceration (n=5 reference), severe weeping/exudate (n=2: 1 test, 1 reference), severe scabbing/crusting/crusted dried pus (n=7: 3 test, 4 reference), lymph or blood and severe vesicles (n=2 reference). Overall, the reference product resulted in numerically more moderate and severe local skin reactions than the test product.*

VI. Relevant Findings From Division of Scientific Investigations, Statistics and/or Other Consultant Reviews

A. Review of the Division of Scientific Investigation (DSI) Report
A DSI inspection was not requested for this study due to the unacceptable study design.

B. Review of the FDA Statistical Report
A FDA statistical analysis was not requested for this study due to the unacceptable study design.

C. Review of DARRTS Supp. Document No. 4
On April 26, 2010, the OGD issued a "refuse to receive" letter for ANDA 200936 under CFR 314.101(d)(3) for the following reasons:

> Your clinical endpoint bioequivalence study did not meet statutory requirements. For optimum sensitivity to detect differences between the test and reference products, the OGD requests that the treatment be administered for only 60 days and the primary endpoint be evaluated at the study day 90, 30 days after the end of treatment. This is the earliest time at which a significant success proportion is expected and would be the most likely time to detect differences between test and reference products. Your study applied the study treatment for 84 days which is longer than the treatment duration recommended for demonstrating bioequivalence of this product. Your longer treatment duration is likely to obscure potential differences in formulation performance. You may submit a protocol for review and concurrence before conducting another study.

On June 3, 2010 (DARRTS received date June 4, 2010), the lawyer representing the sponsor (i.e., Robert C. Thies, Hyman, Phelps & McNamara, P.C.) submitted an 18-page letter appealing the OGD's "refuse to receive" decision (DARRTS Supp. Document No. 4). Their letter requested that the Agency to immediate rescind its April 26, 2010 letter that revoked OGD's prior receipt of ANDA 200936. The letter also stated that "OGD's unilateral revocation of its prior decision is scientifically incorrect and contrary to law and agency precedent." To support this statement, the sponsor argued that their study design was acceptable because: 1) Tolmar had conducted a BE study with a clinical endpoint of the same duration and of a similar design as the Phase 3 efficacy and safety study conducted to support the approval of Solaraze® Gel; and 2) the inactive ingredients used by Tolmar are different than those used in the RLD formulation; thus, Tolmar needed to establish the safety of its formulation by conducting a BE with clinical endpoint study (i.e., by conducting a clinical study with a 90-day treatment duration). In the letter, Tolmar admitted that they had not sought the advice of the Agency prior to conducting their study (i.e., by submitting to the OGD a Controlled Correspondence or Protocol) because they anticipated a lengthy time for OGD response.

The sponsor's argument that the study design of Tolmar's BE study with a clinical endpoint is acceptable because it "matches" the study design of the Phase 3 efficacy and safety study conducted to support the approval of Solaraze® Gel is irrelevant. A BE study with a clinical endpoint study has a completely different purpose (i.e., to determine bioequivalence) than a Phase 3 efficacy and safety study (i.e., to determine efficacy and safety). A BE study with a clinical endpoint must be designed to best reveal whether there is any significant difference

between the test product and the RLD. Thus, the OGD carefully considered what factors would be most likely to mask any such difference for this specific drug product, including a prolonged treatment duration, enrolling subjects with a large number of AK lesions (likely to decrease the possibility of achieving complete clearance of all AK lesions in the treatment area) or enrolling subjects with AKs located in an anatomic area believed to be more difficult to treat (such as the forearm/arm and back of the hand). The posted Draft Guidance on Diclofenac Gel/Topical, 3% specifically addresses these various factors by recommending that subjects be treated for the shortest time period that demonstrated efficacy (i.e., 60 days) and enrolling subjects with a defined number of AK lesions (i.e., at least five and no more than ten) located on the face or bald scalp. The sponsor also argues that the 90-day treatment duration based upon dose-response curved provided as "Figure 1" on p. 8-9. This argument fails to support their position because they failed to connect all of the data points for the active treatment in the first graph for Innovatory Study 03 (90 days). When the three points for the active treatment are connected, it clearly demonstrated that 90 days is at the top of the response curve for the active treatment. In addition, the third graph for Innovator Study 07 (90 days) failed to provide the data point for the active treatment at 90 days, i.e., the only two data points provided for the active treatment were at 60 and 120 days. while data points for the vehicle treatment were provided for baseline and at 60, 90, and 120 days).

The sponsor argued that because the ingredients used by Tolmar are different than those used in the RLD formulation, Tolmar needed to establish the safety of its formulation in a longer clinical study. This is not appropriate for a BE study. If safety issues are such a significant concern that longer safety studies are needed, then Tolmar needs to submit their drug product as a 505(b) NDA, instead of an ANDA. NDA studies must explore a longer duration of treatment to ensure maintenance of the maximal effect and to ensure safety over the maximum period of use. In contrast, an ANDA applicant relies on FDA's previous finding that the RLD is safe and effective. ANDA studies do not include safety and/or efficacy studies, only bioequivalence studies.

VII. Formulation

The active ingredient, route of administration, dosage form, and strength of Tolmar Inc.'s Diclofenac Sodium Gel, 3% is the same as the RLD. The inactive ingredients of Tolmar Inc.'s Diclofenac Sodium Gel, 3% are the same as the RLD with the following exceptions:

- Tolmar Inc. added a (b) (4) PEG-60 Hydrogenated Castor Oil, and (b) (4), Hydroxyethyl Cellulose, NF that are not found in the RLD.
- The RLD contains Hyaluronate Sodium and the Tolmar Inc.'s formulation does not.

Table 24: Formulation Comparison

Tolmar Inc.'s formulation			RLD's formulation	
Ingredient	**Function**	**Amount % w/w**	**Ingredient**	**% (w/w)**
Diclofenac Sodium, USP	Active Pharmaceutical Ingredient	3.0	Diclofenac Sodium	3.0
--	--	--	Hyaluronate Sodium	(b) (4)
Methoxypolyethylene Glycol 350, NF	(b) (4)		Polyethylene Glycol Monomethyl Ether	

Tolmar Inc.'s formulation			RLD's formulation	
Ingredient	Function	Amount % w/w	Ingredient	% (w/w)
PEG-60 Hydrogenated Castor Oil, NF		(b) (4)	--	(b) (4)
Benzyl Alcohol, NF			Benzyl Alcohol	
Hydroxyethyl Cellulose, NF			--	
Purified Water, USP			Purified Water	

Source: ANDA 200936 Section 2.7 Clinical Summary, Summary_Bioequivalence_Tables, Table 6 and Section 3.2.P.1 for Tolmar Inc.'s formulation; ANDA 200936 Section 3.2.P.2.1.2 and Approved Labeling for RLD's

(b) (4)

Reviewer's comments: *The test formulation is qualitatively and quantitatively different from the reference product. While the active pharmaceutical ingredient is the same, the test product was formulated with PEG-60 hydrogenated Castor Oil, NF as* (b) (4) *instead of the Hyaluronate Sodium in the RLD. The test formulation also differs from the reference by including Hydroxyethyl Cellulose, NF as* (b) (4) (b) (4) *However, there is limited in-vitro data in the scientific literature demonstrating in an in-vitro Franz cell model, that the diffusion of 14C-labeled diclofenac was sustained and controlled by hyaluronan as compared to a butter control, that a depot or reservoir of the drug was formed in the epidermis, and that it was probably this layer that determined the rate of release of diclofenac within the skin.*[29] *Thus, decreased efficacy might result if a generic sponsor, such as Tolmar, deletes the hyaluronate sodium from the formulation of Diclofenac Sodium Gel/Topical, 3%.*

VIII. Conclusions and Recommendation

A. Conclusions

1) The bioequivalence study with clinical endpoint TOL-AK-2008-02 submitted in ANDA 200936 is unacceptable due to study design elements that would tend to mask a significant difference in performance between the test and reference products. Due to these unacceptable design flaws, neither an FDA statistical analysis nor a DSI inspection was requested.

2) The OGD finds the design of TOL-AK-2008-02 unacceptable because it may not be adequately sensitive to detect a difference in product performance. It should be noted per 21 CFR 320.24 (b)(4), that well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately

(b) (4)

Brown MB et al. The effect of hyaluronan on the in vitro deposition of diclofenac within the skin. *International Journal of Tissue Reactions*. 1995; 17(4):133 -140.

designed comparative clinical trials, for the purposes of demonstrating bioequivalence, are the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence. It has been recommended that clinical trials as an approach to demonstrate bioequivalence generally are considered insensitive.[30] To improve the sensitivity of comparative clinical trials, the dosing regimen and period of dosing must be carefully selected. If the doses chosen for both agents are too high then subjects may reach an upper threshold in response, leading to a false conclusion of equivalence.[31] We consider the same to be true for longer treatment durations. In all 3 of the Innovator's pivotal Phase 3 clinical studies supporting approval, the primary efficacy variable was evaluated at the 30-day post-treatment visit and the dosing regimen was twice daily with approximately 0.5 gram of gel per "block" of affected skin. The primary difference between the 3 pivotal Phase 3 clinical studies supporting approval was the duration of treatment (i.e., 30, 60 or 90 days). The shortest treatment duration demonstrating a statistically significant difference between active drug and placebo (vehicle) for the primary endpoint was 60 days of treatment. Increasing the treatment duration to 90 days resulted in an overall higher complete clearance rate for the vehicle and did not consistently produce significantly higher cure rates for the active treatment. Thus, the 90 day treatment duration is more likely to capture only the maximum effect and not the rate and extent of drug delivery to the site of action. The OGD recommends that Diclofenac Sodium Gel/Topical 3% be administered twice daily for 60 days with the primary efficacy endpoint evaluated at the 30-day post-treatment assessment has been recommended by OGD in the bioequivalence study with a clinical endpoint. The study design of TOL-AK-2008-02 with an 84-day treatment duration, as it is likely to minimize any differences between the test and reference treatments.

3) The Inclusion criteria for TOL-AK-2008-02 did not specify either an upper limit on the number of AKs contained in the treatment area or a minimum size for the AKs counted in the treatment area. These factors would tend to increase the variability, as subjects with >10 AKs may differ in the rate of complete clearance of all lesions. Per the clinical reviewer's analysis of the baseline AK data submitted to ANDA 200936 in the DAS dataset , no subject was enrolled with less than 5 AKs within the treatment area; however, 23 subjects (7 test, 13 reference and 3 vehicle) were enrolled with 11-24 AKs within the treatment area at the baseline visit. The imbalance between the test and reference groups, with almost twice as many reference subjects than test subjects having >10 AKs within the treatment area at baseline, may change the rate of complete clearance of AKs and therefore decrease any apparent difference between the test and reference. The success rates by treatment group for the 23 subjects with 11-24 baseline AKs in the mITT population were all lower than the success rates in the corresponding treatment groups for all subjects in the mITT population. In addition, the success rates by treatment group for the 18 subjects with 11-24 baseline AKs in the PP population were all lower than the success rates in the corresponding treatment groups for all subjects in the PP population. We also note that 85 subjects (33 test, 31 reference, and 21 vehicle) with AKs located in treatment areas that are believed to be more difficult to eradicate, i.e., on the arms or back of the hands enrolled in TOL-AK-2008-02.

[30] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Bioavailability and bioequivalence studies for orally administered drug products-general considerations. March 2003; pg. 9.
[31] Jones B et al. Trials to assess equivalence: the importance of rigorous methods. *BMJ.* 1996; 313: 36-9.

The success rates by treatment group for the 85 subjects with AKs located on the arms or back of the hands in the mITT population were all lower than the success rates in the corresponding treatment groups for all subjects in the mITT population. In addition, the success rates by treatment group for the 69 subjects with AKs located on the arms or back of the hands in the PP population were all lower than the success rates in the corresponding treatment groups for all subjects in the PP population. The decreased efficacy of all three treatments for AKs located on the arms or back of the hands will tend to obscure any difference in the success rates between the three treatments. In the posted Draft Guidance on Diclofenac Sodium Gel/Topical, 3%, the OGD recommends including "Immunocompetent male or nonpregnant female at least 18 years of age with at least five (5) and no more than ten (10) clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AK lesions, each at least 4 mm in diameter, contained within a 25-cm^2 treatment area located on the face or bald scalp."

4) The clinical reviewer was not able to verify that the study protocol was approved by the two IRBs, and therefore is not able to conclude that study TOL-AK-2008-02 was in compliance with accepted ethical standards.

5) A draft guidance providing individual product bioequivalence recommendations for this product is available at the following website: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240969.pdf

B. Recommendation

Recommend issuing a complete response letter that incorporates the two CMC comments previously provided to us (i.e., the following Comments #1 and 2) and the Clinical Team comments (i.e., the following Comments #3 and 4):

(b) (4)

1)

2)

3) The design of TOL-AK-2008-02 is unacceptable because it may not be adequately sensitive to detect a difference in product performance. According to 21 CFR 320.24 (b)(4), well-

controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for the purposes of demonstrating bioequivalence, are the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence. Clinical trials as an approach to demonstrate bioequivalence generally are considered insensitive.[32] To improve the sensitivity of comparative clinical trials, the dosing regimen and period of dosing must be carefully selected. If the doses chosen for both agents are too high then subjects may reach an upper threshold in response, leading to a false conclusion of equivalence.[33] We consider the same to be true of longer treatment durations.

4) The primary difference between the 3 pivotal Phase 3 clinical studies supporting approval of the RLD was the duration of treatment (i.e., 30, 60 or 90 days). The shortest treatment duration demonstrating a statistically significant difference between active drug and placebo was 60 days of treatment. Increasing the treatment duration to 90 days resulted in an overall higher complete clearance rate only for the vehicle. Thus, the 90 day treatment duration is more likely to capture only the maximum effect and not the rate and extent of drug delivery to the site of action. The OGD recommends that Diclofenac Sodium Gel/Topical 3% be administered twice daily for 60 days with the primary efficacy endpoint evaluation at the 30-day post-treatment assessment in the bioequivalence study with clinical endpoint. Thus, the study design of TOL-AK-2008-02 with an 84-day treatment duration and the primary efficacy endpoint evaluation at the 28-day post-treatment assessment is not acceptable. The longer, 84-day treatment duration is likely to minimize any differences between the test and reference treatment effects.

_____ _____
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Barbara M. Davit, Ph.D., J.D. Date
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[32] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Bioavailability and bioequivalence studies for orally administered drug products-general considerations. March 2003; pg. 9.
[33] Jones B et al. Trials to assess equivalence: the importance of rigorous methods. *BMJ.* 1996; 313: 36-9.

VIV. Appendix

References:

1) Aithal GP et al. Hepatic adducts, circulating antibodies, and cytokine polymorphisms in patients with diclofenac hepatotoxicity. *Hepatology*. 2004 May; 39 (5): 1430-1440.
2) Banks AT et al. Diclofenac-associated hepatotoxicity: analysis of 180 cases reported to the Food and Drug Administration as adverse reactions. *Hepatology*. 1995 Sep; 22(3): 820-7.
3) Bhogaraju A et al. Diclofenac-associated hepatitis. *South Med J.* 1999 Jul; 92(7): 711-3.
4) Bjornsson E et al. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. *Scandinavian J Gastroenterology*. 2005; 40: 1095-1101.
5) Boelsterli UA. Diclofenac-induced liver injury: a paradigm of idiosyncratic drug toxicity. *Toxicology and Applied Pharmacology.* 2003; 192: 307-322.
6) Brown MB et al. The effect of hyaluronan on the in vitro deposition of diclofenac within the skin. *International Journal of Tissue Reactions*. 1995; 17(4):133 -140.
7) Brown MB et al. An in vitro investigation into the effect of glycosaminoglycans on the skin partitioning and deposition of NSAIDs. *Int J Pharm.* 2001 Aug 28; 225(1-2): 113-21.
8) Brown MB and Jones SA. Hyaluronic acid: a unique topical vehicle for the localized delivery of drugs to the skin. *J Eur Acad Dermatol Venereol.* 2005 May; 19(3): 308-18.
9) De Abajo FJ et al. Acute and clinically relevant drug-induced liver injury: a population based case-control study. *Br J Clin Pharmacol*. 2004: 58(1):71 -80.
10) Greaves RRS et al. Inadvertent diclofenac rechallenge from generic and non-generic prescribing, leading to liver transplantation for fulminant liver failure. *Eur J Gastroenterol Hepatol.* 2001; 13: 71-73.
11) Griffiths C. Drug treatment of photoaged skin. *Drugs & Aging*. 1999 Apr; 14(4): 289-301.
12) Helfgott SM et al. Diclofenac-associated hepatotoxicity. *JAMA.* 1990 Nov 28; 264(20): 2660-2.
13) Jarvis B and DP Figgitt. Topical 3% diclofenac in 2.5% hyaluronic acid gel: A review of its use in patients with actinic keratosis. *Am J Clin Dermatol*. 2003; 4(3): 203-213.
14) Jones AL et al. Fulminant hepatic failure due to diclofenac treated successfully by orthotopic liver transplantation. *Transplantation Proceedings.* 1998; 30: 192-194.
15) Liao YH et al. Hyaluronan: pharmaceutical characterization and drug delivery. *Drug Deliv.* 2005 Nov-Dec; 12(6): 327-42.
16) Merk HF. Topical diclofenac in the treatment of actinic keratoses. *International Journal of Dermatology*. 2007; 46: 12-18.
17) Peters DC and RH Foster. Diclofenac/hyaluronic acid. *Drugs & Aging*. 1999 Apr; 14(4): 313-9.
18) Rivers JK. Diclofenac/hyaluronic acid: A viewpoint by Jason K. Rivers. *Drugs & Aging*. 1999 Apr; 14(4): 320-1.
19) Rossi R et al. Actinic keratosis. *International Journal of Dermatology*. 2007; 46: 895-904.
20) Rostom A et al. Nonsteroidal anti-inflammatory drugs and hepatic toxicity: a systematic review of randomized controlled trials in arthritis patients. *Clinical Gastroenterology and Hepatology.* 2005; 3: 489-498.
21) Willoughby DA. Diclofenac/hyaluronic acid: A viewpoint by Derek A. Willoughby. *Drugs & Aging*. 1999 Apr; 14(4): 320-1.
22) Wolf JE et al. Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratosis. *International Journal of Dermatology*. 2001; 40: 709-713.

Table 25: Diclofenac Sodium Gel NDAs (n=2: Approved=2)

Active Ingredient; Form/Route; Strength	RLD; Approval Date; Sponsor; Marketing Status; IND	Approved Indication	OND Review Division
Diclofenac Sodium; Gel/Topical; 3% (a) (b)	NDA 021005 Solaraze®; Approved 10/16/00; Nycomed US Inc; Prescription; Related IND 041931 for treatment of simple basal cell carcinoma was submitted by Hyal Pharmaceutical Corporation Inc (Canada) on 4/1/93 (stamp date), is regulated by DDDP, is active (latest submission received 3/13/08) and current sponsor is Nycomed US Inc.	"for the topical treatment of actinic keratoses"	DDDP [Drug Classification listed in DARRTS is non-steroidal anti-inflammatory skin agents (4020700)]
Diclofenac Sodium; Gel/Topical; 1%	NDA 022122 Voltaren® Gel; Approved 10/17/07; Novartis Consumer Health, Inc; Prescription; Related IND 064334 for treatment of osteoarthritis was submitted on 11/28/00 (stamp date), is regulated by DAARP, is active (latest submission received 1/25/10) and current sponsor is Novartis Consumer Health, Inc.	"for the relief of the pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands"	DAAP [Drug Classification listed in DARRTS is non-narcotic analgesics (5030250)]

Source: Search by this reviewer of DARRTS, Orange Book, Daily Med and Drugs@ FDA conducted on 5/9/11.
DAAP=Division of Anesthesia and Analgesia Products
DARRTS=Document Archiving, Reporting & Regulatory Tracking System
DDDP=Division of Dermatology and Dental Products

(a) Regarding the pivotal Phase 3 clinical trials supporting approval of NDA 012005, per the Medical Officer Review of Original NDA 021005 and the Solaraze® Gel, 3% approved product labeling, three pivotal Phase 3 clinical trials were conducted in a total of 427 subjects (213 were randomized to Hyal's 3% diclofenac gel and 214 to gel vehicle):
   1) Study **CT1101-03** (US) randomized 120 subjects [59 were treated with diclofenac (27 with one treatment "block", 25 with two treatment "blocks", 7 with 3 treatment "blocks") [**NOTE**: if all lesions completely resolved in any given treatment 30-day "block", the subject was considered to have successfully completed the trial and could stop study drug]; 59 treated with vehicle (32 with one treatment "block", 21 with two treatment "blocks" and 6 with three treatment "blocks"); 2 subjects were excluded after randomization without evidence of drug use) at 4 sites.
   2) Study **CT1101-04** (Canada) randomized 195 subjects [97 treated with diclofenac (49 randomized to 30 days treatment with 1.2 "blocks" per subject; 48 for 60 days with 1.4 "blocks" per subject); 98 treated with vehicle (49 randomized to 30 days treatment with 1.3 "blocks" per subject; 49 for 60 days with 1.3 "blocks" per subject) at 6 sites.
   3) Study **CT1101-07** (US) randomized 112 subjects [56 were treated with diclofenac (54 with one treatment "block"; 2 with 2 treatment "blocks"); 55 treated with vehicle (all with 1 treatment "block"); 1 did not apply treatment] at one site.

Each subject had no fewer than five AK lesions in a major body area, contained in one to three (i.e., up to three major body areas were studied in any subject) 5 cm x 5 cm areas in a defined body region (i.e., scalp, forehead, face, forearm and back of hand). All subjects were 18 years of age or older (male and female) with no clinically significant medical problems outside of the AK lesions and had undergone a 60-day washout period from disallowed medications (masoprocol, etretinate, 5-fluorouracil, cyclosporine, retinoids, trichloroacetic acid/lactic acid/peel, 50% glycolic acid peel) and hyaluronan-containing cosmetics. Subjects were excluded from participation for reasons of known or suspected hypersensitivity to any Hyal's diclofenac gel ingredient, pregnancy, allergies to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), or other dermatological conditions in the designated treatment site

which might affect the absorption of the study medication. Application of dermatologic products such as sunscreens, cosmetics, and other drug products was not permitted. Subjects were instructed to avoid sun exposure.

Duration of treatment was 30 or 60 days in CT1101-04, and up to 90 days in the other two pivotal Phase 3 studies. Subjects were instructed to apply twice daily a small amount (i.e., approximately 0.5 g; however, some subjects used a plastic vaginal applicator adapted for use on the medication tubes and indicating when 0.5 gm of gel had been expressed into it, others were instructed to apply an amount of gel the "size of a pea or "one finger tip unit") of Hyal's 3% diclofenac gel or vehicle gel onto each "block" of affected skin using their fingers, followed by gently smoothing the gel into the affected skin. For subjects with 3 blocks of affected skin, the maximum daily dose was 3.0 grams. Every effort was to be made to apply the study medication at the same times during the day.

The primary efficacy variable was complete clearing of the AK lesions at the 30-day post-treatment visit in all treated major body sites (see Tables 26 and 27). No long term subject follow-up (i.e., after the 30-day post-treatment assessment) was performed for the detection of recurrence. Compliance was determined by both "actual weight of medication used/expected use x 100%" and by "actual number of applications/expected number x 100%".The sponsor also conducted studies assessing the primary skin irritation potential, contact sensitization potential and phototoxicity potential of Hyal's 3% diclofenac gel and subjects were assessed for the presence of serum antidiclofenac antibodies.

Table 26: Complete Clearance of Actinic Keratosis Lesions at 30 Days Post-Treatment (all locations)

		Solaraze® Gel	Vehicle	p-value
Study 1	90 days treatment	27/58 (47%)	11/59 (19%)	<0.001
Study 2	90 days treatment	18/53 (34%)	10/55 (18%)	0.061
Study 3	60 days treatment	15/48 (31%)	5/49 (10%)	0.021
	30 days treatment	7/49 (14%)	2/49 (4%)	0.221

Source: Solaraze® Approved Labeling dated 11/06 available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=2508

Table 27: Complete Clearance of Actinic Keratosis Lesions at 30 Days Post-Treatment (by location)

		Scalp	Forehead	Face	Arm/ Forearm	Back of Hand
Study 1	**90 days treatment**					
	Solaraze®	1/4 (25%)	17/30 (57%)	9/17 (53%)	4/12 (33%)	6/16 (38%)
	Vehicle	3/9 (33%)	8/24 (33%)	5/17 (29%)	4/12 (33%)	0/14 (0)
	p-value	0.7646	0.0908	0.1682	1.000	0.0650
Study 2	**90 days treatment**					
	Solaraze®	2/6 (33%)	9/19 (47%)	4/5 (80%)	5/8 (63%)	1/17 (6%)
	Vehicle	0/4 (0)	6/22 (27%)	2/8 (25%)	0/5 (0)	3/16 (19%)
	p-value	0.4235	0.1870	0.0727	0.0888	0.2818
Study 3	**60 days treatment**					
	Solaraze®	3/7 (43%)	13/31 (42%)	10/19 (53%)	0/1 (0)	2/8 (25%)
	Vehicle	0/6 (0)	5/36 (14%)	2/13 (15%)	0/2 (0)	1/9 (11%)
	p-value	0.2271	0.0153	0.0433	–	0.4637
	30 days treatment					
	Solaraze®	2/5 (40%)	4/29 (14%)	3/14 (21%)	0/0 (0)	0/9 (0)
	Vehicle	0/5 (0)	2/29 (7%)	2/18 (11%)	0/1 (0)	1/9 (11%)
	p-value	0.2299	0.3748	0.4322	–	0.6521

		Scalp	Forehead	Face	Arm/ Forearm	Back of Hand
All data combined						
	Solaraze®	8/22 (36%)	43/109 (39%)	26/55 (47%)	9/21 (43%)	9/50 (18%)
	Vehicle	3/24 (13%)	21/111 (19%)	11/56 (20%)	4/20 (20%)	5/48 (10%)
	p-value	0.0903	0.0013	0.0016	0.2043	0.3662

Source: Solaraze® Approved Labeling dated 11/06 available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=2508

(b) Regarding the systemic absorption of topical Diclofenac Sodium Gel, 3%, the **Pharmacokinetics**, Absorption section of the approved **Solaraze**® labeling states:

> When Solaraze® is applied topically, diclofenac is absorbed into the epidermis. In a study in subjects with compromised skin (mainly atopic dermatitis and other dermatitic conditions) of the hands, arms or face, approximately 10% of the applied dose (2 grams of 3% gel over 100 cm^2) of diclofenac was absorbed systemically in both normal and compromised epidermis after seven days, with four times daily applications.
>
> After topical application of 2 g Solaraze® three times daily for six days to the calf of the leg in healthy subjects, diclofenac could be detected in plasma. Mean bioavailability parameters were AUC^{0-t} 9±19 ng/hr/mL (mean±SD) with a C_{max} of 4±5 ng/mL and a T_{max} of 4.5±8 hours. In comparison, a single oral 75 mg dose of diclofenac (Voltaren®) produced an AUC of 1600 ng/hr/mL. Therefore, the systemic bioavailability after topical application of Solaraze® is lower than after oral dosing.
>
> Blood drawn at the end of treatment from 60 subjects with AK lesions treated with Solaraze® in three adequate and well-controlled clinical trials was assayed for diclofenac levels. Each subject was administered 0.5 g of Solaraze® Gel twice a day for up to 105 days. There were up to three 5 cm × 5 cm treatment sites per subject on the face, forehead, hands, forearm, and scalp. Serum concentrations of diclofenac were, on average, at or below 20 ng/mL. These data indicate that systemic absorption of diclofenac in subjects treated topically with Solaraze® is much lower than that occurring after oral daily dosing of diclofenac sodium.
>
> No information is available on the absorption of diclofenac when Solaraze® is used under occlusion.

Table 28: Diclofenac Sodium Gel ANDAs (n=4)

ANDA Number	Submission Date (letter)	Product	Sponsor	Indications	Status
(b) (4)					
200936	12/14/09 (stamp date 12/16/09)	Diclofenac Sodium Gel, 3%	Tolmar Inc	Topical treatment of actinic keratoses	Pending (as of 12/16/09)
202531	12/8/10 (stamp date 12/8/10)	Diclofenac Sodium Gel, 1%	Perrigo Israel Pharmaceuticals Ltd	Indicated for the relief of the pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands.	Refuse to Receive 2/4/11

Source: Search by reviewer of Agency Document Archiving, Reporting & Regulatory Tracking System (DARRTS) conducted on 5/6/11.

(a) **ANDA 200936** submitted by Tolmar Inc for Diclofenac Sodium Gel, 3% contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) (i.e., Paragraph IV Certification) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. The first filing review for this ANDA resulted in "Filing Acknowledgement" letter being issued on 3/18/10. After the OGD Clinical Team finalized their Filing Review on 4/12/10, a "Refuse to Receive" letter issued on 4/26/10. After receiving correspondence from Tolmar on 6/3/10, the "Refuse to Receive" letter was rescinded on 6/11/10. ANDA 200936 contains the results of the bioequivalence study with clinical endpoint #TOL-AK-2008-02, a double blind, 2:2:1 randomized, parallel-group, vehicle-controlled multicenter study conducted in 609 subjects with 5 or more clinically typical visible, discrete, nonhyperkeratotic, non-hypertrophic lesions contained in one 25 cm^2 treatment area in one major body area (as defined in this study: forehead, central face, scalp, back of hands, and forearms). The primary efficacy variable was the percentage of subjects in the Per Protocol (PP) achieving complete clearance (defined as achieving 100% clearance of AK lesions in the designated treatment area) at Visit 6/Day 112/End of Treatment after 84 days of treatment. Per the sponsor, complete clearance (i.e., "success") was achieved in the PP population at Day 112 by 43 subjects (23.0%) treated with Tolmar's Diclofenac Sodium Gel, 3% and by 57 subjects (31.7%) treated with Solaraze® (diclofenac sodium) Gel, 3% (Doak Dermatologics, a division of Nycomed US) with the 90% CI (-16.8%, -0.5%). The primary superiority comparisons between each active treatment and the vehicle control were evaluated in the mITT population. Per the sponsor, complete clearance (i.e., "success") was achieved in the mITT population at Day 112 by 53 subjects (22.0%) treated with Tolmar's Diclofenac Sodium Gel, 3%. by 70 subjects (28.7%) treated with Solaraze®, and by 12 subjects (10.0%) treated with vehicle and both p-values for the comparison of active versus vehicle were statistically significant (i.e., $p<0.05$). Based upon the results of this study, the sponsor also concluded that the safety profile of the test product was not statistically or clinically different than that of the reference product.

Table 29: Diclofenac Sodium Gel, 3% Protocols Submitted to the OGD (n=1: closed=1)

Protocol Number; Available Documents	Drug Name; Dosage Form	Firm	Rec'd Date	Date of FDA Letter
(b) (4)				

Source: Search by reviewer conducted on 5/9/11 of OGD Tracking Systems, DBE Tracking Systems, Protocol Database at: http://cdsogd1/seltrack/Protocols.ASP

(a) (b) (4)

(b) (4)

On 8/27/09, a 4-page document entitled "Request for Consultation", the draft Clinical Team review of OGD (b) (4) and the Draft Guidance on Diclofenac (Gel, 3%) were consulted to the OND DDDP. The OGD Request for Consultation stated:

> The OGD is preparing to post individual product bioequivalence recommendations on the FDA Guidance for Industry Webpage for generic versions of diclofenac sodium gel, 3% (reference listed drug, Solaraze® Gel, 3%). Please review the attached Draft Guidance on Diclofenac, in particular the recommended study design and endpoints for the clinical endpoint bioequivalence study in the treatment of actinic keratosis, and provide any comments. (b) (4)

The DDDP then requested the advice of the Capt. E. Dennis Bashaw, Pharm. D., Director, Division of Clinical Pharmacology 3 (DCP3) in OND. The DDDP Request for Consultation to DCP3 included the three documents previously sent by OGD to DDDP (in their Request for Consultation) and it stated:

> OGD has consulted DDDP regarding a draft guidance that they will post regarding diclofenac as it concerns bioequivalence for generic products. Please advise if Biopharm has any concerns from a biopharmaceutics viewpoint. Please comment on the paragraph under "Systemic Exposure" in the "Request for Consultation" letter, where OGD will not ask for any pharmacokinetic bioequivalence studies. Do you agree with this in the light of the fact that Solaraze may be getting new warnings in the label consistent with clinically significant systemic exposure?

The DCP3 response finalized on 10/1/09 contained the following conclusion and recommendation:

> While it is analytically feasible to detect in vivo plasma levels of diclofenac following topical application, the levels detected do not rise to the regulatory standard of assessing bioavailability at the site of action (as the blood is neither the site of action or intimately linked). Nor are the levels associated in a predictive fashion with toxicity such that they can be used to assure safety for the product. The proposed use of a bioequivalency study with clinical endpoints for the assessment of equivalency between topically applied generic and reference product is appropriate from a clinical pharmacology standpoint and supported by the regulations (see 21 CFR 320.24 (b)(4)).[34]

The DDDP response received on 11/6/09 contained the following recommendations:

> 1. It is recommended that the BE trial follow the protocol of the innovator studies where subjects should have no fewer than 5 AK lesions in a major body area, which was defined as one of five 5cm x 5cm regions: scalp (doesn't need to be bald), forehead, face, forearm, and hand. Subjects should be limited to 3 body areas as defined in the innovator studies. This will allow for maximum use and reflect clinical practice, as the indication for Solaraze does not limit treatment of AKs to only the face and bald scalp. The reason for this may have been that when all areas were combined, clearance of AKs reached statistical significance.

[34] NDA 021005 Memorandum by Capt. E. Dennis Bashaw, Pharm.D., Director, Division of Clinical Pharmacology-3, finalized on 10/1/09, pg. 9 of 10.

2. It is recommended that 5 cm by 5 cm regions be allowed in the trial rather than one contiguous 25 cm area, as AKs are discreet lesions that may or may not be clustered in one area. Using a 25 cm^2 contiguous area will limit the number of AKs that may be treated and may also increase the amount of non-diseased skin that would be exposed. It also will decrease the amount of drug product that the subject will be exposed to, as subjects used 0.5 gms per body region treated twice a day (3 regions = 1.5 gms). Thus the maximum used in the trials was 3.0 grams a day.

3. It is recommended that the statement in the guidance under the heading **"Additional comments regarding the BE study with clinical endpoint"**, in item #1: …Normally 0.5 gram of gel is used to cover one contiguous 25-cm^2 treatment area" should be deleted, as it is a not an accurate statement for the reasons sited above.

4. It is recommended that the statement in the guidance under the heading **"Additional comments regarding the BE study with clinical endpoint"**, in item #2: ….a disease such as AK, in which spontaneous resolution may occur" be deleted, as AKs very seldom, if ever spontaneously resolve. Actinic keratoses are precancerous lesions in which a significant percentage (from 6% - 12%) will evolve to squamous cell carcinoma, which depending on the location, can be fatal.

5. Regarding systemic bioavailability, although the systemic absorption of Solaraze is less than that of the oral drug product, the systemic bioavailability of Solaraze is 1/6th that of the oral product. In a recent consult from the Office of Clinical Pharmacology-3, when comparing the topical diclofenac products, under maximum usage plasma AUC values of Solaraze where only 1/3 lower than Voltaren gel, and 7-10x higher than Flector patch and Solaraze shows some accumulation with multiple dosing.[35] These former two products have had reports of systemic toxicity, particularly hepatic toxicity. There has been one confounding report of interstitial nephritis associated with Solaraze use (Subject was also on prilosec) and in the clinical trials for this product, 2-3% of subjects treated with Solaraze had elevated LFTs compared to none in placebo.

The Office of Clinical Pharmacology states that although the topical diclofenac products have been associated with systemic toxicity, without a concentration effect relationship, the value of in vivo plasma level equivalence requirements in preventing or managing this risk is speculative. While it is analytically feasible to detect in vivo plasma levels of diclofenac following topical application, the levels detected do not rise to the regulatory standard of assessing bioavailability at the site of action (as the blood is neither the site of action or intimately linked). Nor are the levels associated in a predictive fashion with toxicity such that they can be used to assure safety for the product. The proposed use of a bioequivalency study with clinical endpoints for the assessment of equivalency between topically applied generic and reference product is appropriate from a clinical pharmacology standpoint and supported by the regulations (see 21 CFR 320.24 (b)(4)).2[36] Thus, while the Offices of DDDP and Clinical Pharmacology agree with OGD that a PK trial for bioequivalence is not necessary and that it will not inform for safety, the proposed BE trial design should evaluate subjects for possible systemic effects through clinical monitoring of adverse events and monitoring of laboratory parameters that include routine chemistries, hematology parameters, and urinalysis as markers of systemic effects.

This protocol was closed after posting the Draft Guidance on Diclofenac Sodium Gel/Topical, 3% on 1/25/11 and sending an OGD regulatory letter containing responses to the sponsor's questions on 2/1/11.

Table 30: Diclofenac Sodium Gel, 3% Controlled Correspondences Submitted to the OGD

(b) (4)

CTL No.	Title	Description	Status	Doc Date	From
(b) (4)					

[35] Office of Clinical Pharmacology-3 Consult: Memo-to-file, NDA 021005, N000; 21-Oct-1998; 26-Jun-2009, pages 9, 11-12.
[36] Office of Clinical Pharmacology-3 Consult; Memo-to-file, NDA 021005, N000; Finalized in DARRTS on 10/1/09, pg. 8.

(b) (4)

Source: Search by reviewer conducted on 5/7/11 of OGD-Controls (Correspondence) Document Tracking System at: http://cdsogd1/SelTrack/DOC.ASP

(a)

(b) (4)

(b)

(c)

(d)

(e)

Table 31: Lesion Counts in Subjects with Lesions on Back of Hands or Arm/Forearm Locations in the Modified Intent-to-Treat (mITT) Population

Unique Subject Number	Treatment	Body Area	Lesion Count Visit 1	Lesion Count Visit 6

Unique Subject Number	Treatment	Body Area	Lesion Count Visit 1	Lesion Count Visit 6
Diclofenac Sodium n=33 (Arms=9; Back of hands=24); Success 3/33=9.1%				
(b) (6)	Diclofenac Sodium	Back of hands	9	3
	Diclofenac Sodium	Back of hands	6	0
	Diclofenac Sodium	Back of hands	12	2
	Diclofenac Sodium	Back of hands	6	5
	Diclofenac Sodium	Back of hands	6	2
	Diclofenac Sodium	Arms	12	8
	Diclofenac Sodium	Back of hands	5	5
	Diclofenac Sodium	Back of hands	5	2
	Diclofenac Sodium	Back of hands	5	1
	Diclofenac Sodium	Arms	6	0
	Diclofenac Sodium	Arms	7	0
	Diclofenac Sodium	Back of hands	9	2
	Diclofenac Sodium	Arms	5	6
	Diclofenac Sodium	Back of hands	6	6
	Diclofenac Sodium	Arms	6	1
	Diclofenac Sodium	Back of hands	8	3
	Diclofenac Sodium	Arms	6	1
	Diclofenac Sodium	Back of hands	5	5
	Diclofenac Sodium	Back of hands	5	2
	Diclofenac Sodium	Arms	6	6
	Diclofenac Sodium	Back of hands	6	2
	Diclofenac Sodium	Back of hands	7	5
	Diclofenac Sodium	Back of hands	6	6
	Diclofenac Sodium	Back of hands	9	9
	Diclofenac Sodium	Back of hands	6	6
	Diclofenac Sodium	Back of hands	6	2
	Diclofenac Sodium	Back of hands	7	6
	Diclofenac Sodium	Back of hands	9	4
	Diclofenac Sodium	Back of hands	5	1
	Diclofenac Sodium	Back of hands	5	4
	Diclofenac Sodium	Back of hands	7	5
	Diclofenac Sodium	Arms	7	3
	Diclofenac Sodium	Arms	6	1
Solaraze n=31 (Arms=15; Back of hands=16); Success 4/31=12.9%				
(b) (6)	Solaraze	Back of hands	7	1
	Solaraze	Back of hands	5	0
	Solaraze	Back of hands	5	7
	Solaraze	Arms	6	3
	Solaraze	Back of hands	7	1
	Solaraze	Arms	6	5
	Solaraze	Back of hands	10	7
	Solaraze	Arms	7	4

Unique Subject Number	Treatment	Body Area	Lesion Count Visit 1	Lesion Count Visit 6
(b) (6)	Solaraze	Back of hands	12	12
	Solaraze	Arms	5	1
	Solaraze	Arms	5	3
	Solaraze	Back of hands	6	6
	Solaraze	Back of hands	6	1
	Solaraze	Back of hands	5	8
	Solaraze	Arms	7	7
	Solaraze	Arms	5	2
	Solaraze	Arms	6	6
	Solaraze	Arms	11	5
	Solaraze	Arms	6	6
	Solaraze	Back of hands	5	5
	Solaraze	Back of hands	6	4
	Solaraze	Arms	5	5
	Solaraze	Back of hands	6	6
	Solaraze	Back of hands	6	6
	Solaraze	Back of hands	6	6
	Solaraze	Arms	5	4
	Solaraze	Back of hands	6	0
	Solaraze	Arms	8	7
	Solaraze	Back of hands	5	0
	Solaraze	Arms	7	4
	Solaraze	Arms	8	0
Vehicle n=21 (Arms=13; Back of hands=8); Success 0/21=0%				
(b) (6)	Vehicle	Back of hands	5	3
	Vehicle	Arms	7	6
	Vehicle	Back of hands	6	3
	Vehicle	Back of hands	6	3
	Vehicle	Arms	5	6
	Vehicle	Arms	7	14
	Vehicle	Arms	5	3
	Vehicle	Arms	10	8
	Vehicle	Back of hands	7	5
	Vehicle	Arms	6	2
	Vehicle	Arms	5	5
	Vehicle	Back of hands	6	6
	Vehicle	Arms	5	5
	Vehicle	Arms	6	6
	Vehicle	Back of hands	5	5
	Vehicle	Back of hands	7	7
	Vehicle	Arms	7	2
	Vehicle	Back of hands	7	2
	Vehicle	Arms	5	2

Unique Subject Number	Treatment	Body Area	Lesion Count Visit 1	Lesion Count Visit 6
(b) (6)	Vehicle	Arms	24	7
	Vehicle	Arms	5	7

Source: Analysis by this reviewer of Appendix Listing 16.2.6.2 entitled "Listing of Lesion Counts in mITT (LOCF) Population": p.235-539.

(b) (4)

Table 32: Lesion Counts in Subjects with Lesions on Back of Hands or Arm/Forearm Locations in the Per Protocol (PP) Population

Unique Subject Number	Treatment	Body Area	Lesion Count Visit 1	Lesion Count Visit 6
Diclofenac Sodium n=28 (Arms=9; Back of hands=19); Success 3/28=10.7%				
(b) (6)	Diclofenac Sodium	Back of hands	9	3
	Diclofenac Sodium	Back of hands	6	0
	Diclofenac Sodium	Back of hands	6	2
	Diclofenac Sodium	Arms	12	8
	Diclofenac Sodium	Back of hands	5	5
	Diclofenac Sodium	Back of hands	5	2
	Diclofenac Sodium	Back of hands	5	1
	Diclofenac Sodium	Arms	6	0
	Diclofenac Sodium	Arms	7	0
	Diclofenac Sodium	Arms	5	6
	Diclofenac Sodium	Back of hands	6	6
	Diclofenac Sodium	Arms	6	1
	Diclofenac Sodium	Back of hands	8	3
	Diclofenac Sodium	Arms	6	1
	Diclofenac Sodium	Back of hands	5	5
	Diclofenac Sodium	Arms	6	6
	Diclofenac Sodium	Back of hands	6	2
	Diclofenac Sodium	Back of hands	7	5
	Diclofenac Sodium	Back of hands	6	6
	Diclofenac Sodium	Back of hands	9	9
	Diclofenac Sodium	Back of hands	6	2
	Diclofenac Sodium	Back of hands	7	6
	Diclofenac Sodium	Back of hands	9	4
	Diclofenac Sodium	Back of hands	5	1
	Diclofenac Sodium	Back of hands	5	4
	Diclofenac Sodium	Back of hands	7	5
	Diclofenac Sodium	Arms	7	3
	Diclofenac Sodium	Arms	6	1
Solaraze n=24 (Arms=12; Back of hands=12); Success 4/24=16.7%				
(b) (6)	Solaraze	Back of hands	7	1
	Solaraze	Back of hands	5	0

Unique Subject Number	Treatment	Body Area	Lesion Count Visit 1	Lesion Count Visit 6
(b) (6)	Solaraze	Arms	6	3
	Solaraze	Back of hands	7	1
	Solaraze	Arms	6	5
	Solaraze	Back of hands	10	7
	Solaraze	Arms	7	4
	Solaraze	Arms	5	1
	Solaraze	Arms	5	3
	Solaraze	Back of hands	6	1
	Solaraze	Arms	5	2
	Solaraze	Arms	6	6
	Solaraze	Arms	11	5
	Solaraze	Back of hands	5	5
	Solaraze	Back of hands	6	4
	Solaraze	Back of hands	6	6
	Solaraze	Back of hands	6	6
	Solaraze	Back of hands	6	6
	Solaraze	Arms	5	4
	Solaraze	Back of hands	6	0
	Solaraze	Arms	8	7
	Solaraze	Back of hands	5	0
	Solaraze	Arms	7	4
	Solaraze	Arms	8	0
Vehicle n=17 (Arms=12; Back of hands=5); Success 0/17=0%				
(b) (6)	Vehicle	Back of hands	5	3
	Vehicle	Back of hands	6	2
	Vehicle	Arms	5	6
	Vehicle	Arms	7	14
	Vehicle	Arms	5	3
	Vehicle	Arms	10	8
	Vehicle	Arms	6	2
	Vehicle	Arms	5	5
	Vehicle	Back of hands	6	6
	Vehicle	Arms	5	5
	Vehicle	Arms	6	6
	Vehicle	Back of hands	7	7
	Vehicle	Arms	7	2
	Vehicle	Back of hands	7	2
	Vehicle	Arms	5	2
	Vehicle	Arms	24	7
	Vehicle	Arms	5	7

Source: Analysis by this reviewer of Appendix Listing 16.2.6.1 entitled “Listing of Lesion Counts in PP Population”; p. 2-234.

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

/s/

BRENDA S GIERHART
07/07/2011

DENA R HIXON
07/07/2011
I concur.

BARBARA M DAVIT
07/10/2011

DIVISION OF BIOEQUIVALENCE II REVIEW

ANDA No.	200936
Drug Product Name	Diclofenac Sodium Topical Gel
Strength(s)	3%
Applicant Name	Tolmar Inc.
Address	701 Centre Avenue, Fort Collins, CO 80526
Applicant's Point of Contact	Michelle R. Ryder, Senior Director, Regulatory Affairs
Contact's Telephone Number	970-212-4901
Contact's Fax Number	970-212-4950
Original Submission Date(s)	December 14, 2009
Submission Date(s) of Amendment(s) Under Review	August 8, 2013 (Request for Dispute Resolution) August 14, 2013 (Meeting request)
Reviewer	Sriram Subramaniam, Ph.D.
In Vitro Study Site	(b) (4)
In Vitro Study Site Address	

OVERALL REVIEW RESULT		**ADEQUATE**	
OSI REPORT RESULT		**ADEQUATE**	
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**Formulation**	**3%**	**ADEQUATE**
14, 23, 24	**In Vitro Permeation Study**	**3%**	**INADEQUATE***

*** Not required for approval (See Sections 1 and 5.2)**

1 EXECUTIVE SUMMARY

This is an amendment to the Division of Bioequivalence II's (DB II) earlier review[1] (dated April 3, 2013) in response to the issues raised by the Tolmar Inc. ("Tolmar") in their Dispute Resolution (DR) request dated August 8, 2013.

In their original submission, the firm provided the results of a clinical endpoint (CE) bioequivalence (BE) study comparing its Diclofenac Sodium Topical Gel, 3%, to the corresponding reference product, Fougera Pharmaceuticals' Solaraze® (diclofenac sodium) Topical Gel, 3% . The study was designed as a double-blind, multi-center, parallel group study in subjects with actinic keratoses lesions. The review of CE BE study was assigned to the Office of Generic Drugs' (OGD) Division of Clinical Review (DCR). Prior to acceptability of the CE BE study, the OGD requested, among other things, that the firm demonstrate that the selected excipient in its test product performs similar to hyaluronate sodium (HA)[2,3], and the gel retention on the skin and in the epidermis is similar to the reference product[3] (see Section 3 for complete history of the ANDA). Specifically, the OGD recommended the firm conduct an in vitro permeation (IVP) study[4]. The DB II recommended that the IVP study should include evaluation of distribution release-rate across the skin and drug accumulation within skin layers[5,6]. In addition, the DB II recommended the firm use human cadaver skins, and follow the recommendations in the SUPAC SS[5] guidance for study design and statistical analysis for the IVP study. It should be noted that current BE guidance for this drug product (effective January 25, 2011) only recommends a CE BE study[7].

On November 1, 2012, Tolmar submitted IVP Study R12-0512 comparing the test and reference products. Following evaluation, the DB II concluded that the firm's IVP study was not adequate[8], and requested additional Stage 2[5] testing to demonstrate BE of drug accumulation within the epidermis between the test and reference products. The DB II's deficiencies were issued to the firm on June 14, 2013[9]. In the meantime, the DCR found the firm's CE BE study acceptable[10]. On August 8, 2013, the Tolmar requested a DR and responded to the DB II's deficiencies.

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[1] DARRTS N200936 REV-BIOEQ-21 04/03/2013

[2] The test product is not qualitatively and quantitatively (Q1/Q2) similar to that of the RLD. Unlike the RLD, the test formulation does not contain (b) (4) hyaluronate sodium (HA). Per literature and NDA sponsor's patent in the Orange Book, HA is suggested to aid drug penetration across stratum corenum, and retention in the epidermis. Also, the viscosity of the test product is (b) (4) than the RLD, which leads to concerns of product retention on the skin

[3] DARRTS N200936 COR-ANDAACTION-09 07/11/2011

[4] There is no precedence for use of IVP study for demonstration of BE and no guidance available for conduct of IVP study for BE purposes.

[5] Non Steroidal Semisolid Dosage Forms Scale-Up and Post Approval Changes (SUPAC): CMC: In Vitro Release Testing & In Vivo BE Documentation (1997)
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070930.pdf

[6] DARRTS N200936 REV-BIOEQ-01 04/18/2012

[7] BE Recommendation for Specific Drug Products: Draft guidance for Diclofenac Sodium Topical Gel (1/11).
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240969.pdf

[8] DARRTS N200936 REV-BIOEQ-21 04/03/2013

[9] DARRTS N200936 COR-ANDAACTION-09 06/14/2013

[10] DARRTS N200936 REV-CLBIOEQ-21 06/12/2013

In the current review, the DB II evaluated the firm's response to the deficiencies in their August 2013 DR request, and re-examined the flux and mass balance data in IVP Study R12-0512. Following evaluation of the firm's response and the data in the IVP study, the DB II disagrees with the sponsor's claim that the IVP study shows that the drug accumulation within the skin layers is bioequivalent between test and reference products. The DB II concludes that the IVP study is not sensitive to show equivalency within skin layers, considering the negligible absorption in skin (less than 1% of the applied dose), high variability in study data, and lack of sensitivity in the in vitro method.

Nonetheless, the current BE guidance for this drug product recommends only a CE BE study[7], and DCR concluded that Tolmar's CE BE study TOL-AK-2008-02 demonstrates BE between the test and reference products and is adequate to support approval of the application[10]. Also, an internal meeting involving the pertinent OGD divisions concluded that Tolmar's ANDA 200936 is adequate for approval, and the previous OGD deficiencies regarding IVP study will be not pursued (Section 5.2).

The Office of Scientific Investigations' (OSI) inspection of (b) (4) is pending for the current application[11]. However, since the IVP study is no longer required for approval, the inspection is moot.

Therefore, the DB II concludes that BE between Tolmar's Diclofenac Sodium Topical Gel, 3% and the RLD, Solaraze® (diclofenac sodium) Topical Gel, 3% , has been demonstrated under Section 21 CFR § 320.24(b)(4).

The DB II review is now **adequate**.

[11] DARRTS N200936 FRM-CONSULT-09 11/30/2012

2 TABLE OF CONTENTS

3 BACKGROUND

12/14/2009: Tolmar submits ANDA 200936, Diclofenac Sodium Gel, 3%.

- Diclofenac Sodium Gel, 3%, is indicated for the treatment of actinic keratoses.
- The reference listed drug (RLD) is Fougera Pharmaceuticals Inc.'s Solaraze® (diclofenac sodium) Topical Gel, 3% (NDA 021005, approved on 10/16/00).
- Submits a double-blind, multi-center, parallel group clinical endpoint (CE) BE study.
- The test product is not qualitatively and quantitatively (Q1/Q2) similar to that of the RLD

03/08/10: DB I concluded ANDA acceptable for filing from a pharmacokinetic (PK) perspective[12]. However, determination of completeness of the CE BE study was pending the filing review by the DCR.

04/12/10: DCR finds the study unacceptable for filing as the study design was not sensitive to detect differences in the formulations[13,14].

04/26/10: OGD issues a Refuse to Receive (RTR) letter[15].

06/11/10: OGD rescinds the RTR following Tolmar's response[16].

01/25/11: BE recommendations for the drug product posted on the FDA's website[7].

07/2011: DCR and Division of Chemistry I (DC I) reviews[17] of the CE BE study recommend the firm repeat the study using appropriate dosing and duration of treatment. Also firm should demonstrate that the excipient in the test product performs similar to RLD[2] as:

- there is concern of drug penetration across stratum corenum, and retention in epidermis.
- the viscosity of the test product (b) (4) than the RLD, which is a concern for product retention on the skin.

07/11/11: OGD issues a Complete Response - Fatal Flaw Letter[3]; Not approvable as:

- inactive ingredients of the test drug raise serious questions of safety or efficacy.
- the CE BE study is not adequate to demonstrate BE of test and RLD.
- Briefly, Tolmar was requested to:
  1) demonstrate that its selected excipient performs similarly to HA. Conduct an IVP study[4] and a well-designed comparative PK BE study.
  2) demonstrate gel retention on the skin and in the epidermis for test is similar to the RLD.
  3) conduct a CE BE study designed to achieve maximum sensitivity for detecting product differences.

09/27/11: In response to the fatal flaw letter Tolmar's attorney submits a Request for DR

11/22/11: In an internal OGD meeting[18], it was determined that:

- an IVP study can be used to support equivalency.

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[12] DARRTS N200936 REV-BIOEQ-07 03/08/2010
[13] No BE guidance for this drug product was available at this point.
[14] DARRTS N200936 REV-CLINICAL-06 04/12/2010
[15] DARRTS N200936 COR-ANDAFILE-03 04/26/2010
[16] DARRTS N200936 COR-ANDAFILE-02 and COR-ANDARESCIND-03 06/11/2010
[17] DARRTS N200936 REV-CLINICAL-03 07/10/2011, and DARRTS N200936 REV-QUALITY-03 07/11/2011
[18] DARRTS N200936 FRM-MINUTES-01 12/12/2011

- DB II stated that a PK BE study is not warranted as NDA indicates no correlation between plasma levels and efficacy.
- DB II determined that the design of the IVP study submitted in DR request is not acceptable. DCR stated that the CE BE study was eligible for a full review.

12/13/11: DCR accepts the CE BE study for a full review[19].

12/20/11: OGD denies DR request[20]. Recommends the sponsor conduct an IVP study to address Items 1 and 2 above, and states that CE BE study is acceptable for full review and PK BE study is not required.

04/18/12: DB II's review recommends Tolmar repeat the IVP study to determine distribution release-rate across the skin, and a mass balance to estimate drug accumulation within skin layers. Tolmar requested to follow the SUPAC-SS Guidance[5] for study design and statistical analysis, and use human cadaver skins (≥ 6) with 6 replicates[6].

11/01/12: Tolmar submits a new IVP study.

01/08/13: DC I completes their review with no further deficiencies[21].

04/03/13: DB II review finds the IVP study unacceptable as the 90% confidence intervals (CI) were not within 75-133% (per SUPAC SS) between the test and RLD for the drug within epidermis[5]. DB II requests additional Stage 2 testing to demonstrate BE between the test and RLD in epidermis.

06/12/13: DCR finds the CE BE study acceptable[10].

06/14/13: OGD issues a CR to Tolmar stating DB II's 04/03/13 conclusions on IVP study[9].

08/08/13: Tolmar submits a second request for DR asking that OGD withdraw its request for IVP study, since (1) the firm disagrees with this approach, (2) the NDA applicant and RLD label have no claims on the function of HA, (3) the CE BE study demonstrates BE between the test and RLD, (4) SUPAC SS is designed to demonstrate BE for flux and not within skin layers and the current in vitro study shows BE for flux, and (5) the IVP study demonstrates similar amount of drug between the test and RLD within skin layers.

08/13/13: Tolmar submits a meeting request to OGD on August 14, 2013.

4 SUBMISSION SUMMARY

4.1 Drug Product Information

Test Product	Diclofenac Sodium Topical Gel, 3%
Reference Product	Solaraze® (diclofenac sodium topical gel), 3%
RLD Manufacturer	Almirall Hermal GmbH, D-21465 Reinbek, Germany for PharmaDerm®, a Division of Fougera Pharmaceuticals Inc., Melville, NY 11747

[19] DARRTS N200936 REV-CLINICAL-03 12/13/2011
[20] DARRTS N200936 COR-DISP-05 12/20/2011
[21] DARRTS N200936 REV-QUALITY-21 01/08/2013

NDA No.	021005
RLD Approval Date	October 16, 2000
Indication	Solaraze® is indicated for the topical treatment of actinic keratoses (AK)

4.2 Review of In Vitro Skin Permeation Study Data

In response to the DB II deficiencies, the firm submitted a new IVP Study R12-0512[22]. For details of the study conduct refer to DB II's earlier review[8] and DARRTS[22]. Briefly, the study included evaluation of 1) distribution release rate (i.e., estimating flux across the skin, appearance of drug in receptor solution at various time points) and 2) mass balance [estimation of drug in donor and receptor compartments, surface wash[23], and in various layers of the skin, including stratum corneum (SC), epidermis and dermis (Figure 1)]. The study used human cadaver skins from six different donors (from same body region, trunk skin), with six replicates per donor. To assure skin integrity, only donor skins with acceptable water permeability were used in the study. The skin sections were mounted on Franz cells with the dermis facing the receptor compartment (see Figure 1). 5 mg of the test or reference product was dispensed by dosing pipette onto the center of skin & rubbed with glass rod for 5 sec and the drug was removed 24 hours after application. At various time points following application of the dose (i.e., at 0, 2, 4, 8, 12, 24, 32, and 48 hr post dose), the drug in the receptor solution was measured using a validated analytical method. After the final sample collection at 48 hours, the skin was dismounted, and the amount of drug in SC, epidermis and dermis were determined. For each skin donor, six replicate skin sections, each for the test and reference products, were evaluated at the same time.

Figure 1

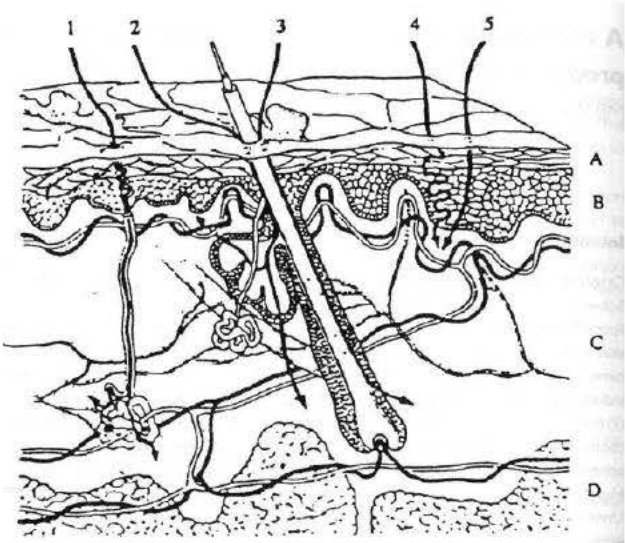
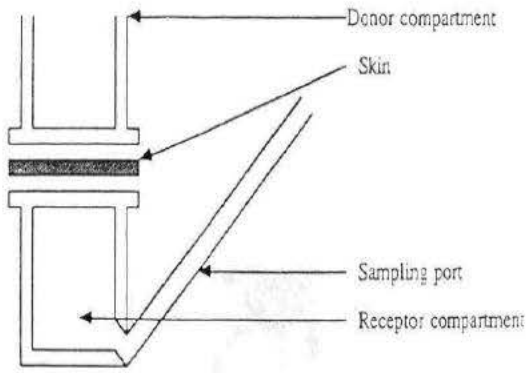


FIGURE 1 Cross-section of human skin. (A) Stratum corneum; (B) viable epidermis; (C) dermis;

Figure 2



IGURE 2 Diagrammatic representation of a Franz cell.

[22] DARRTS ANDA 200936 Supporting Document #14 (submitted 11/01/2012): Module 5.3.1.2,
[23] Represents drug in the wash solution used to remove the applied dose from the skin surface.

4.2.1 DB II Evaluation of the Data

Although the study was evaluated by DB II earlier, the data from the study was re-examined in light of the issues raised in Tolmar's August 2013 DR request.

The DB II reviewer's evaluation shows high variability in the data.

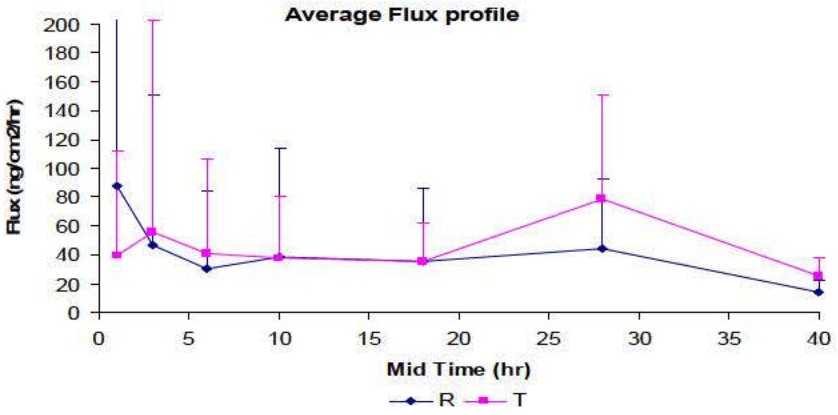
Distribution Release-Rate

The Table 1 and Figure 3 show the variability (% CV) in flux data in the pooled and individual skin donors. As shown in Table 1, there is high variability in the flux data, both within and between donors at various times post-dose. It should be noted that water permeation of the donor skins were not evaluated at the completion of the study (i.e., 48 hours) or validated prior to the study to assure that skin integrity is maintained.

Table 1: Variability in Flux data between skin donors

Time hr	Flux (ng/cm2/hr)		Donor 1	Donor 2	Donor 3	Donor 4	Donor 5	Donor 6
	Average	%CV	%CV	%CV	%CV	%CV	%CV	%CV
1	87.746	251	286	154	67	41	5	120
3	46.850	104	223	60	70	41	5	97
6	30.431	54	176	67	83	86	142	95
10	38.827	75	194	77	111	114	159	64
18	35.547	50	141	79	109	131	116	74
28	44.119	49	110	33	76	191	59	47
40	14.064	8	58	54	170	277	46	71

Figure 3: Mean Flux data



Mass Balance Data

The amount absorbed in the skin for the test and RLD in the current study is only 1% of the applied dose (Table 4). This contrasts with data in literature[24] (Figure 424), where almost 15-20% of the applied dose of diclofenac topical gel (with and without HA) was absorbed in the skin.

Figure 4[24]

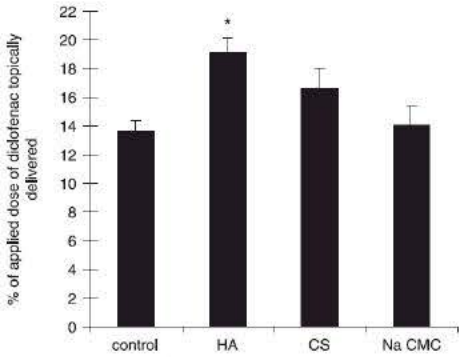


fig. 2 The effect of 1% w/w polysaccharide on the percentage of applied diclofenac (1.75% w/w) delivered to the skin, 48 h after application of the formulation ($n = 4$, mean ± SD, $^*P < 0.001$ compared with control).

Since total recovery in mass balance experiments is an indicator of data reliability, recovery data in the study was carefully examined. Of the six donor skins, it was found that three donor skins (Donors 4, 5, and 6 highlighted in Table 2) have consistently high recovery (>100%) . While mean recovery >100% is expected due to variability in measurement, consistently high recovery in all replicates within each of the three donors is of concern, and is indicative of potential method conduct problems. In contrast, the recovery for replicates of Donors 1 to 3 was randomly distributed (Table 2). Also, surface wash[23] data shows that all replicates for Donors 4 to 6 have recovery consistently >100% (Table 2). In addition, the same three donor skins have no measurable drug concentration in epidermis for majority of the replicates. Finally, all replicates in 4 of the 6 donor skins have no measurable drug in the dermis.

Table 3 shows higher variability in total drug absorbed in the skin, and drug absorbed in the epidermis and dermis for Donors 4-6 compared to Donors 1-3. Due to lack of measurable concentrations within skin layers in majority of the skin donors, and the low (1% of applied dose) total absorption in skin, there is high variability in the mass balance data. The firm analyzed the data by log transformation and assigning values of ½ LOQ for data with no measurable concentrations, to reduce variability. Assigning ½ LOQ to zero values is not an acceptable bioanalytical practice, and artificially reduces variability in the dermis and epidermis in the current study.

Table 2: Recovery within Donor Skins

Donor	% Recovery (%CV)	Range	Surface Wash

[24] J Eur Acad Dermatol Venerol 19:305-318, 2005

1	95.65 ± 3.63 (3.8)	65.93* – 101.4	95.65 ± 3.63 (3.8)
2	98.73 ± 4.64 (4.7)	93.61 – 109.9	96.06 ± 4.04 (4.2)
3	99.11 ± 4.89 (4.9)	85.9 - 105.6	97.12 ± 5.33 (5.5)
4	106.59 ± 2.04 (1.9)	103.7 - 110.0	104 ± 2.32 (2.2)
5	107.55 ± 1.83 (1.7)	104.0 - 110.3	105.1 ± 2.45 (2.3)
6	105.63 ± 6.36 (6.0)	87.2 – 112.0	102.0 ± 6.31 (6.2)

* excluded

Table 3: % of Dose Applied within Skin Layer for RLD

Skin Layers	Donors 1-3		Donors 4-6	
	Mean	%CV	Mean	%CV
T Absorbed	0.63	92.04	1.51	139.44
Dermal	0.01	168.28	0.00	---
Epidermal	0.81	57.50	0.11	165.50
SC	0.45	73.23	0.49	55.31
Surf Wash	95.15	4.66	105.14	2.73
Total Recovery	97.06	4.65	107.25	2.24

Table 4: Distribution and Recovery: Across Skin Donors (Non-Transformed Data)

Parameter	Reference Product (Formulation A)	Test Product (Formulation B)
Mass Recovered		
Total Absorption (ng)	1,484.1 ± 629.0	1,849.5 ± 434.4
Dermis (ng)	11.44 ± 5.41	17.73 ± 9.22
Epidermis (ng)	693.6 ± 242.0	894.8 ± 298.0
Stratum corneum (ng)	631.5 ± 46.4	1462.7 ± 334.3
Surface Wash (ng)*	146,353 ± 1,386	146,833 ± 1,527
Percent of Applied Dose		
Total Absorption (%)	1.02 ± 0.43	1.26 ± 0.30
Dermis (%)	0.01 ± 0.00	0.01 ± 0.01
Epidermis (%)	0.46 ± 0.16	0.60 ± 0.20
Stratum corneum (%)	0.44 ± 0.04	1.00 ± 0.24
Surface Wash (%)*	100.55 ± 2.16	99.77 ± 1.73
Total Recovery		
Total Recovery (%)	102.6 ± 2.2	102.8 ± 1.9

*Surface Wash was performed 24 hours post-dosing
Data source: 0075dicl_Tol-Summary_S1_V5 Across Donor Summary (Zeros).xls

4.2.2 DB II Conclusion

Due to the lack of sensitivity in the method and high variability in raw data, the DB II concludes that the IVP study is not sensitive to detect differences within skin layers between the test and RLD products.

4.3 Deficiency Comment

None

4.4 Recommendations

1. The DB II finds the IVP Study R12-0512 not acceptable. Tolmar conducted the study comparing their Diclofenac Sodium Topical Gel, 3% (lot #2315-30A) against the RLD, Fougera's Solaraze® (diclofenac sodium) Topical Gel, 3% (lot #1062701). Nonetheless, the current BE guidance for this drug product recommends only a CE BE study[7], and DCR concluded that Tolmar's CE BE study TOL-AK-2008-02 demonstrates BE between the test and reference products and is adequate to support approval of the application[10]. Also, an internal OGD meeting concluded that Tolmar's ANDA 200936 is adequate for approval and the previous OGD deficiencies regarding IVP study will be not pursued (Section 5.2).

2. The DB II concludes that BE between Tolmar's Diclofenac Sodium Topical Gel, 3% and the RLD, Solaraze® (diclofenac sodium) Topical Gel, 3%, has been demonstrated under Section 21 CFR § 320.24(b)(4).

4.5 Comments for Other OGD Disciplines

Discipline	Comment
All	None

5 APPENDIX

5.1 Formulation Data

Formulation Comparison between Test Product and RLD

Tolmar's formulation			RLD formulation	
Ingredient	**Function**	**Amount % w/w**	**Ingredient**	**% (w/w)**
Diclofenac Sodium, USP	Active Pharmaceutical Ingredient	3.0	Diclofenac Sodium	3.0
--	(b) (4)		Hyaluronate Sodium	(b) (4)
Methoxypolyethylene Glycol 350 NF			Polyethylene Glycol Monomethyl Ether	
PEG-60 Hydrogenated Castor Oil, NF			--	
Benzyl Alcohol, NF			Benzyl Alcohol	
Hydroxyethyl Cellulose, NF			--	
Purified Water, USP			Purified Water	

Source: ANDA 200936 Section 2.7 Clinical Summary, Summary_Bioequivalence_Tables, Table 6 and Section 3.2.P.1 for Tolmar's formulation; ANDA 200936 Section 3.2.P.2.1.2 and Approved Labeling for RLD's formulation; RLD=Reference Listed Drug

(b) (4)

(b) (4)

(b) (4)

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BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200936

APPLICANT: Tolmar Inc.

DRUG PRODUCT: Diclofenac Sodium Topical Gel, 3%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

5.3 Outcome Page

Completed Assignment for 200936 ID: 20869

Reviewer: Subramaniam, Sriram **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Diclofenac Sodium Topical Gel, 3%

Productivity:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Productivity***	***Subtotal***
20869	11/1/2012	Other (REGULAR)	In Vitro Study (nasal or other dosage forms, each study type)	1	1
20869	8/8/2013	Other (REGULAR)	Study Amendment	1	1
				Total:	2

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

/s/

SRIRAM SUBRAMANIAM
10/04/2013

Parthapratim CHANDAROY
10/04/2013

ETHAN M STIER
10/04/2013

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	200936
Drug Product Name	Diclofenac Sodium Topical Gel
Strength(s)	3%
Applicant Name	Tolmar Inc.
Address	701 Centre Avenue Fort Collins, CO 80526
Applicant's Point of Contact	Michelle R. Ryder, Senior Director, Regulatory Affairs
Contact's Telephone Number	970-212-4901
Contact's Fax Number	970-212-4950
Original Submission Date(s)	December 14, 2009
Submission Date(s) of Amendment(s) Under Review	October 31, 2012 (Response to deficiency letter)
Reviewer	Josephine Aimiuwu, Ph.D.
In Vitro Study Site	(b) (4)
In Vitro Study Site Address	

OVERALL REVIEW RESULT		**INADEQUATE**	
OSI REPORT RESULT		**INADEQUATE**	
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
13, 15, 20	**In Vitro Skin Permeation Study**	**3%**	**INADEQUATE**

1 EXECUTIVE SUMMARY

This application contains the waiver request of *in vivo* bioequivalence study requirements for Tolmar Inc.'s proposed test product Diclofenac Sodium Topical Gel, 3% (w/w) under 21 CFR §320.22(b)(3). The Reference Listed Drug (RLD) is Fougera Pharmaceuticals Inc's Solaraze® (diclofenac sodium) Topical Gel), 3% (w/w) (NDA #021005). This is a review of an amendment dated 10/31/2012 in response to the Division of Bioequivalence II (DB II)'s deficiencies.

The original application contained a formulation of the test product and RLD that was **not** qualitatively and quantitatively (Q1/Q2) similar to that of the RLD (DARRTS ANDA 200936 REV-BIOEQ-01 (General Review); final date 04/18/2012). In an amendment submitted on September 27, 2011, the firm submitted a major amendment in the form of a Request for Dispute Resolution in response to the deficiency letter sent by the Clinical Review Team. In addition to the Dispute Resolution letter, the firm also submitted an in vitro skin permeation study to evaluate the percutaneous absorption of diclofenac sodium using the human cadaver skin model. The in vitro skin permeation study was conducted to address potential concerns that the absence of hyaluronate sodium in the test product may increase the systemic exposure of diclofenac sodium, and/or alter the deposition of diclofenac sodium within the epidermal layer of the skin in comparison to the RLD. However, the vitro skin permeation study data was found inadequate and the firm was requested to conduct a more appropriate in vitro skin permeation study using several recommendations provided by the DB II in a deficiency letter sent on 04/19/2012.

In the current amendment, the firm submitted a new in vitro skin permeation study. However, the study is not acceptable as it does not show bioequivalence at the first stage, based on a CI approach of 75%-133.33%, between the test and reference product for deposition of the drug within the epidermal layer. The firm is requested to conduct an additional second stage study to show bioequivalence between the test and reference product.

(b) (4)

The DB II does not deem the test product, Tolmar's Diclofenac Sodium Topical Gel, 3% (w/w) to be bioequivalent to the corresponding reference product, Fougera Pharmaceuticals Inc's Solaraze® (diclofenac sodium) Topical Gel, 3% w/w, at this time due to deficiencies mentioned in section 3.2 Deficiency Comments and pending OSI inspection.

The in vitro skin permeation study is **inadequate**.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

This is a review of the firm's response dated 10/31/2012 to the DB II deficiencies. A summarized version of the firm's response is provided below *(in italics).*

FDA Deficiency 1:
Your proposal to use human cadaver skin is acceptable. However, please repeat the in vitro permeation bioequivalence study using at least 6 skin sample replicates. The skin samples should preferably be obtained from the same region of the body of all donors (at least 6 donors in total).

Firm's response 1 :
The in vitro skin permeation bioequivalence study was repeated using 6 donors in total and all samples were taken from the posterior torso of each donor. Detailed information on the donors and samples may be found in Report R12-0075, Section 9.1.

Reviewer's comment 1
Each formulation was evaluated on six replicate sections from six *ex vivo* human posterior torso skin donors. Please see section 4.1 Appendix for details. The firm's response is **adequate**.

FDA Deficiency 2:
Please validate the integrity of the human cadaver skin samples to be used in the in vitro permeation bioequivalence study to ensure that there are no areas of unusual permeability in the cadaver skin samples.

Firm's response 2 :
Report R12-0075, also details the procedure to determine the permeability of the samples prior to use. Samples were exposed to ^3H_2O for 30 minutes and the receptor solution was tested via liquid scintillation spectroscopy. Skin sections in which the absorption of ^3H_2O was less than 1.56 $\mu L/cm^2$ were considered acceptable.

Table 1: Donor Demographics, Mean Skin Thickness and Mean Integrity Results

Donor ID	Age	Race	Sex	Location	Mean Skin Thickness (mm)	Integrity Test Results*
(b) (6)	52	Black	Female	Posterior Torso	0.33 ± 0.08	0.36 ± 0.09
	58	Black	Male	Posterior Torso	0.31 ± 0.09	0.13 ± 0.04
	65	Hispanic	Female	Posterior Torso	0.53 ± 0.11	0.33 ± 0.12
	50	White	Female	Posterior Torso	0.43 ± 0.11	0.21 ± 0.05
	53	Asian	Male	Posterior Torso	0.37 ± 0.05	0.44 ± 0.09
	45	Caucasian	Male	Posterior Torso	0.22 ± 0.06	0.42 ± 0.17

*Results are reported as µL-equ ± SD $^3H_20$; Acceptance < 1.56 µl-equ/cm²
Water integrity data source: 0075dicl_Tol_D1_S1_V2
Skin thickness data source: zero value data/skin thickness_with Blank chambers v1a with Std Dev

Reviewer's comment 2:
Based on the criteria set by the firm, skin sections in which the absorption of ^3H_2O was less than 1.56 µL/cm^2 were considered acceptable. Therefore, the data provided by the firm adequately evaluate the integrity of each skin section of the human cadaver skin and validate the integrity of skin sections dosed in the study. The firm's response is **adequate**.

FDA Deficiency 3:
Please conduct your study using one lot each of your 'to be marketed' test product (ANDA formulation) and reference product.

Firm's response 3 :
SOLARAZE® Gel Lot 1203901 and Diclofenac Sodium Gel, 3% Lot 5919A was used as reference and test products respectively. Lot 5919A was manufactured by TOLMAR using the 'to be marketed' manufacturing process, materials, and was packaged in the to be marketed container.

Table 2: Test Articles and Materials Provided by the Study Sponsor

Component Type	Formulation Identity	Formulation Type	Manufacture Date	Expiration Date	Batch Size	Lot Number
Test Article Received but Not Used						
Test Article	SOLARAZE® Gel, Diclofenac Sodium 3%	Gel	Not Available	Not Available	Not Available	1203901
Used in the Pivotal Study						
Test Article "A"	SOLARAZE® Gel, Diclofenac Sodium 3% (identity known following unblinding)	Gel	Not Available	November 2013	Not Available	1485001
Test Article "B"	Diclofenac Sodium 3%	Gel	April 27, 2012	April 2014		5919A

Reviewer's comment 3:
Firm's response is **adequate**.

FDA Deficiency 4:
Please repeat the in vitro permeation study, which consists of Distribution Release-rate study and Mass-balance study, comparing your test product with the reference listed drug (RLD). In order to support a finding of pharmaceutical equivalence between the test and reference product, the following comments are provided for future in vitro permeation studies:

FDA Deficiency 4a:
Appropriately validated specific and sensitive analytical procedure should be used to analyze the sample and to determine the drug concentration and the amount of drug release.

Firm's response 4a :
Document R12-0512 reports the result of the method validation for the determination of diclofenac sodium in various sample matrices in support of the in vitro skin permeation study.

Reviewer's comment 4a:
The firm provided appropriate validated specific and sensitive analytical procedure and used it to analyze the samples. Please see section 4.5 Appendix for details. The firm's response is **adequate**.

FDA Deficiency 4b:
For the Distribution Release-rate study, 5 or more time points (at least 6 replicates per time-point) over an appropriate time period should be used per lot of test product and RLD. Mass-balance would be determined from the drug accumulation in the different skin layers (e.g. stratum corneum, epidermis, dermis). The Mass-balance study may be conducted at an appropriate time-point, using at least 6 replicates per lot of test product and RLD.

Firm's response 4b :
Samples were taken at 2, 4, 8, 12, 24, 32, and 48 hours after dose application as noted in Report R12-0075. The mass balance results are provided in Report T12-0075, Section 9.3.1.

Reviewer's comment 4b:
Please see sections 4.2-4.4 Appendix for details. The firm's response is **incomplete**.

FDA Deficiency 4c:
The DB II also recommends randomization, using appropriate software, of the test product and the RLD in each run of the experiment. This approach of including both products in each run of the in vitro apparatus will help ensure an unbiased comparison in the event of a systematic difference between runs. Please follow the Guidance for Industry: Non-sterile Semisolid Dosage Forms; Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation (SUPAC-SS) for the study design, as well as setup and operation of the Vertical (Franz) Diffusion Cell.

Firm's response 4c :
Randomization was achieved using SAS and both products were included in each run of the experiment as noted in the SUPAC-SS guidance. The randomization scheme is described in Report R12-0075.

Reviewer's comment 4c:
The firm utilized two sequences for dosing. In each sequence the test and reference product were dosed to replicate diffusion cells for a donor in an alternating pattern, in a design compatible with that specified by the *SUPAC-SS* Guidance. Specifically, the blinded reference and test products were each designated as either "A" or "B" and dosed to six replicate diffusion cells for each donor. The firm's response is **adequate**.

Treatment Randomization Generated: 10:59:30 Monday, August 20, 2012
A: SOLARAZE® GEL 3% (LOT.: 1485001; EXP.: 11/2013)
B: Diclofenac Sodium 3% (LOT: 5919A; Mfg. Date: 04/27/12)

Randomization Number	Sequence	Treatment
01	1	ABABABABABAB
02	2	BABABABABABA
03	1	ABABABABABAB
04	2	BABABABABABA
05	2	BABABABABABA
06	1	ABABABABABAB

FDA Deficiency 4d:
Please provide full details of the method of extraction and recovery of the drug from the different layers of the skin samples, and how the skin was separated into different layers (stratum corneum, epidermis, dermis).

Firm's response 4d :
Report R12-0075, Section 9.3.1 provides a detailed description of the methods used to separate the skin layers for analysis.

Reviewer's comment 4d:
The firm provided detailed explanation of the method of extraction and recovery of diclofenac sodium from the different layers of the skin. The skin was separated into stratum corneum, epidermis, dermis by tape-stripping with five successive strips of (b) (4) tape. The tapes were pooled as one sample and saved for analysis. Twenty minutes following the tape stripping procedure, the remaining skin section from each diffusion cell was then dismounted from the diffusion cell for isolation of the epidermis and dermis. This separation was performed by manual dissection involving the use of a scalpel blade to scribe the peripheral edge of the epidermis and dissociating it from the underlying dermis. The epidermal tissue is collected onto itself like a sachet, to mitigate exposure of the outermost surface of the epidermis to the underlying dermis. The remaining dermis sample was biopsied using a circular punch encompassing the nominal 1 cm^2 dosing area, and the biopsy was retained for analysis. All samples were stored at approximately -20°C pending analysis. The firm's response is **adequate**.

FDA Deficiency 4e:
Please submit all your pre-study bioanalytical method validation (including reproducibility, evaluation of sink conditions, skin binding), and 20% of the chromatograms.

Firm's response 4e :
Document R12-0512 is the method validation report which includes the noted parameters and to which at least 20% of the chromatograms have been provided.

Reviewer's comment 4e:
The firm submitted pre-study bioanalytical method using HPLC to analyze diclofenac sodium in multiple sample matrices relevant to an In Vitro Permeation Test (IVPT). Additionally, the

firm's approach was designed to characterize the solubility of diclofenac sodium in the receptor solution and skin binding. The firm provided validation parameters such:

- Specificity, Selectivity and Identification
- Linearity and Range
- Accuracy and Precision
- Sensitivity (Detection Limit and Quantitation Limit)
- Robustness
- Stability
- Recovery
- Solubility (in the receptor solution matrix)
- Skin Binding

Please see section 4.5 Appendix for details. The firm also provided 20% chromatograms. The firm's response is **adequate**.

FDA Deficiency 4f:

Please submit Distribution Release-rate study data and Mass-balance study data electronically as SAS (.xpt) data files(s). Data should be analyzed statistically using the approach outlined in the SUPAC-SS guidance referred in comment 4c above.

Firm's response 4f :

SAS data is provided in the following files as part of Appendix VII to Report R12-0075.

Reviewer's comment 4e:

The firm provided only the average data for each of the six replicate samples for all the donors. For completeness, the firm is requested to provide the complete raw data of each replicate time-point for all the donors for the un-transformed and transformed data. The firm's response is **inadequate**.

FDA Deficiency 4g:

The final report of the study should include lot numbers, date of manufacture, expiration date, and batch size of the test product and RLD, as applicable.

Firm's response 4g :

Neither TOLMAR, nor our contracted research organization (b) (4)*, has any way to confirm the exact manufacturing date or the batch size of the RLD lot that was used for this study. This information has been provided for the TOLMAR formulation only. All other information requested above is provided in R012-0075.*

Component Type	Formulation Identity	Formulation Type	Manufacture Date	Expiration Date	Batch Size	Lot Number
Test Article Received but Not Used						
Test Article	SOLARAZE® Gel, Diclofenac Sodium 3%	Gel	Not Available	Not Available	Not Available	1203901
Used in the Pivotal Study						
Test Article "A"	SOLARAZE® Gel, Diclofenac Sodium 3% (identity known following unblinding)	Gel	Not Available	November 2013	Not Available	1485001
Test Article "B"	Diclofenac Sodium 3%	Gel	April 27, 2012	April 2014	(b) (4)	5919A

<u>Reviewer's comment 4g:</u>
The firm's response is **adequate**.

3.1 Waiver Request(s)

Strengths for which waivers are requested	3%
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	No
If not then why?	Please see section 3.2 below for deficiency comments

3.2 Deficiency Comments

1. The firm provided only the mean flux data from the six replicate samples at each time-point. For completeness, the firm is requested to submit all the individual flux data in SAS (.xpt) data file (s) for each replicate sample at each time-point.

2. The firm provided a 90% confidence interval (CI) of diclofenac sodium deposition in the epidermis of 72.3% - 145.8%, and median T/R ratio (%) of 101.9. The 90% CI is **not** within the bioequivalence acceptable limits of 75% to133.33% per *SUPAC-SS* guidance. Therefore, the firm's data at first stage level do not show that diclofenac deposition in the epidermis is similar between the test and reference product, which is where the drug should primarily be absorbed. Since the firm utilized the first stage in vitro release approach per *SUPAC-SS* (a two-stage test) in its studies, which did not pass the 90% CI for epidermis, the DB II requests the firm to complete the full study and perform the additional second stage test to determine whether the 90% CI of diclofenac sodium deposition in the epidermis, as well as other layers, will fall within the limits of 75% to 133.33%, indicating bioequivalence between the test and the reference product. In addition, the firm should submit the complete un-transformed and transformed raw data in SAS (.xpt) data file (s) for each replicate time-point of all donors for the two stages.

3.3 Recommendations

The Division of Bioequivalence II does not agree that the information submitted by Tolmar Inc. demonstrates that its Diclofenac Sodium Topical Gel, 3% (w/w), meets the requirements specified under Section 21 CFR § 320.22 (b) (3). The DB II does not grant the waiver of in vivo bioequivalence testing requirements for the test product at this time due to the deficiency comments mentioned above.

3.4 Comments for Other OGD Disciplines

Discipline	Comment
All	There is a pending OSI inspection requested for the current application for the (b) (4) (b) (4)

4 APPENDIX – RESULTS

4.1 Donor Demographics (Specificity, Selectivity, and Identification)

Donor ID*	Age	Race	Sex	Location
Used for Receptor Solution Matrix*				
(b) (6)	68	Caucasian	Male	Posterior Torso
	44	Caucasian	Male	Posterior Torso
	58	Black	Male	Posterior Torso
	60	Caucasian	Male	Posterior Torso
	53	Asian	Male	Posterior Torso
	65	Hispanic	Female	Posterior Torso
	65	Caucasian	Male	Posterior Torso
	50	Hispanic	Male	Posterior Torso
	55	Black	Male	Posterior Torso
	45	Caucasian	Male	Posterior Torso
	50	Caucasian	Female	Posterior Torso
	52	Black	Female	Posterior Torso
Used for all other Matrices				
(b) (6)	51	Caucasian	Male	Posterior Torso
	67	Caucasian	Male	Posterior Torso
	38	Hispanic	Male	Posterior Torso
	58	Caucasian	Male	Posterior Torso
	58	Caucasian	Male	Posterior Torso
	61	Black	Male	Posterior Torso

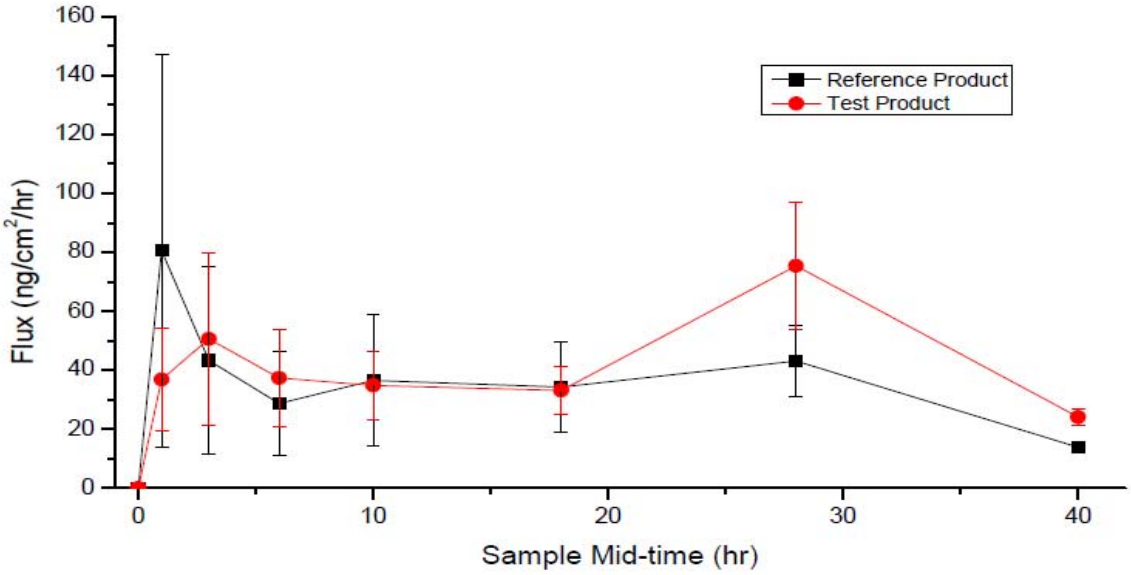
4.2 Absorption

Table 3: Mean Flux (ng/cm^2/hr) and Total Absorption Results: Across Donor Summary

Time (hr)*	Reference Product (Formulation A)	Test Product (Formulation B)
Flux Results		
1.0	80.59 ± 66.71	36.81 ± 17.40
3.0	43.34 ± 31.99	50.56 ± 29.37
6.0	28.69 ± 17.78	37.39 ± 16.60
10.0	36.46 ± 22.18	34.76 ± 11.77
18.0	34.23 ± 15.39	33.12 ± 8.06
28.0	43.03 ± 11.89	75.41 ± 21.46
40.0	13.79 ± 1.81	24.09 ± 2.73
Total Absorption Results (0-48 hrs)		
Receptor (ng)	1484.1 ± 629.0	1849.5 ± 434.4
Receptor (%)	1.02 ± 0.43	1.26 ± 0.30

* Time as midpoint between samples.
Data Source: 0075dicl_Tol_Summary_S1_V5 Across Donor Summary (Zeros).xls

Figure 1: Mean Flux (ng/cm^2/hr) and Total Absorption Results: Across Donor Summary (Non-Transformed Data)



Percutaneous absorption of diclofenac sodium through ex vivo, human torso skin over 48 hours from a single 24 hour application (Mean ± SE, n=6 Donors).

Reviewers' comment:
The study was designed to compare the percutaneous absorption of diclofenac sodium from one formulation lot of the test product (#5919A) and the RLD (#1485001) using a finite dose technique and Vertical (Franz) Diffusion cells. The dosing was done using a single application over 48 hours. From the firm's data, the test product and the RLD in the reservoir (i.e. equivalent to total absorption) account for 1.26% ± 0.30 to 1.02% ± 0.43, respectively, of the applied dose (5 mg formulation/cm^2/skin).

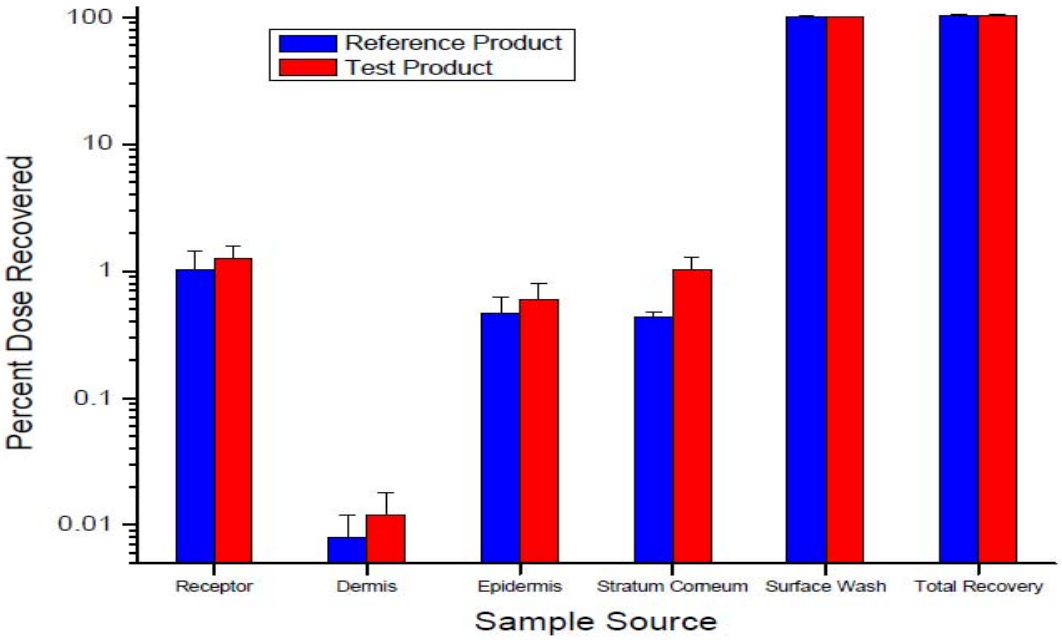
4.3 Distribution and Recovery: Across Skin Donors

Table 4: Distribution and Recovery: Across Skin Donors (Non-Transformed Data)

Parameter	Reference Product (Formulation A)	Test Product (Formulation B)
Mass Recovered		
Total Absorption (ng)	1,484.1 ± 629.0	1,849.5 ± 434.4
Dermis (ng)	11.44 ± 5.41	17.73 ± 9.22
Epidermis (ng)	693.6 ± 242.0	894.8 ± 298.0
Stratum corneum (ng)	631.5 ± 46.4	1462.7 ± 334.3
Surface Wash (ng)*	146,353 ± 1,386	146,833 ± 1,527
Percent of Applied Dose		
Total Absorption (%)	1.02 ± 0.43	1.26 ± 0.30
Dermis (%)	0.01 ± 0.00	0.01 ± 0.01
Epidermis (%)	0.46 ± 0.16	0.60 ± 0.20
Stratum corneum (%)	0.44 ± 0.04	1.00 ± 0.24
Surface Wash (%)*	100.55 ± 2.16	99.77 ± 1.73
Total Recovery		
Total Recovery (%)	102.6 ± 2.2	102.8 ± 1.9

*Surface Wash was performed 24 hours post-dosing
Data source: 0075dicl_Tol-Summary_S1_V5 Across Donor Summary (Zeros).xls

Figure 2: Distribution and Recovery of Diclofenac Sodium (Non-Transformed Data)



Distribution of diclofenac sodium into and through human ex vivo torso skin at 24 or 48 hours from a single 24 hour application. Mean ± SE (n=6 Donors) as Percent of Applied Dose and Total Mass (ng/ cm^2)

Reviewer's comment:
The vast majority of the applied dose of the test and the RLD remained on the surface of the skin and was recovered in the surface wash. Out of the applied dose, 0.60% ± 0.20 and 0.46% ± 0.16 for the test and RLD formulations, respectively, were found in the **epidermis**, while 0.01% ± 0.01 and 0.01% ± 0.00 for the test and RLD, respectively, were found in the **dermis**, and 1.00% ± 0.24 and 0.44% ± 0.04 for the test and RLD, respectively, were found in the **stratum corneum**. The total recovery of the applied dose was 102.8% ± 1.9 for the test and 102.6% ± 2.2 for the RLD formulations.

4.4 Firm's Statistical Summary

Table 5: Final Statistical Summary (<LLQ values as zero values; non-transformed)

Statistic	Average Total Receptor Penetration	Average Dermis Amount	Average Epidermis Amount	Average Stratum Corneum Amount	Average Surface Wash Amount
N (Donors)	6	6	6	6	6
Minimum	16.9	0	1.0	69.8	94.0
Median	175.6	44.6	114.9	198.0	100.3
Maximum	796.0	322.0	8258.3	536.7	107.0
Lower Limit of 90% CI**	67.9	34.6	13.5	123.3	98.1
Upper Limit of 90% CI	349.0	Not Calculable	964.5	370.8	102.8

* Data are rounded to 1 decimal place for viewing convenience. See Appendices for complete data.
** CI = Confidence Interval
Data Source : compiled zerovalues 17OCT12.pdf

Table 6: Final Statistical Summary (<LLQ values as 1/2 LOQ- Log Transformed)

Statistic	Average Total Receptor Penetration	Average Dermis Amount	Average Epidermis Amount	Average Stratum Corneum Amount	Average Surface Wash Amount
N (Donors)	6	6	6	6	6
Minimum	79.0	79.8	47.1	94.6	99.5
Median	107.9	100.0	101.9	110.4	100.0
Maximum	133.5	137.7	206.3	127.2	100.6
Lower Limit of 90% CI**	94.6	88.1	72.3	103.1	99.8
Upper Limit of 90% CI	119.9	116.2	145.8	120.0	100.2

* Data are rounded to 1 decimal place for viewing convenience. See Appendices for complete data.
**CI = Confidence Interval
Data Source: compiled results halfloq_ln 17Oct12

Distribution of diclofenac sodium into and through human ex vivo torso skin after 24 or 48 hours from a single 24 hour application. Mean ± SE (n=6 Donors) as Total Mass (ng/ cm^2)

Table 7: In Vitro Release Rate – Reviewer Calculated

Comparison Results (90% CI) Comparison Limits: 75% to 133.33%			
Stage One	**Epidermis**	**Dermis**	**Stratum Corneum**
8th ordered ratio (%)	72.27	88.06	103.14
29th ordered ratio (%)	145.80	116.16	119.99

	% Ratio (Sorted)			
Ratio	**Epidermis**	**Dermis**	**Stratum Corneum**	**Sorted Rank**
T1/R1	47.0776784	79.81278	94.60956665	1
T2/R1	47.7348245	79.81278	96.2097868	2
T3/R1	47.7972551	84.3726	96.22588831	3
T4/R1	56.6701032	84.3726	99.61535441	4
T5/R1	61.0316156	85.56293	99.66828397	5
T6/R1	61.8835414	85.56293	101.964607	6
T1/R2	61.9644766	85.89122	103.112454	7
T2/R2	72.2786824	88.06843	103.1443398	8
T3/R2	73.4672582	90.7983	104.8564914	9
T4/R2	92.8401009	92.07929	104.87404	10
T5/R2	93.7022579	93.0999	104.8889165	11
T6/R2	94.9673701	94.41336	104.9064705	12
T1/R3	96.2929971	99.68764	108.5681291	13
T2/R3	96.418935	100	108.5806168	14
T3/R3	98.0510261	100	108.601702	15
T4/R3	99.4196972	100	108.6258156	16
T5/R3	99.5497244	100	108.6594063	17
T6/R3	101.233	100	110.4171424	18
T1/R4	102.646088	100	110.4356216	19
T2/R4	102.780335	105.3829	111.1285171	20
T3/R4	104.612931	106.8697	111.1628817	21
T4/R4	106.073198	107.6159	114.3256122	22
T5/R4	106.211928	107.6159	114.3863579	23
T6/R4	114.317673	107.6159	116.234457	24
T1/R5	118.029647	109.8844	117.0217802	25
T2/R5	120.35813	110.3438	118.0029889	26
T3/R5	121.859972	110.3438	118.2004391	27
T4/R5	125.928589	110.3438	118.220221	28
T5/R5	145.804054	116.1623	119.9988839	29
T6/R5	150.538413	117.8011	120.0189667	30
T1/R6	155.423719	124.9018	122.3844167	31
T2/R6	160.612951	124.9018	122.4494443	32
T3/R6	187.281542	124.9018	124.2465215	33
T4/R6	193.362703	137.6777	124.3125386	34
T5/R6	199.637753	137.6777	125.2706374	35
T6/R6	206.303187	137.6777	127.1766567	36

Reviewer's note:
As per *SUPAC-SS* guidance, the in vitro release comparison should be carried out as a two-stage test. At the first stage, two runs of the (six cells) in vitro apparatus should be carried out, yielding six slopes (estimated in vitro release rates) for the test and reference, respectively, in this case. A 90% CI for the ratio of the median in vitro release rate for the test over the median in vitro release rate for the reference should be computed, expressed in percentage terms. If, at the first stage, this 90% CI falls within the limits of 75% to 133.33%, no further in vitro testing is necessary.

If the test does not pass at the first stage, 4 additional runs of the (six cells) in vitro apparatus should be carried out, yielding 12 additional slopes for each product, or 18 in all (including the first stage results). The 90% CI should be computed using all 18 slopes for each product, including the first stage results. At the second stage, this 90% CI should fall within the limits of 75% to 133.33%.

Comments on Study Results:

- The firm provided only the average data for each of the six replicate samples for all the donors. For completeness, the firm is requested to provide the complete raw data of each replicate time-point for all the donors for the un-transformed and transformed data.
- The firm obtained its data by using the Wilcoxon Rank Sum/Mann-Whitney Rank Test, and a Test-to-Reference Median statistical evaluation performed with log-transformed data. The firm followed the *SUPAC-SS* guidance[1] for its statistical analyses. Comparisons were determined using the 90% CI for the ratio of the median diclofenac sodium absorption to the reference. The firm's result agrees with the reviewer's analysis.
- Sample Concentration values less than the LLQ were represented at a value corresponding to 1/2LOQ (one half the theoretical limit of quantification) for a particular matrix, in order to generate a parallel data set that could be log-transformed for Wilcoxon/Mann-Whitney statistical analysis.
- The firm evaluated each study parameter (surface wash, stratum corneum tape strips, epidermis, dermis, and total receptor solution absorption).
- Per the firm's study protocol, if the upper boundary of the CI for the ratio of total diclofenac sodium absorption into the receptor solution (test/reference) did not exceed 133.33%, it concluded that the total absorption into the receptor solution of diclofenac sodium from the test product is not greater than that from the reference product.
- The firm also specified other criteria defined in its study protocol, stating that if the gel (diclofenac sodium) retention on the skin is similar between the test and reference products the median T/R ratio would be expected to fall between 65% and 154%, based upon a 35% difference between the test and reference product.

[1] Guidance for Industry: Nonsterile Semisolid Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation (*SUPAC-SS*)

Reviewer's comment:

1. The firm's data show that the average total receptor penetration has a 90% CI of 94.6% - 119.9%, and median T/R ratio (%) of 107.9%. Both the 90% CI and the T/R are within the bioequivalence acceptable limits of 75% - 133.33% per *SUPAC-SS* guidance. The data indicates that the test and reference products may have comparable absorption and that the test does no significantly increase the systemic exposure of diclofenac sodium.

2. The average surface wash amount has a 90% CI of 99.8% - 100.2%, and median T/R ratio (%) of 100.0. Both the 90% CI and the T/R are within the bioequivalence acceptable limits of 75% - 133.33% per *SUPAC-SS* guidance. The data indicates that diclofenac sodium penetration in the skin may be similar between formulations of the test and reference products.

3. The average stratum corneum amount has a 90% CI of 103.1% - 120.0%, and median T/R ratio (%) of 110.4. Both the 90% CI and the T/R are within the bioequivalence acceptable limits of 75% - 133.33% per *SUPAC-SS* guidance.

4. The average dermis amount has a 90% CI of 88.1% - 116.2%, and median T/R ratio (%) of 100.0. Both the 90% CI and the T/R are within the bioequivalence acceptable limits of 75% - 133.33% per *SUPAC-SS* guidance. The data indicates that diclofenac sodium retention in the dermis is similar between formulations following application of test and reference products.

5. The average epidermis amount has a 90% CI of 72.3% - 145.8%, and median T/R ratio (%) of 101.9. The 90% CI is not within the bioequivalence acceptable limits of 75% to133.33% per *SUPAC-SS* guidance. Therefore, the in vitro release data at first stage does not indicate bioequivalence between the test and reference formulations, at least in the epidermis. The data may not completely show that diclofenac sodium retention in the epidermis is similar between formulations of its test product and reference, as diclofenac should primarily be absorbed into the epidermis. Therefore, since the firm utilized the first stage in vitro release approach per *SUPAC-SS* (a two-stage test) in its studies, which did not pass the 90% CI for epidermis, the DB II request the firm to complete the full study and perform the additional second stage test to determine whether the 90% CI of the epidermis will fall within the limits of 75% to 133.33%.

4.5 Pre-Study Bioanalytical Method Validation

Information Requested	
Bioanalytical method validation report location	Module 5.3.1 Title: HPLC Analytical Method Qualification with Sample Matrices Relevant to the Evaluation of the In Vitro Percutaneous Absorption of Diclofenac Sodium from a Gel Formulation into and through Human Torso Skin using the Franz Finite Dose Model
Study Report Number	R12-0512_Final_Report
Analyte:	Diclofenac sodium
Method description	HPLC method

Linearity and Range:

Acceptance criteria:

Lowest Standard or LLOQ	± 20%;	Pass
Others	±15%	Pass
CV	±15%	Pass

	Linearity	Range
Dermis, Epidermis, and Glass Rod	>0.999	0.05-20 µg/mL
Receptor Solution Samples	>0.999	3-300 ng/mL
Surface Wash Samples	>0.999	5-200 µg/mL
Tape Strip Samples	>0.999	10-500 ng/mL

Accuracy and Precision:

			Accuracy (% Actual)	Precision (%CV)
Dermis, Epidermis, and Glass Rod	Inter-Batch	Standards	99.5% - 100.7%	1.4% - 5.5%
		Validation (QC) samples	99.9% - 111.5%	2.5 % - 6.5 %
	Intra-Batch	Batch 1 Batch 2 Batch 3 Batch 4	104.1% - 114.8% 98.2% - 107.9% 98.0% - 111.2% 99.5% - 118.5%	0 % - 6% 0 % - 4% 0 % - 6% 0 % - 3%
Receptor Solution Samples			**Accuracy (% Actual)**	**Precision (%CV)**
	Inter-Batch	Standards	99.0% - 100.9%	1.2% - 4.4%
		Validation (QC) samples	106.7% - 111.6%	1.7% - 3.5%
	Intra-Batch	Batch 1 Batch 2 Batch 3	108.0% - 113.1% 108.3% - 113.8% 103.7% - 109.9%	1% - 2% 0% - 2% 2% - 3%

			Accuracy (% Actual)	Precision (%CV)
Surface Wash Samples	Inter-Batch	Standards	99.2% - 100.4%	0.2% - 0.5%
		Validation (QC) samples	99.1% - 102.0%	0.9% - 2.3%
	Intra-Batch	Batch 1 Batch 2 Batch 3 Batch 4	100.8% - 103.8% 98.3% - 101.8% 98.9% - 102.4% 97.0% - 100%	0% - 0% 0% - 0% 0% - 0% 0% - 1%
Tape Strip Samples			**Accuracy (% Actual)**	**Precision (%CV)**
	Inter-Batch	Standards	97.5% - 101.9%	0.7% - 2.3%
		Validation (QC) samples	96.4% - 107.8%	1.6% - 7.5%
	Intra-Batch	Batch 1 Batch 2 Batch 3	96.5% - 103.6% 95.2% - 105.9% 96.8% - 113.8%	1% - 1% 1% - 2% 1% - 1%

Sensitivity – Detection Limit and Quantitation Limit:

	Average	Theoretical Detection Limit (ng/mL)	Theoretical Quantitation Limit (ng/mL)
Dermis, Epidermis, and Glass Rod	13.6	0.01	0.04
Receptor Solution Samples	19.95	0.45	1.50
Surface Wash Samples	357.0	0.04	0.14
Tape Strip Samples	52.50	0.57	1.90

Robustness:

Dermis, Epidermis, and Glass Rod:

Different Column Temperature:
Accuracy (% Actual) 101.2% - 112.4% Acceptable
Precision (% CV) 0% - 3% Acceptable

Different Column Serial Number:
Accuracy (% Actual) 98.0% - 111.2% Acceptable
Precision (% CV) 0 % - 6 % Acceptable

Different Person Spiking Curve:
Accuracy (% Actual) 99.5% - 118.5% Acceptable
Precision (% CV) 0 % - 3% Acceptable

Receptor Solution Samples:

Different Column Temperature:
Accuracy (% Actual) 109.6% - 113.8% Acceptable
Precision (% CV) 0% - 3% Acceptable

Different Column Serial Number:
Accuracy (% Actual) 108.3% - 113.8% Acceptable
Precision (% CV) 0% - 3% Acceptable

Different Person Spiking Curve:
Accuracy (% Actual) 103.7% - 109.9% Acceptable
Precision (% CV) 2% - 3% Acceptable

Surface Wash Samples:

Different Column Temperature:		
Accuracy (% Actual)	102.0% - 104.7%	Acceptable
Precision (% CV)	0% - 0%	Acceptable
Different Column Serial Number:		
Accuracy (% Actual)	99.0% - 102.4%	Acceptable
Precision (% CV)	0 % - 0%	Acceptable
Different Person Spiking Curve:		
Accuracy (% Actual)	97.0% - 100.0%	Acceptable
Precision (% CV)	0% - 1%	Acceptable

Tape Strip Samples:

Different Column Temperature:		
Accuracy (% Actual)	96.1% - 106.1%	Acceptable
Precision (% CV)	1% - 1%	Acceptable
Different Column Serial Number:		
Accuracy (% Actual)	95.2% - 105.9%	Acceptable
Precision (% CV)	1% - 2 %	Acceptable
Different Person Spiking Curve:		
Accuracy (% Actual)	96.8% - 113.8%	Acceptable
Precision (% CV)	1% - 1%	Acceptable

Stability:

Stock Solution (Methanol):

Stock Solution Stability:

Short-Term (Room Temperature)	1297:47 hrs-min.
Alternative (4°C)	1297:47 hrs-min.

Dermis, Epidermis, and Glass Rod:

Stability in Sample Matrix:

Freeze and Thaw	3 cycles
Short-Term (Room Temperature)	650:33 hrs-min.
Long Term (Freezer)	49 days

Receptor Solution Samples:

Stability in Sample Matrix:

Freeze and Thaw	3 cycles
Short-Term (Room Temperature)	171:02 hrs-min.
Long Term (Freezer)	44 days
Alternative (35°C)	27:13 hrs-min.

Surface Wash Samples:

Stability in Sample Matrix:

Freeze and Thaw	3 cycles
Short-Term (Room Temperature)	387:27 hrs-min.
Long Term (Freezer)	86 days

Tape Strip Samples:

Stability in Sample Matrix:

Freeze and Thaw	3 cycles
Short-Term (Room Temperature)	144:54 hrs-min.
Long Term (Freezer)	40 days

Recovery:

Recovery of Dermis, Epidermis, and Glass Rod in 50:50 EtOH:

Positive control injections			
Replicate	Sample	Concentration (ug/mL)	Average
1	Positive Low-1	0.0953	
2	Positive Low-1	0.0941	0.0947
1	Positive Low-2	0.0982	
2	Positive Low-2	0.1009	0.0995
1	Positive Low-3	0.0996	
2	Positive Low-3	0.0999	0.0998
			0.0980

Replicate	Sample	Concentration (ug/mL)	Average
1	Positive Mid-1	1.1800	
2	Positive Mid-1	1.1802	1.1801
1	Positive Mid-2	1.1727	
2	Positive Mid-2	1.1765	1.1746
1	Positive Mid-3	1.2209	
2	Positive Mid-3	1.2205	1.2207
			1.1918

Replicate	Sample	Concentration (ug/mL)	Average
1	Positive High-1	14.0877	
2	Positive High-1	14.0854	14.0865
1	Positive High-2	14.5669	
2	Positive High-2	14.5715	14.5692
1	Positive High-3	13.5254	
2	Positive High-3	13.5142	13.5198
			14.0585

Recovery Samples		
Sample	Concentration (ug/mL)	Average
Dermis Low-1	0.0819	
Dermis Low-2	0.0797	
Dermis Low-3	0.0967	0.0861
	% Recovery	88%
Sample	Concentration (ug/mL)	Average
Epidermis Low-1	0.0666	
Epidermis Low-2	0.1027	
Epidermis Low-3	0.0990	0.0895
	% Recovery	91%
Sample	Concentration (ug/mL)	Average
Glass Rod Low-1	0.0825	
Glass Rod Low-2	0.0673	
Glass Rod Low-3	0.1050	0.0849
	% Recovery	87%

Sample	Concentration (ug/mL)	Average
Dermis Mid-1	1.0403	
Dermis Mid-2	1.0558	
Dermis Mid-3	0.9944	1.0302
	% Recovery	86%
Sample	Concentration (ug/mL)	Average
Epidermis Mid-1	0.8889	
Epidermis Mid-2	1.0004	
Epidermis Mid-3	0.9379	0.9424
	% Recovery	79%
Sample	Concentration (ug/mL)	Average
Glass Rod Mid-1	1.1303	
Glass Rod Mid-2	1.2149	
Glass Rod Mid-3	1.1931	1.1794
	% Recovery	99%

Sample	Concentration (ug/mL)	Average
Dermis High-1	11.6251	
Dermis High-2	13.0918	
Dermis High-3	12.7433	12.4867
	% Recovery	89%
Sample	Concentration (ug/mL)	Average
Epidermis High-1	9.6571	
Epidermis High-2	12.5004	
Epidermis High-3	12.9493	11.7022
	% Recovery	83%
Sample	Concentration (ug/mL)	Average
Glass Rod High-1	12.5721	
Glass Rod High-2	13.7759	
Glass Rod High-3	12.1675	12.8385
	% Recovery	91%

Negative control injections			
Replicate	Sample	Concentration (ug/mL)	Average
1	Neg Dermis	0.0000	
2	Neg Dermis	0.0000	0.0000

Replicate	Sample	Concentration (ug/mL)	Average
1	Neg Epidermis	0.0000	
2	Neg Epidermis	0.0000	0.0000

Replicate	Sample	Concentration (ug/mL)	Average
1	Neg Glass Rod	0.0000	
2	Neg Glass Rod	0.0000	0.0000

Recovery of Tape Strips in ACN:

Positive control injections			
Replicate	Sample	Concentration (ng/mL)	Average
1	Positive Low-1	20.5711	
2	Positive Low-1	20.2934	20.4323
1	Positive Low-2	28.6797	
2	Positive Low-2	28.6481	28.6639
1	Positive Low-3	28.4321	
2	Positive Low-3	27.5800	28.0061
			25.7007

Replicate	Sample	Concentration (ng/mL)	Average
1	Positive Mid-1	94.2781	
2	Positive Mid-1	92.2467	93.2624
1	Positive Mid-2	96.5273	
2	Positive Mid-2	94.3605	95.4439
1	Positive Mid-3	96.0951	
2	Positive Mid-3	95.9852	96.0402
			94.9155

Replicate	Sample	Concentration (ng/mL)	Average
1	Positive High-1	301.5320	
2	Positive High-1	298.9460	300.2390
1	Positive High-2	309.7970	
2	Positive High-2	310.2700	310.0335
1	Positive High-3	308.6690	
2	Positive High-3	308.9030	308.7860
			306.3528

Recovery samples		
Sample	Concentration (ng/mL)	Average
Tape strip Low-1	25.7378	
Tape strip Low-2	25.5354	
Tape strip Low-3	25.8340	25.7024
	% Recovery	**100%**
Sample	Concentration (ng/mL)	Average
Tape strip Mid-1	81.3657	
Tape strip Mid-2	*	
Tape strip Mid-3	76.9838	79.1748
	% Recovery	**83%**
Sample	Concentration (ng/mL)	Average
Tape Strip High-1	293.8890	
Tape Strip High-2	277.4430	
Tape Strip High-3	248.4150	273.2490
	% Recovery	**89%**

Negative control injections			
Replicate	Sample	Concentration (ng/mL)	Average
1	Neg with SC	0.0000	
2	Neg with SC	0.0000	0.0000

Replicate	Sample	Concentration (ng/mL)	Average
1	Neg without SC	0.1152	
2	Neg without SC	0.1729	0.1441

Solubility:

Replicate	Diclofenac sodium Minimum Solubility (mg/mL)
1-1	1.133
1-2	1.194
1-3	1.081
Average	**1.136**

Skin Binding:

Sample	Average Incubation Recovery	Average Extraction Recovery	Total Recovery for Skin binding
Low (0.100 µg/mL)	78.41%	BLQ*	BLQ*
Mid (1.2 µg/mL)	82.14%	15.56%	97.69%
High (15 µg/mL)	84.86%	17.03%	101.89%
Average	81.80%	16.30%	**99.79%**

*Due to the Recovery Low samples being <LLOQ, no quantifiable data were achieved. The Total Recovery was calculated using only the Mid and High levels.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 200936

APPLICANT: Tolmar Inc.

DRUG PRODUCT: Diclofenac Sodium Topical Gel, 3%

The Division of Bioequivalence has completed its review and the following deficiencies have been identified.

1. You provided only the mean flux data from the six replicate samples at each time-point. For completeness, please submit all the individual flux data in SAS (.xpt) data file(s) for each replicate sample at each time-point.

2. You provided a 90% confidence interval (CI) of diclofenac sodium deposition in the epidermis of 72.3% - 145.8%, and median T/R ratio (%) of 101.9. The 90% CI is not within the bioequivalence acceptable limits of 75% to 133.33% per Scale-Up and Postapproval Changes - Semisolid Dosage Forms (SUPAC-SS) guidance. Your data, at first stage level, do not show that diclofenac deposition in the epidermis is similar between the test and reference product, which is where the drug should primarily be absorbed. Since you utilized the first stage in vitro release approach per SUPAC-SS (a two-stage test) in your studies, which did not pass the 90% CI for epidermis, please complete the full study and perform the additional second stage test to determine whether the 90% CI of diclofenac sodium deposition in the epidermis, as well as all other layers, will fall within the limits of 75% to 133.33%, indicating bioequivalence between your test and the reference product. In addition, please submit the complete raw un-transformed and transformed data in SAS (.xpt) data file(s) for each replicate time-point of all donors for the two stages.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Director, Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.6 Outcome Page

ANDA: 200936

Completed Assignment for 200936 ID: 18625

Reviewer: Aimiuwu, Josephine

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Diclofenac Sodium Topical Gel Waiver, 3% (w/w) from Tolmar Inc.

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
18625	10/31/2012	Other (REGULAR)	Study Amendment	1	1
				Total:	1

DB II REVIEW COMPLEXITY SUMMARY

ANDA: 200936

Topical Gel Waiver:

Study Amendment	1
Study Amendment Total	*1*
Total	***1***

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

/s/

JOSEPHINE E AIMIUWU
03/29/2013

Parthapratim CHANDAROY
03/29/2013

ETHAN M STIER on behalf of BARBARA M DAVIT
04/03/2013

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	200936
Drug Product Name	Diclofenac Sodium Topical Gel
Strength(s)	3%
Applicant Name	Tolmar Inc.
Address	701 Centre Avenue Fort Collins, CO 80526
Applicant's Point of Contact	Michelle R. Ryder, Director, Regulatory Affairs
Contact's Telephone Number	970-212-4901
Contact's Fax Number	970-212-4950
Original Submission Date(s)	December 14, 2009
Submission Date(s) of Amendment(s) Under Review	September 27, 2011 (Request for Dispute Resolution in response to deficiencies) March 23, 2012 (information on the test lots used in the in vitro permeation study)
Reviewer	Parthapratim Chandaroy, Ph.D.
OUTCOME DECISION	**INADEQUATE**
OSI REPORT	**INADEQUATE**
In Vitro Study Site	(b) (4)
In Vitro Study Site Address	

OVERALL REVIEW RESULT	**INADEQUATE**
OSI REPORT RESULT	**INADEQUATE**

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	Formulation	3%	INADEQUATE
13, 15	In Vitro Permeation Study	3%	INADEQUATE

1 EXECUTIVE SUMMARY

This application contains the waiver request of *in vivo* bioequivalence study requirements for Tolmar Inc.'s proposed test product Diclofenac Sodium Topical Gel, 3% (w/w) under 21 CFR §320.22(b)(3). The Reference Listed Drug (RLD) is Fougera Pharmaceuticals Inc's Solaraze® (diclofenac sodium topical gel), 3% (w/w) (NDA #021005). This review includes the original and amendment submissions.

The formulation of the test product is **not** qualitatively and quantitatively (Q1/Q2) similar to that of the RLD. Therefore, the Division of Bioequivalence II (DB II) does not deem the test product Diclofenac Sodium Topical Gel, 3% (w/w) bioequivalent to the corresponding reference product, Fougera Pharmaceuticals Inc's Solaraze® (diclofenac sodium topical gel), 3% w/w, based on criteria set forth in 21 CFR §320.22(b)(3).

Upon review of the ANDA #200936 by the Clinical Review Team, Tolmar Inc.'s Diclofenac Sodium Gel, 3% was deemed to have a markedly different formulation than that of the RLD. The RLD formulation contains (b) (4) sodium hyaluronate, (b) (4) (b) (4). The firm's test product does not contain hyaluronate, and instead contains hydroxyethyl cellulose as (b) (4) (b) (4) along with PEG-60 hydrogenated castor oil. Therefore, the resulting viscosity is only (b) (4) (b) (4) of that of the RLD, and could result in a difference in efficacy that could be missed on a clinical endpoint study that is not adequately sensitive. A "fatal flaw" deficiency letter was sent to the firm in this regard (DARRTS ANDA 200936 COR-ANDAACTION-11 (Complete Response-Fatal Flaw) Final date: 07/11/2011).

On September 27, 2011, Tolmar Inc. submitted a major amendment in the form of a Request for Dispute Resolution in response to the deficiency letter sent by the Clinical Review Team. The Dispute Resolution was sent by the firm to appeal the non-approval of the ANDA application and to also address some of the deficiencies. The firm submitted an in vitro skin permeation study as Exhibit-9 to evaluate the percutaneous absorption of diclofenac sodium using the human cadaver skin model (please see section 3.5 In Vitro Skin Permeation Study for details). Based on a review of the firm's in vitro skin permeation study data, the Division of Bioequivalence II (DB II) concludes that the in vitro skin permeation study is **inadequate.** The firm is requested to incorporate the deficiency comments in its study design and repeat the in vitro skin permeation study comparing its test product with the RLD. The Division of Clinical Review (DCR), following the submission of the Request for Dispute Resolution by Tolmar, re-evaluated the submitted clinical endpoint study and found it eligible for a full review (DARRTS ANDA 200936 REV-CLINICAL-03 (General Review) Final date: 12/13/2011).

An Office of Scientific Investigations (OSI) inspection has been completed for the clinical site (NDA #22497; 06/20/2011) and analytical site (NDA #21342; 09/07/2010) of (b) (4) (b) (4) The outcome of both requests is No Action Indicated (NAI). (b) (4) (b) (4) Therefore, an OSI inspection was requested on 12/15/2011 for the current application. The application is **inadequate** due to several deficiencies (please see section 3.7 Deficiency Comments) and pending OSI inspection.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Diclofenac Sodium Topical Gel, 3%
Reference Product	Solaraze® (diclofenac sodium topical gel), 3%
RLD Manufacturer	Almirall Hermal GmbH, D-21465 Reinbek, Germany for PharmaDerm®, a Division of Fougera Pharmaceuticals Inc., Melville, NY 11747
NDA No.	021005
RLD Approval Date	October 16, 2000
Indication	Solaraze® is indicated for the topical treatment of actinic keratoses (AK)[1]

3.2 PK/PD Information[2]

Bioavailability	When Solaraze® is applied topically, diclofenac is absorbed into the epidermis. In a study in patients with compromised skin (mainly atopic dermatitis and other dermatitic conditions) of the hands, arms or face, approximately 10% of the applied dose (2 grams of 3% gel over 100 cm^2) of diclofenac was absorbed systemically in both normal and compromised epidermis after seven days, with four times daily applications. The systemic bioavailability after topical application of Solaraze® is lower than after oral dosing. A cross-study evaluation of the data indicates that diclofenac is more bioavailable when applied to diseased skin and less bioavailable when applied to intact skin.
Food Effect	N/A
Tmax	4.5 ± 8 hours (topical application of 2 g Solaraze® three times daily for six days to the calf of the leg in healthy subjects)
Metabolism	Biotransformation of diclofenac following oral administration involves conjugation at the carboxyl group of the side chain or single or multiple hydroxylations resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, however to a much smaller extent than diclofenac. Metabolism of diclofenac following topical administration is thought to be similar to that after oral administration. The small amounts of diclofenac and its metabolites appearing in the plasma following topical administration makes the quantification of specific metabolites imprecise.
Excretion	Diclofenac and its metabolites are excreted mainly in the urine after oral dosing.
Half-life	Terminal half-life is 1 – 2 hours. Four of the metabolites also have short terminal half-lives of 1 – 3 hours.
Dosage and Administration	Solaraze® Gel is applied to lesion areas twice daily. It is to be smoothed onto the affected skin gently. The amount needed depends upon the size of the lesion site, and assure that enough Solaraze® Gel is applied to adequately cover each lesion. Normally 0.5 g of gel is used on each 5 cm x 5 cm lesion site. The recommended duration of therapy is from 60 days to 90 days. Complete healing of the lesion(s) or optimal therapeutic effect may not be evident for up to 30 days following cessation of therapy. Lesions that do not respond to therapy should be carefully re-evaluated and management reconsidered.

[1] Sun avoidance is indicated during therapy
[2] RLD label (Approved 12/8/2011 in DRUGS@FDA; http://www.accessdata fda.gov/drugsatfda_docs/label)

	General Precautions • Solaraze® (diclofenac sodium) Topical Gel should be used with caution in patients with active gastrointestinal ulceration or bleeding and severe renal or hepatic impairments. • Solaraze® should not be applied to open skin wounds, infections, or exfoliative dermatitis. • It should not be allowed to come in contact with the eyes. • The safety of the concomitant use of sunscreens, cosmetics or other topical medications and Solaraze® is unknown.
Drug Specific Issues (if any)	As with other NSAIDs, anaphylactoid reactions may occur in patients without prior exposure to diclofenac. Diclofenac sodium should be given with caution to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs.

3.3 Formulation

Location in appendix	Section 4.4 Page 11
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	No
If not acceptable, why?	The test product is not qualitatively and quantitatively (Q1/Q2) similar to that of the RLD

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	---	---
Single-dose fed	---	---
Steady-state	---	---
In vitro dissolution	---	---
Waiver requests	Yes	1
BCS Waivers	---	---
Clinical Endpoints	Yes	1
Failed Studies	---	---
Amendments	Yes	2

3.5 In Vitro Skin Permeation Study

In the submission, dated September 27, 2011, the firm responded (Dispute Resolution Letter) to some of the deficiencies sent by the Clinical Review Team (DARRTS ANDA 200936 COR-ANDAACTION-11 (Complete Response-Fatal Flaw) 07/11/2011). The firm conducted studies to establish that the penetration profiles for its test product and the RLD is identical. Below is a summarized version of the deficiencies and the firm's response:

Deficiencies 1 - 3:

1. Demonstrate that your selected excipient performs similarly to hyaluronate sodium. This may be accomplished through in vitro skin permeation studies and a well-designed comparative pharmacokinetic bioequivalence study.
2. Explain your rationale for not matching the viscosity of the RLD.
3. Demonstrate that the gel retention on the skin and in the epidermis after application is similar to that of the RLD.

Firm's Response:

IV. TOLMAR Has Conducted an In Vitro Study Showing That Its Formulation Has a Similar Penetration Profile Compared to the RLD

TOLMAR was aware that viscosity may possibly affect drug delivery and penetration via the skin. Consequently, TOLMAR conducted an in vitro penetration study of two lots of its formulation and compared them to a lot of the RLD prior to initiation of the clinical endpoint study. A finite dose (4-7 mg/cm^2), which is considered more relevant than infinite dosing as it better represents "in use" conditions,[9,10] with three replicates from three different human cadaver skin donors was used to determine the equivalence between the TOLMAR gel (b) (4) and the RLD (b) (4) (b) (4) This study, which was conducted by (b) (4) established that the penetration profiles for the test formulation and the RLD was essentially identical. Total absorption through the skin accounted for only 1.3%-1.8% of the applied dose. The vast majority of the dose remained on the surface of the skin with 3.0%-3.8% found in the epidermis.

This study was not submitted as part of ANDA No. 200936 because it was not considered to be a bioequivalence or bioavailability study. It is provided as a part of this appeal (**Exhibit 9**) because it addresses OGD's stated concerns about the possible effect of formulation and viscosity differences. As shown in this study and in the clinical endpoint bioequivalence study conducted by TOLMAR, the differences in viscosity and formulation have no adverse effect on product performance, and performance of the test drug is similar in all respects to the RLD.

9 Cross SE. et al., *Can increasing the viscosity of formulations be used to reduce the human skin penetration of the sunscreen oxybenzone?* The Journal of Investigative Dermatology (2001); 117:147-150 (**Exhibit 8**).

10 EPA/600/R-07/040F. *Dermal Exposure Assessment: A Summary of EPA Approaches.* National Center for Environmental Assessment Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC (September 2007), at 5 (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=183584) (accessed September 7, 2011).

Table 1. Diclofenac Sodium Total Absorption Results across Donors

Test Article	Total Absorption (µg) (Reservoir*)	Total Absorption (%) (Reservoir*)
3% Diclofenac Sodium Gel (Lot # 1168-93A)	2.502 ± 0.281	1.668 ± 0.187
3% Diclofenac Sodium Gel (Lot # 1168-94A)	1.975 ± 0.473	1.316 ± 0.315
Solaraze Gel® (Diclofenac Sodium, 3% Lot HZ09)	2.722 ± 0.497	1.814 ± 0.331

*Amount of penetration through the skin into the dermal reservoir solution.

Reviewer's note:
The firm conducted an in vitro permeation study (#R08-0063) using **Human Cadaver Skin** model which is found acceptable by the reviewer[3]. The study was designed to compare the percutaneous absorption of diclofenac sodium from two different formulations of the test product (#1168-93A and #1168-94A) and one lot of the RLD (#HZ09) using a finite dose technique and Vertical (Franz) Diffusion cells. The dosing was done using a single application over 48 hours. From the firm's data, the test products and the RLD in the reservoir (i.e. equivalent to total absorption) account for 1.3% - 1.8% of the applied dose (4-7 mg/cm^2). The vast majority of the applied dose of the test and the RLD remained on the surface of the skin and was recovered in the surface wash. Out of the applied dose, 3.8% and 3.4% for the two test formulations and 3.1% for the RLD formulation was found in the **epidermis**, while 0.19 and 0.28% for the two test formulations and 0.29% for the RLD formulation was found in the **dermis**. The total accountability of the applied dose was about 106% - 111% of the applied dose (108% and 111.4% for the two test formulations and 106.0% for the RLD formulation).

The firm submitted another amendment dated 03/23/2012, containing additional information regarding the two test formulations used in the in vitro skin permeation study submitted as Exhibit-9 (dated 09/27/2011), that evaluates the percutaneous absorption of diclofenac sodium using the human cadaver skin model. The firm explained that the in vitro skin permeation study it provided was performed early in the development process when the two test formulations (lot #1168-93A and 1168-94A) were under concurrent evaluation, and therefore, used for comparison in the in vitro study. Only one test formulation (lot #1168-94A) is similar to the 'to be marketed product formulation' (ANDA formulation) (See Appendix 4.4 Formulation Data for details).

[3] Hasler-Nguyen, Nathalie. et al., Evaluation of the in vitro skin permeation of antiviral drugs from penciclovir 1% cream and acyclovir 5% cream used to treat herpes simplex virus infection. BMC Dermatology (2009); 9: 3, 1-10

Reviewer's Comments:

- The firm's use of human cadaver skin and the skin integrity validation study is acceptable.

- The finite dose technique used for the in vitro permeation study is acceptable.

- The number of replicates of skin used by the firm for the in vitro permeation study (n=3) is too few for meaningful comparison. The firm should repeat the study using at least 6 replicates, and the skin samples should preferably be obtained from the same region of the body of all donors (at least 6 donors in total).

- The firm did not submit all its pre-study bioanalytical method validation, including 20% chromatograms.

- The firm did not include a detailed explanation on how the skin was separated; and did not account for the Stratum Corneum (SC), if it was tape stripped or was a part of the epidermis. The firm should use and submit a validated method to account for variability and reproducibility.

- The firm did not provide details on the method of extraction and recovery of the drug from the skin samples.

3.6 Waiver Request(s)

Strengths for which waivers are requested	3%
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	No
If not then why?	The test product is not qualitatively and quantitatively (Q1/Q2) similar to that of the RLD. The firm needs to conduct an in vitro skin permeation study to show that differences in inactive ingredients between the test and reference formulation will not adversely impact the efficacy of the test formulation.

3.7 Deficiency Comments

1. Human cadaver skin sample used by the firm to conduct in vitro permeation study is acceptable. However, the number of replicates used by the firm for the in vitro permeation study (n=3) is too few for a meaningful comparison. The firm should repeat the study using at least 6 replicates, and the skin samples should preferably be obtained from the same region of the body of all donors (at least 6 donors in total).

2. The firm should validate the integrity of the human cadaver skin samples to be used for the in vitro permeation bioequivalence study to ensure that there are no areas of unusual permeability in the cadaver skin samples.

3. The firm should conduct the study using one lot each of its 'to be marketed' test product (ANDA formulation) and reference product.

4. The firm should repeat the in vitro permeation study, which consists of Distribution Release-rate study and Mass-balance study, comparing its test product with the RLD. In order to support a finding of pharmaceutical equivalence between the test and reference product, the following comments are provided for future in vitro permeation studies:

    a. Appropriately validated specific and sensitive analytical procedure should be used to analyze the samples and to determine the drug concentration and the amount of drug release.

    b. For the Distribution Release-rate study, 5 or more time-points (at least 6 replicates per time-point) over an appropriate time period should be used per lot of test product and RLD. Mass-balance would be determined from the drug accumulation in the different skin layers (e.g. **stratum corneum, epidermis, dermis**). The Mass-balance study may be conducted at an appropriate time-point, using at least 6 replicates per lot of test product and RLD.

    c. The DB II also recommends randomization, using appropriate software, of the test product and the RLD in each run of the experiment. This approach of including both products in each run of the *in vitro* apparatus will help ensure an unbiased comparison in the event of a systematic difference between runs. The firm should follow the *Guidance for Industry: Nonsterile Semisolid Dosage Forms*; *Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation (SUPAC-SS)*[4] for the study design, as well as setup and operation of the Vertical (Franz) Diffusion Cell.

    d. The firm should provide full details of the method of extraction and recovery of the drug from the different layers of the skin samples, and how the skin was separated into different layers (e.g. stratum corneum, epidermis, dermis).

[4] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070930.pdf

e. The firm should submit all its pre-study bioanalytical method validation (including reproducibility, evaluation of sink conditions, skin binding), and 20% of the chromatograms.

f. The firm should submit Distribution Release-rate study data, and Mass-balance study data electronically as SAS (.xpt) data file(s). Data should be analyzed statistically using the approach outlined in the SUPAC-SS guidance referred in comment 4c above.

g. The final report of the study should include lot numbers, date of manufacture, expiration date, and batch size of the test product and RLD, as applicable.

3.8 Recommendations

1. The Division of Bioequivalence II does not agree that the information submitted by Tolmar Inc. demonstrates that Diclofenac Sodium Topical Gel, 3% (w/w), meets the requirements specified under Section 21 CFR § 320.22 (b) (3). The DB II does not grant the waiver of in vivo bioequivalence testing requirements for the test product at this time.

3.9 Comments for Other OGD Disciplines

Discipline	Comment
All	None

4 APPENDIX

4.1 Product Information

Product	Test	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Treatment ID	Actinic Keratosis	Actinic Keratosis	Actinic Keratosis	Actinic Keratosis	Actinic Keratosis	Actinic Keratosis	Actinic Keratosis	Actinic Keratosis	Actinic Keratosis
Product Name	Diclofenac Sodium Gel, 0.3%	Solaraze® (diclofenac sodium) Gel, 0.3%	Solaraze® (diclofenac sodium) Gel, 0.3%	Solaraze® (diclofenac sodium) Gel, 0.3%	Solaraze® (diclofenac sodium) Gel, 0.3%	Solaraze® (diclofenac sodium) Gel, 0.3%	Solaraze® (diclofenac sodium) Gel, 0.3%	Solaraze® (diclofenac sodium) Gel, 0.3%	Solaraze® (diclofenac sodium) Gel, 0.3%
Manufacturer	TOLMAR	Nycomed	Nycomed	Nycomed	Nycomed	Nycomed	Nycomed	Nycomed	Nycomed
Batch/Lot No.	3241A	8064201	8346601	8346401	8205401	8205301	8205201	8205101	8346301
Manufacture Date	November 2008	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Expiration Date	N/A	February 2010	August 2010	August 2010	May 2010	May 2010	May 2010	May 2010	August 2010
Strength	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%
Dosage Form	Gel	Gel	Gel	Gel	Gel	Gel	Gel	Gel	Gel
Bio-batch Size	(b) (4)								
Production Batch Size									
Potency	100.0%	98.5%	99.3%	99.1%	99.1%	98.4%	98.5%	99.8%	99.6%
Content Uniformity (mean, %CV)	Mean = 101.5% %CV – 0.2%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Dose Administered	Gel applied to designated area(s) twice daily for 84 days.	Gel applied to designated area(s) twice daily for 84 days.	Gel applied to designated area(s) twice daily for 84 days.	Gel applied to designated area(s) twice daily for 84 days.	Gel applied to designated area(s) twice daily for 84 days.	Gel applied to designated area(s) twice daily for 84 days.	Gel applied to designated area(s) twice daily for 84 days.	Gel applied to designated area(s) twice daily for 84 days.	Gel applied to designated area(s) twice daily for 84 days.
Route of Administration	Topical	Topical	Topical	Topical	Topical	Topical	Topical	Topical	Topical

4.2 Donor Demographics

Donor ID	Age	Race	Sex	Integrity Test Result*
(b) (6)	64	Caucasian	Female	0.34 ± 0.11
	73	Caucasian	Male	0.36 ± 0.12
	52	Caucasian	Male	0.33 ± 0.06

*Results are reported as µL-equ $^3H_20$; Acceptance ≤ 1.56 µl-equ/cm^2

4.3 Test and Reference Formulations Evaluated

Formulation Identity	Lot Number
Diclofenac Socium Gel 3%	1168-93A
Diclofenac Socium Gel 3%	1168-94A
Solaraze Gel® (Diclofenac Sodium, 3%)	HZ09

4.4 Formulation Data

The firm submitted an amendment dated 03/23/2012, containing additional information regarding the two test formulations used in the in vitro skin permeation study submitted as Exhibit-9 (dated 09/27/2011), that evaluates the percutaneous absorption of diclofenac sodium using the human cadaver skin model. The firm explained that the in vitro skin permeation study it provided was performed early in the development process when the two test formulations (lot #1168-93A and 1168-94A) were under concurrent evaluation, and therefore, used for comparison in the in vitro study. Only one test formulation (lot #1168-94A) is similar to the 'to be marketed' product formulation (ANDA formulation). The test formulation compositions compared to the ANDA formulation are presented in Table 3 below:

Table 1

Ingredient	% w/w	Amount (mg) / 1g Gel
Diclofenac Sodium, USP	3.0	30
Methoxypolyethylene Glycol 350	(b) (4)	
PEG-60 Hydrogenated Castor Oil, NF		
Benzyl Alcohol, NF		
Hydroxyethyl Cellulose, NF		
Purified Water, USP		
Total	**100.0%**	(b) (4)

a Approximate concentration

Table 2

Soloraze® (diclofenac sodium) Gel, 3% Inactive Ingredients[a]	TOLMAR Inc.'s Inactive Ingredients	Safety Criteria
Polyethylene Glycol Monomethyl Ether	Methoxypolyethylene Glycol 350, NF	Present in RLD and USP/NF Ingredient
Hyaluronate Sodium	---	Not present in TOLMAR's product
Benzyl Alcohol	Benzyl Alcohol, NF	Present in RLD and USP/NF Ingredient
---	PEG-60 Hydrogenated Castor Oil	Not present in RLD; not USP/NF Ingredient. (b) (4)
---	Hydroxyethyl Cellulose, NF	Not present in RLD; USP/NF Ingredient. (b) (4) (b) (4)
Purified Water	Purified Water, USP	Present in RLD and USP/NF Ingredient

[a] Soloraze® inactive ingredient disclosure is obtained from the current package insert labeling. Refer to 1.14.3.2 Approved Labeling Text for Listed Drug for a copy of the RLD insert.

Table 3

Table 2.2-1: Report R08-0063 Formulations Compared to TOLMAR ANDA Formulation (% w/w)

	Diclofenac Sodium Gel, 3% ANDA Formulation	Formulation 1168-93A	Formulation 1168-94A
Diclofenac Sodium, USP	3.0%	3.0%	3.0%
Methoxypolyethylene Glycol 350, NF*			(b) (4)
Benzyl Alcohol, NF			
PEG-60 Hydrogenated Castor Oil			
Ethanol			
Hydroxyethyl Cellulose, NF			
Purified Water, USP			

(b) (4)

Table 4 Formulation Comparison between Test Product and RLD

Tolmar Inc.'s formulation			RLD's formulation	
Ingredient	Function	Amount % w/w	Ingredient	% (w/w)
Diclofenac Sodium, USP	Active Pharmaceutical Ingredient	3.0	Diclofenac Sodium	3.0
--	--	--	Hyaluronate Sodium	(b) (4)
Methoxypolyethylene Glycol 350, NF	(b) (4)		Polyethylene Glycol Monomethyl Ether	

Tolmar Inc.'s formulation			RLD's formulation	
Ingredient	Function	Amount % w/w	Ingredient	% (w/w)
PEG-60 Hydrogenated Castor Oil, NF	(b) (4)		--	(b) (4)
Benzyl Alcohol, NF			Benzyl Alcohol	
Hydroxyethyl Cellulose, NF			--	
Purified Water, USP			Purified Water	

Source: ANDA 200936 Section 2.7 Clinical Summary, Summary_Bioequivalence_Tables, Table 6 and Section 3.2.P.1 for Tolmar Inc.'s formulation; ANDA 200936 Section 3.2.P.2.1.2 and Approved Labeling for RLD's formulation; RLD=Reference Listed Drug

(b) (4)

Table 5

Ingredient	Grade	Function	IIG Limit[a] (%)	% w/w
Diclofenac Sodium	USP	Active	NA	3.0
Methoxypolyethylene Glycol 350	NF			(b) (4)
Benzyl Alcohol	NF			
PEG-60 Hydrogenated Castor Oil	NA			
Hydroxyethyl Cellulose	NF			
Purified Water	USP			

(b) (4)

Reviewer's Comments:

- The major difference between Tolmar Inc.'s test product and the RLD is that the firm's test product does not contain hyaluronate sodium, [redacted] (b) (4) excipient, and instead contains hydroxyethyl cellulose as [redacted] (b) (4) along with PEG-60 hydrogenated castor oil.

- The viscosity of the firm's drug product [redacted] (b) (4) compared to that of the RLD ([redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4) (DARRTS ANDA 200936 REV-CLINICAL-03 (General Review 07/10/2011). However, from a regulatory stand-point, viscosity of the test product formulation does not need to match that of the RLD formulation.

Table 1: Mean Flux (μg/cm²/hr) Results: Across Donor Summary

Percutaneous Absorption of Diclofenac Sodium through Human Cadaver Skin over 48 hours from a Single Application (Mean ± SE, n=3 Donors).

Time (hr)*	3% Diclofenac Sodium Gel (Lot # 1168-93A)	3% Diclofenac Sodium Gel (Lot # 1168-94A)	Solaraze Gel® (Diclofenac Sodium, 3% Lot HZ09)
1	0.004 ± 0.004	0.022 ± 0.006	0.036 ± 0.025
3	0.017 ± 0.006	0.016 ± 0.009	0.029 ± 0.007
6	0.029 ± 0.008	0.035 ± 0.007	0.046 ± 0.005
10	0.047 ± 0.002	0.040 ± 0.008	0.051 ± 0.005
18	0.053 ± 0.004	0.037 ± 0.010	0.049 ± 0.007
28	0.065 ± 0.007	0.059 ± 0.017	0.070 ± 0.013
40	0.063 ± 0.009	0.044 ± 0.009	0.066 ± 0.015

* Time as midpoint between samples.

Figure 1: Percutaneous Absorption Flux Profile of Diclofenac Sodium:

(Mean from 3 Donors as µg/cm²/hr)

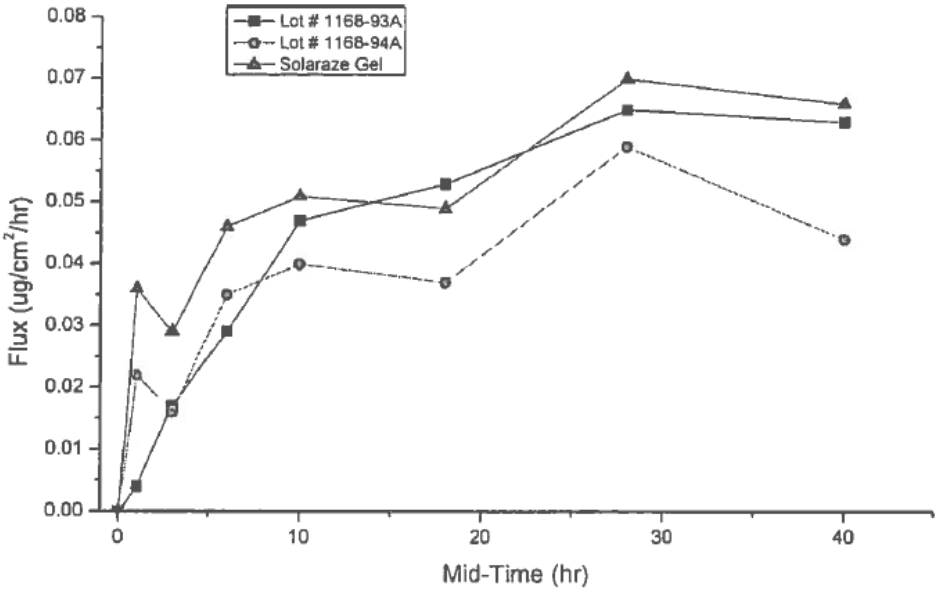
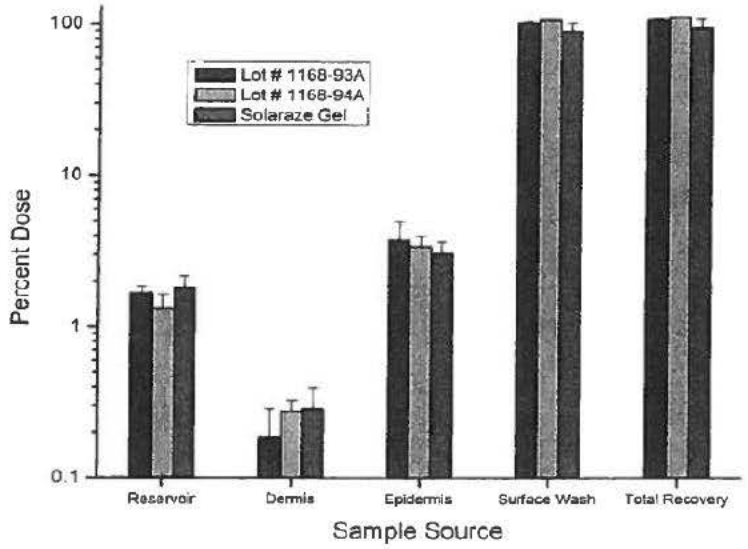


Table 2: Total Absorption and Mass Balance Results Across Skin Donors: Arithmetic Mean

Percutaneous Absorption and Penetration of Diclofenac sodium into and through Intact Human Cadaver Skin over 48 hours from a Single Application. Mean ± SE as Percent of Applied Dose and Total Mass (µg/cm²).

Parameter	3% Diclofenac Sodium Gel (Lot # 1168-93A)	3% Diclofenac Sodium Gel (Lot # 1168-94A)	Solaraze Gel® (Diclofenac Sodium, 3% Lot HZ09)
Total Absorption (µg/cm²)	2.502 ± 0.281	1.975 ± 0.473	2.722 ± 0.497
Dermis (µg/cm²)	0.278 ± 0.152	0.414 ± 0.072	0.430 ± 0.162
Epidermis (µg/cm²)	5.634 ± 1.835	5.118 ± 0.918	4.611 ± 0.902
Surface Wash (µg/cm²)	153.515 ± 3.217	159.532 ± 2.487	151.279 ± 2.881
Total Absorption (%)	1.668 ± 0.187	1.316 ± 0.315	1.814 ± 0.331
Dermis (%)	0.185 ± 0.101	0.276 ± 0.048	0.287 ± 0.108
Epidermis (%)	3.756 ± 1.223	3.412 ± 0.612	3.074 ± 0.601
Surface Wash (%)	102.344 ± 2.145	106.355 ± 1.658	100.852 ± 1.920
Total Recovery (%)	107.953 ± 0.988	111.359 ± 0.987	106.027 ± 2.739

Figure 2: Total Absorption and Mass Balance Results: Across Skin Donors
Percutaneous Absorption of Diclofenac sodium through Intact Human Cadaver Skin over 48 hours from a Single Application. Mean ± SE as Percent of Applied Dose.



Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	N/A

4.5 Detailed Regulatory History (If Applicable)

None

4.6 Consult Reviews

(10/1/09)

Memorandum

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

DATE: September 23, 2009

FROM: CAPT E. Dennis Bashaw, Pharm.D.
Director, Division of Clinical Pharmacology-3
Center for Drug Evaluation and Research, FDA

TO: Susan Walker, M.D., Director
Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research, FDA

SUBJECT: Consult Request for Topical Diclofenac Bioequivalence Guidance (Dated 8/31/09)

Background

The Office of Generic Drugs (OGD) is preparing to post individual product bioequivalence recommendations on the FDA Guidance for Industry Webpage for generic versions of diclofenac sodium gel, 3% (reference listed drug, Solaraze® Gel, 3%). The draft guidance document has been forwarded to the DDDP for consideration of the trial design to be utilized. As part of the review by DDDP the Office of Clinical Pharmacology was asked to weigh in on the use of or the need for in vivo pharmacokinetics as a component of a generic approval standard for topical diclofenac.

Solaraze® (diclofenac sodium) Gel is indicated for the topical treatment of actinic keratoses (AK). It is formulated as 3%w/w gel

Diclofenac Sodium	3%*
Benzyl Alcohol	(b) (4)
Polyethylene glycol monomethyl ether 350	
Sodium hyaluronate	
Purified Water	

*All % are w/w

The label contains the following usage instructions:

Solaraze™ Gel is applied to lesion areas twice daily. It is to be smoothed onto the affected skin gently. The amount needed depends upon the size of the lesion site. Assure that enough Solaraze™ Gel is applied to adequately cover each lesion. Normally 0.5 g of gel is used on each 5 cm x 5 cm lesion site. The recommended duration of therapy is from 60 days to 90 days. Complete healing of the lesion(s) or optimal therapeutic effect may not be evident for up to 30 days following cessation of therapy. Lesions that do not respond to therapy should be carefully re-evaluated and management reconsidered.

Summary of the NDA Data for Solaraze®

The PK portion of the original NDA was reviewed by Dr. Veneeta Tandon. In her review, she discussed the in vivo pk results of one pivotal pharmacokinetic study (EPI05) in subjects with compromised skin (ie., defined as subjects with inflammatory skin lesions a/k/a actinic keratosis), where the levels of serum diclofenac have been compared to in a cross-over fashion to an equivalent area of intact skin following seven days of use. In addition there is one supportive trial in healthy volunteers (BP329), where 3% diclofenac topical gel has been compared to orally administered Voltaren® Tablets (diclofenac sodium extended release 75mg). Finally the applicant has also conducted a retrospective analysis where serum levels of diclofenac within 24 hours after cessation of treatment have been evaluated from three well controlled clinical trials to study accumulation of diclofenac following chronic use. A final study using 1% diclofenac gel in healthy subjects was also submitted, but as it is was in healthy subjects, and used a lower strengths gel than that proposed (and marketed), it was adjudged to be of little regulatory use and was not reviewed.

SOLARAZE™ NDA 21-005

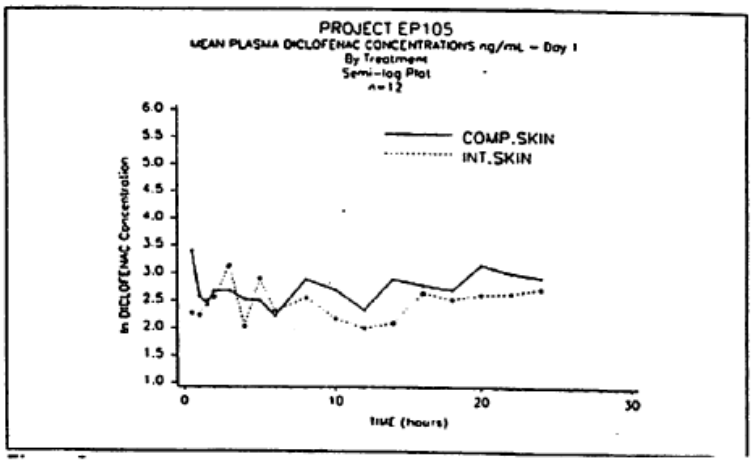
EP105

NDA: 21-005 **Volume 40**
Study Type*:** **Multiple dose Bioavailability** ***Study # EP105
***Study Title*:** **Pharmacokinetic study of Hyal topical 3% diclofenac-2.5%hyaluron gel in volunteers with compromised skin**

As noted earlier, this was a two-way cross over study with subjects with AK. They applied topical diclofenac gel 3% to diseased or "compromised" skin for one week and then following a washout period, applied a similar amount to "intact" skin for another week. PK samples were determined on day 1 and 7 of each period. It should be noted that in this study the dosing interval was not the approved interval of 12hrs but instead 6hrs. No explanation is provided in the review as to why this dosing regimen was used, but it is mentioned as such in the package insert. The data for both treatment periods are provided below:

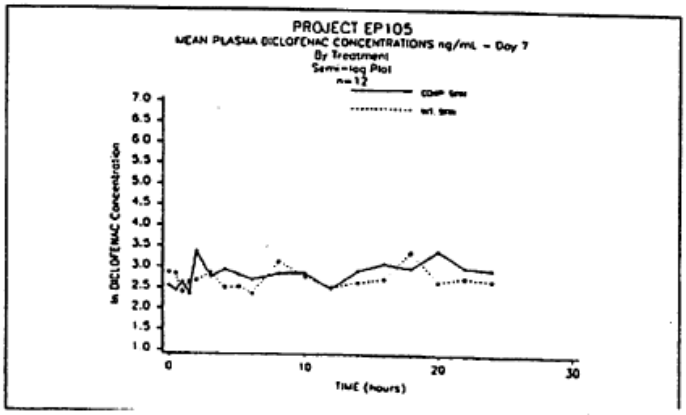
Please note that in the following figures for this study that have been extracted from the original review for NDA 21-005, the "y-axis scale" is a NATURAL log scale

DAY 1



Parameters	Comp Skin Mean(%CV)	Intact Skin Mean(%CV)	Ratio of Means	ANOVA p-value (treatment factor)
AUC0-t (ng.hr/ml)	396.33(105)	193.49(93)	2.05	0.1053 (NS)
Cmax0-6 (ng/ml)	24.51 (178)	10.53(142)	2.33	0.2173(NS)
Cmax (ng/ml)	49.40 (126)	23.02(65)	2.15	0.1501(NS)
Tmax0-6 (hrs)	2.89(62)	2.57 (66)	1.12	0.5698(NS)
Tmax (hrs)	16.40(43)	21.17 (12)	.77	0.0660 (NS)

Day 7



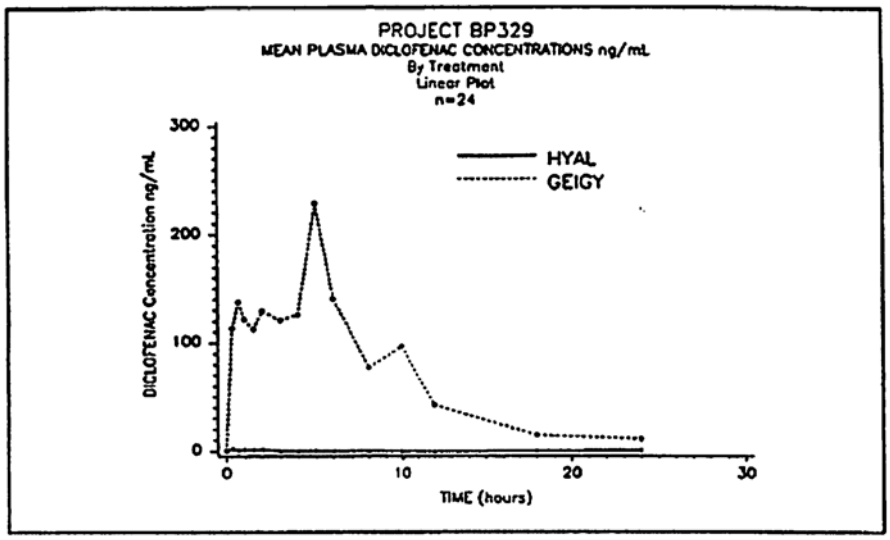
Parameters	Comp Skin Mean(%CV)	Intact Skin Mean(%CV)	Ratio of Means	ANOVA p-value (treatment factor)
AUC0-t (ng.hr/ml)	632.06(91)	468.18(83)	1.35	0.3621 (NS)
AUC0-∞ (ng.hr/ml)	1138.9(126)			
Cmax (ng/ml)	76.08(107)	57.59 (93)	1.32	0.3523 (NS)
Tmax (hrs)	12.67(56)	12.58 (57)	1.01	0.8311(NS)
Kel (1/hrs)	0.11(83)			
T1/2 (hrs)	11.21 (77)			

The results of this study show that topical diclofenac is absorbed and reaches systemic circulation in both normal and diseased skin. There does "appear" to be about a 30% increased absorption in diseased skin following 7 days of use, but the number of subjects (too few, N=12) and the variability in both AUC and Cmax (approaching 100%) were such that the differences were not statistically significant. Absorption does appear to very prolonged as Tmax is not achieved until approximately 12 hrs after dosing (approximately the time of the next dose) and the terminal elimination rate is also prolonged to ~11hrs (normally following oral dosing the t1/2 of diclofenac is on the order of 4hrs).

BP329

NDA/IND#: **21-005** **Volume 37**
Study Type: **Multiple dose Bioavailability** ***Study # BP329***
Study Title: ***Concentrations of Diclofenac in human plasma from a study comparing 3% topical gel and Voltaren (Geigy) 75 mg film coated tablets in healthy volunteers***

In this study 2 g diclofenac sodium 3% topical gel was applied to the calf of the leg t.i.d. for 5 days and one application on Day 6 for a total of 16 un-occluded applications. Each application contained approximately 60 mg diclofenac. The reference product was 75 mg slow release film coated tablets (Voltaren®, Geigy) once daily for 6 days for a total of 6 doses. Blood samples were taken pre-dose on Day 1 and 6 and at specific time points for 24 hours post dose on Day 6.



The results of this study showed that the gel formulation displayed little or no systemic absorption. Only 12 of the 23 subjects had detectable levels of plasma diclofenac. As can be seen in the table below, a very high variability was seen the plasma levels and the pharmacokinetic parameter derived thereof. Furthermore the fact that 11 subjects did not show any detectable plasma levels with the topical formulation would indicate that the

systemic bioavailability from the topical 3% formulation appears to be low, although highly variable.

Bioavailability Parameters	Hyal topical Mean (CV %)	Hyal topical Mean (CV %) Dose-adjusted	Geigy oral Mean (CV %)	Ratio of means	ANOVA** p-value
AUC0-t (ng.hr/ml)	9.09 (210)	11.37 (210)	1598.8 (26)	0.01	0.0001
AUCinf	-		1696.9 (27)		
AUC0-t/AUCinf	-		0.95 (6)		
Cmax (ng/ml)	4.49 (117)	5.61 (117)	316.05 (38)	0.01	0.0001
Tmax (hours)	4.50 (175)	4.50 (175)	4.72 (59)	0.95	0.6058
Kel (1/hours)	-		0.23 (48)		
T1/2 (hours	-		3.94 (61)		

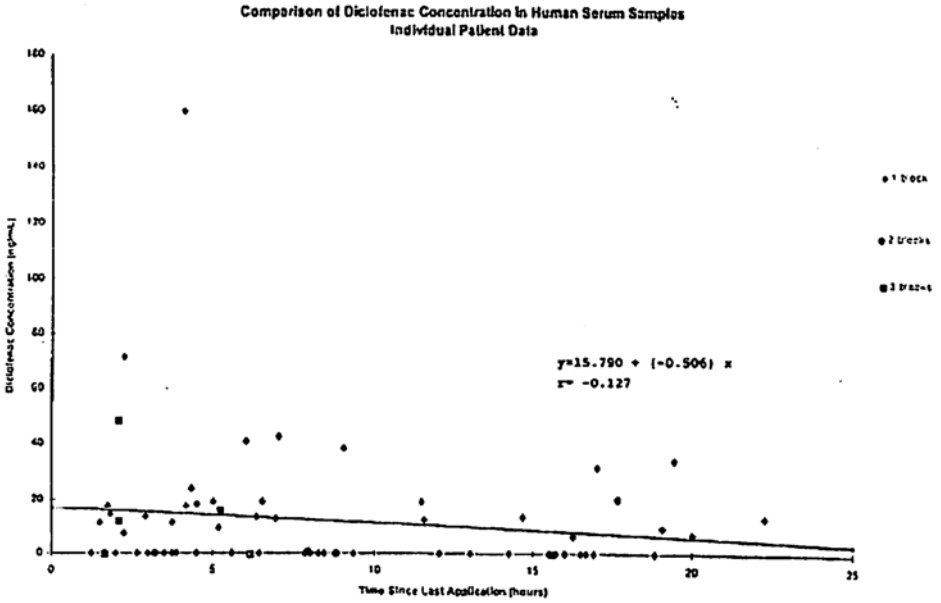
** ANOVA model has treatment.period.sequence and subject (sequence) as factors

RCT PK

As mentioned earlier, three adequate well controlled clinical trial (CT-1101-03, CT-1101-04 and CT-1101-07) were carried out across the US and Canada to evaluate the safety and efficacy of Solarase® in the topical treatment of Actinic keratoses (AK). Patients were eligible for these studies if they had at least five AK lesions in up to three 5x5 cm 'blocks of skin'. The dosing schedule was 0.5g of gel b.i.d. per treatment block on up to a maximum of three blocks. The intended duration of gel application was 30, 60 and 90 days respectively, for the above mentioned three studies.

Blood samples were drawn from the patients in these studies with the intention of assessing sensitization of patients to the active ingredient, diclofenac. Serum samples were collected from each patient at the Screening Visit and at the end of Treatment Visit and were labeled pre-PUT1 and pre-PUT3, respectively. PUT2 (a Provocative Use Test) was drawn if a dermal reaction occurred. Only a small sample was needed to perform the anti-diclofenac antibody testing, hence the applicant used the excess sample to analyze the diclofenac levels post treatment (PUT3 samples). Only those patients were assessed in this retrospective analysis whose time between application of their last dose and blood sampling was known. For this analysis those subjects were chosen in whom the time between the last treatment application and blood sampling was known to be less than 24 hours from the last dose.

There were 70 evaluable serum diclofenac levels from 60 patients (out of these, 6 patients had 2 samples and 2 patients has 3 samples each). Not all patients were treated with the same total dose, although the prescribed dose per unit area was constant. 2 patients were treated with two application blocks, 4 were treated on three application blocks. 64 samples represented a single application block.



Diclofenac levels were less than 20 ng/ml in 61 of the 70 samples, regardless of the time post dose. The overall mean serum diclofenac levels over the 24 hours post dose were 11.5 ng/ml and 17.1 ng/ml over the first 6 hours post dose. This can be contrasted indirectly to study BP329, where 75 mg slow release film coated tablet of Diclofenac (Voltaren®, Geigy) on multiple doses for 6 days gave a Cmax of 316.05 ng/ml at 4.72 hours post dose.

These results should be contrasted with the results from the previous study which included multiple dosing of the oral 75mg product. In that study peak plasma levels were in the 220ng/mL range or approximately 10x those seen with topical use in this study. Implying that dermal bioavailability is essentially very low and unlikely to be pharmacologically relevant in terms of systemic effects as contrasted to local dermal effects.

Discussion

What we have been asked to comment on in this consult is the viability or necessity of a requirement for an in vivo comparison of plasma levels using the two 1-sided t-test (90% confidence intervals) as part of a generic drug approval for topical diclofenac. This procedure is well documented in the FDA's "Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations"[1]. The underlying concept is that drug action (and toxicity) are due to or are related to systemic concentrations as measured in the blood. This concept is codified in the Code of Federal Regulations in 21 CFR 320.1:

[1] Currently there is not a companion document for topical drug products, however, in practice this guidance document properly characterizes the Office of Clinical Pharmacology's current thinking on bioequivalency testing methods.

(a)*Bioavailability* means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

The regulations go on to define the different approaches that can be used to support in vivo bioequivalence with a hierarchy of approaches from most to least sensitive (21CFR320.24)

(b) The following in vivo and in vitro approaches, in descending order of accuracy, sensitivity, and reproducibility, are acceptable for determining the bioavailability or bioequivalence of a drug product.

(1)(i) An in vivo test in humans in which the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time. This approach is particularly applicable to dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution within the body; or

(ii) An in vitro test that has been correlated with and is predictive of human in vivo bioavailability data; or

(2) An in vivo test in humans in which the urinary excretion of the active moiety, and, when appropriate, its active metabolite(s), are measured as a function of time. The intervals at which measurements are taken should ordinarily be as short as possible so that the measure of the rate of elimination is as accurate as possible. Depending on the nature of the drug product, this approach may be applicable to the category of dosage forms described in paragraph (b)(1)(i) of this section. This method is not appropriate where urinary excretion is not a significant mechanism of elimination.

(3) An in vivo test in humans in which an appropriate acute pharmacological effect of the active moiety, and, when appropriate, its active metabolite(s), are measured as a function of time if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility. This approach is applicable to the category of dosage forms described in paragraph (b)(1)(i) of this section only when appropriate methods are not available for measurement of the concentration of the moiety, and, when appropriate, its active metabolite(s), in biological fluids or excretory products but a method is available for the measurement of an appropriate acute pharmacological effect. This approach may be particularly applicable to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution.

(4) Well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence. This approach is the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence. For dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution, this approach may be considered acceptable only when analytical methods cannot be developed to permit use of one of the approaches outlined in paragraphs (b)(1)(i) and (b)(2) of this section, when the approaches described in paragraphs (b)(1)(ii), (b)(1)(iii), and (b)(3) of this section are not available. This approach may also be considered sufficiently accurate for measuring bioavailability or demonstrating bioequivalence of dosage forms intended to deliver the active moiety locally, e.g., topical preparations for the skin, eye, and mucous membranes;

oral dosage forms not intended to be absorbed, e.g., an antacid or radiopaque medium; and bronchodilators administered by inhalation if the onset and duration of pharmacological activity are defined.

(5) A currently available in vitro test acceptable to FDA (usually a dissolution rate test) that ensures human in vivo bioavailability.

(6) Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence.

In the case of a topically applied drug product, intended for the local treatment of a topical indication[2], blood levels are not correlated with clinical efficacy as the blood is not the site of action nor is it intimately linked with the site of action per se such that a concentration effect relationship exists. This feature of topical products is allowed for in item (4) above which allows for the use of clinical studies in lieu of in vivo pk studies:

> "*...This approach may also be considered sufficiently accurate for measuring bioavailability or demonstrating bioequivalence of dosage forms intended to deliver the active moiety locally, e.g., topical preparations for the skin..*"

In the case of Solaraze®, clearly there is systemic availability of diclofenac following topical use. The plasma levels are readily detectable, and show some accumulation with multiple dosing. Even so, the plasma levels are far inferior to those produced by oral diclofenac (eg., Voltaren®). The levels seen are, to our current understanding of diclofenac's mechanism of action, lacking in any pharmacologic significance in terms of efficacy. Topical diclofenac use has, however, been associated with systemic toxicity-but without a concentration effect relationship the value of in vivo plasma level equivalence requirements in preventing or managing this risk is speculative.

With regards to the general principle of requiring generics to demonstrate bioequivalence to the innovator product, it should be pointed out that the innovator has themselves never done such a study. Systemic availability for a topical product can be thought of, most simply, as being primarily related to the formulation, the physio-chemical properties of the drug itself, and the disease state. Of these three, quantifying the disease state is highly problematical. From the data seen in the Solaraze® NDA, the %CVs for AUC and Cmax run from 100-200%, to design an in vivo BE study to account for such variability would require an extreme number of subjects. As a further complication it would also need to be a parallel study as (assuming the formulations would have an affect on the lesions being treated) a cross-over design would not be feasible. To put it simply, it would require the generic manufacturer to do a study that the innovator has never attempted, with a very large sample size, with very little ability to assure comparability of disease between groups, with a primary endpoint (plasma levels) whose ability to assure therapeutic equivalence has never been conclusively demonstrated (as it would need to be on a case-by-case basis).

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[2] differing here from a transdermal system applied to the skin but designed to release drug into the systemic circulation for a pharmacologic effect

Thus, the requirement of demonstrating bioequivalence via in vivo pk studies would neither meet the standard of assessing bioavailability at the site of action nor would it help to inform the safety metric. The current draft OGD Guidance calls for:

> "…a bioequivalence study with a clinical endpoint in the treatment of actinic keratoses (AK) of the face and bald scalp comparing the diclofenac sodium 3% gel test product versus the reference listed drug (RLD) and placebo control, each administered as two applications per day (twice daily) for 60 days."

This is totally consistent with the provisions of 21 CFR 320 and better addresses the issue of "therapeutic equivalency" (which in fact is what we are trying to assure with the classical bioequivalency assessments used for systemic drug products) by allowing for a direct comparison of clinical efficacy and also local safety, something which a pharmacokinetic study cannot do in this situation.

It should be noted, however, that while this seemingly calls into question the use of the "maximal usage study" (MUST) as a method of assessment of in vivo bioavailability for NDAs, this is in fact not the case. In the NDA rubric of development, the usage of the data from a MUST trial is related to establishing a bridge both between the animal toxicity data and human exposure and also to allow for an understanding of systemic toxicity assessment when it occurs (in the case of topical corticosteroids, or retinoic acid). In the case of NDA drug development, the MUST design is clearly a safety related trial, focusing on the use of the drug in the maximal exposure setting.

Conclusion and Recommendation

While it is analytically feasible to detect in vivo plasma levels of diclofenac following topical application, the levels detected do not rise to the regulatory standard of assessing bioavailability at the site of action (as the blood is neither the site of action or intimately linked). Nor are the levels associated in a predictive fashion with toxicity such that they can be used to assure safety for the product. The proposed use of a bioequivalency study with clinical endpoints for the assessment of equivalency between topically applied generic and reference product is appropriate from a clinical pharmacology standpoint and supported by the regulations (see 21 CFR 320.24 (b)(4)).

4.7 Additional Attachments

None

4.7.1 DB II Review History

The DB II has received the following controlled correspondence documents and protocols for Diclofenac Sodium Topical Gel.

Controls:

Control No	Letter Date	Firm
02-592		(b) (4)
04-136		
04-944		
06-1336		
08-0338		
08-0687		
08-1031		
09-0065		
09-0255		
09-0324		
09-0389		
09-0464		
09-0644		
10-0469		
11-0157		
11-0393		

Protocols:

(b) (4)

ANDA (from DARRTS):

ANDA #	Firm	Current Status	Status Date
			(b) (4)
200936	Tolmar, Inc.	Complete response (current review)	7/11/2011
			(b) (4)

BIOEQUIVALENCE DEFICIENCES TO BE PROVIDED TO THE APPLICANT

ANDA: 200936

APPLICANT: Tolmar Inc.

DRUG PRODUCT: Diclofenac Sodium Topical Gel, 3%

The Division of Bioequivalence II (DB II) has completed its review and the following deficiencies have been identified.

1. Your proposal to use human cadaver skin is acceptable. However, please repeat the in vitro permeation bioequivalence study using at least 6 skin sample replicates. The skin samples should preferably be obtained from the same region of the body of all donors (at least 6 donors in total).

2. Please validate the integrity of the human cadaver skin samples to be used in the in vitro permeation bioequivalence study to ensure that there are no areas of unusual permeability in the cadaver skin samples.

3. Please conduct your study using one lot each of your 'to be marketed' test product (ANDA formulation) and reference product.

4. Please repeat the in vitro permeation study, which consists of Distribution Release-rate study and Mass-balance study, comparing your test product with the reference listed drug (RLD). In order to support a finding of pharmaceutical equivalence between the test and reference product, the following comments are provided for future in vitro permeation studies:

   a. Appropriately validated specific and sensitive analytical procedure should be used to analyze the samples and to determine the drug concentration and the amount of drug release.

   b. For the Distribution Release-rate study, 5 or more time-points (at least 6 replicates per time-point) over an appropriate time period should be used per lot of test product and RLD. Mass-balance would be determined from the drug accumulation in the different skin layers (e.g. **stratum corneum, epidermis, dermis**). The Mass-balance study may be conducted at an appropriate time-point,

using at least 6 replicates per lot of test product and RLD.

c. The DB II also recommends randomization, using appropriate software, of the test product and the RLD in each run of the experiment. This approach of including both products in each run of the in vitro apparatus will help ensure an unbiased comparison in the event of a systematic difference between runs. Please follow the *Guidance for Industry: Nonsterile Semisolid Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation (SUPAC-SS)* for the study design, as well as setup and operation of the Vertical (Franz) Diffusion Cell.

d. Please provide full details of the method of extraction and recovery of the drug from the different layers of the skin samples, and how the skin was separated into different layers (stratum corneum, epidermis, dermis).

e. Please submit all your pre-study bioanalytical method validation (including reproducibility, evaluation of sink conditions, skin binding), and 20% of the chromatograms.

f. Please submit Distribution Release-rate study data and Mass-balance study data electronically as SAS (.xpt) data file(s). Data should be analyzed statistically using the approach outlined in the *SUPAC-SS guidance* referred in comment 4c above.

g. The final report of the study should include lot numbers, date of manufacture, expiration date, and batch size of the test product and RLD, as applicable.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.8 Outcome Page

ANDA: 200936

Completed Assignment for 200936 ID: 16581

Reviewer: Aimiuwu, Josephine **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Diclofenac Sodium Topical Gel Waiver, 3% (w/w) from Tolmar Inc.

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
16581	12/14/2009	Other	Waiver Topical	1	1
16581	9/27/2011	Other	Study Amendment	1	1
16581	3/23/2012	Other	Study Amendment	1	1
				Bean Total:	3

DIVISION OF BIOEQUIVALENCE II REVIEW COMPLEXITY SUMMARY

ANDA: 200936

Topical Gel Waiver:

Waiver for Topical Gel	1
Topical Gel Waiver Total	*1*
Study Amendment	1
Study Amendment	1
Study Amendment Total	*2*
Total	***3***

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

/s/

Parthapratim CHANDAROY
04/18/2012

ETHAN M STIER on behalf of BARBARA M DAVIT
04/18/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200936

OTHER REVIEWS

M E M O R A N D U M

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

DATE: February 27, 2013

TO: John R. Peters, MD
Director, Division of Clinical Review
Office of Generic Drugs

FROM: Arindam Dasgupta, Ph.D.
Pharmacologist, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering ANDA 200-936, Diclofenac Sodium gel, 3%, sponsored by Tolmar Inc.

At the request of Division of Clinical Review (DCR), OGD, the Division of Bioequivalence and GLP Compliance (DBGLPC) audited the following multi-site clinical endpoint bioequivalence study:

Study Number: TOL-AK-2008-02
Study Title: "A Double-Blind, Randomized, Parallel-Group, Vehicle-Controlled, Multicenter Study to Evaluate the Safety and Bioequivalence of Diclofenac Sodium Gel, 3% (TOLMAR Inc.) and Solaraze™ (Diclofenac Sodium) Gel, 3% and both Active Treatments to a Vehicle Control in the Treatment of Actinic Keratosis"

DCR requested inspections for the following sites:

(Site #1): Sunil S. Dhawan, MD
Center for Dermatology Clinic Research
2557 Mowry Avenue, Suite 34
Freemont, CA 94538

(Site #2): Marina I. Peredo MD
260 Middle Country Road, Suite 208
Smithtown, NY 11787

(Site #3): Stephen Miller MD
8431 Fredericksburg Road, Suite 100
San Antonio, TX 78229

ORA staff conducted inspections at all three requested sites: Site #1: Sunil S. Dhawan, MD, conducted by ORA investigator Timothy C Grome, 8/10-8/23/2012; Site #2: Marina I. Peredo, MD, conducted by ORA investigator Robert C. Steyert 12/10-12/18/2012; and site #3: Stephen Miller, MD, conducted by ORA investigator Joel Martinez 10/02-10/10/2012. The inspections included a thorough examination of study records, facilities and equipment, and interviews and discussions with the firm's management and staff.

Forms FDA-483 were issued at sites #1 and #3 (Attachments 1, 2). There were no objectionable conditions observed at Site #2 and FDA-483 was not issued. The responses from site #2 and site #3 dated 8/30/2012 (Dr. Sunil Dhawan) and 10/29/2012 (Stephen Miller) were received by OSI on 02/19/2013 and 02/20/2013 respectively (Attachment 3 and 4). The Form FDA-483 observations for study TOL-AK-2008-02, the firm’s written responses, and our evaluations follow:

Clinical Site #1: Sunil S. Dhawan, MD, Center for Dermatology Clinic Research, Freemont, CA.

1) **An investigation was not conducted in accordance with the investigational plan. Specifically, for Protocol TOL-AK-2008-02**
   a. **Enrolling subjects with documented and possible exclusion criteria (Protocol section 5.2.2)**
      1. **(b) (6) enrolled on (b) (6): "Chart Notes" included as medical history records on (b) (6) "AKs upper extremity x 2, lower extremity x 2} tx c LN2: Exclusion #8 "Subjects who have been treated with the following in the past 60 days prior to study entry: ... cryodestruction ... "E-mail sent to Clinical Study site on (b) (6)**

"clarification on exclusion #8: It refers to treatment anywhere on the face scalp, back of the hands or forearms."

2. **(b) (6), enrolled on (b) (6): Medical History (b) (6) Peptic Ulcer onset (b) (6), Ongoing, concomitant medications include cimetidine: Exclusion #6 "Subjects with active gastrointestinal ulceration."**

Subjects (b) (6) and DST 4041 should have been excluded from the study if they met the exclusion criteria. Subject (b) (6) had a treatment for actinic keratosis with liquid nitrogen on upper and lower extremities (b) (6) before being enrolled into the study on (b) (6). There was no record to show that the treatment prior to study enrollment was outside the protocol designated treatment area.

Subject (b) (6) was treated with concomitant medication cimetidine during the study. Exclusion criterion #6 (exclusion of subjects with active gastrointestinal ulceration) for the protocol should have excluded this subject because the subject had a history of peptic ulcer since year (b) (6) and subjects medical history listed the treatment for peptic ulcer as ongoing.

In his response, Dr. Dhawan disagreed with the observation and stated that the treatment for subject (b) (6) prior to study enrollment was not in the protocol-designated treatment area. He also stated that subject (b) (6) did not have active gastrointestinal ulceration and was only taking cimetidine on PRN (as needed) basis. Dr. Dhawan, however, promised to review protocol inclusion/exclusion criteria carefully and to document reasons for including a subject if the subject had a possible exclusion criterion.

The OGD reviewer should evaluate whether the observations will impact the study results for subjects (b) (6) and (b) (6).

b) **Persons other than enrolled subjects wrote on subject diaries (Protocol section 8.6 Assessment of Compliance) The following subject diaries had cross-outs initialed and dated by study personnel RMA or CYE:**

   (b) (6)- days 1 to 28: 2 cross outs one for study day initialed by RMA dated (b) (6) (one week

after visit 3) and another for date initialed by RMA on (b) (6) (visit 2)
(b) (6) - Study Days card 1 to 28: date (b) (6) crossed and initialed by CYE (b) (6) (b) (6) - Study Days 16 to 28 Date box (b) (6) crossed out initialed RMA (b) (6) Cross out on Study Days RMA (b) (6) (3 days after visit 1).
(b) (6) Study Days 56 to 84 date cross out for (b) (6) initialed CYE dated (b) (6)
(b) (6) - 1 to 28 AM checked (b) (6) note difference in style between AM and PM checks for (b) (6). Study Days 28 to 56 check crossed out initialed CYE dated (b) (6) (day of visit 4)
(b) (6) - Study Days 1 to 28: 6 dates were corrected "error RMA (b) (6)"
(b) (6) - Study Days 1 to 28: 6 dates were corrected "error RMA (b) (6)"
(b) (6) - Study days 1 to 28: check for AM on (b) (6) was crossed out and initialed CYE (b) (6), the repeated date (b) (6) was crossed out and changed to (b) (6) initialed CYE (b) (6) There is a check for (b) (6) PM that is scratched out without an initial or date. This subject was hospitalized in the afternoon on (b) (6) and was discharged from the study.
(b) (6) - Study Days 1 to 28: date crossed out and initialed CYE (b) (6)

During the inspection, Investigator Grome noted several instances where entries of subject diaries were altered. Some of the altered entries were dated and initialed by the study coordinators and some changes were not dated and initialed.

In his response, Dr. Dhawan acknowledged the observation. He stated that the alterations were made by study coordinators after discussions with the subjects. He promised that for future studies, the subjects would sign and date any corrections.

This DBGLPC reviewer recommends that the above observations did not impact study outcome.

c) Did not remove subjects from study for significant protocol deviations (Protocol section 7.0) Protocol requires that the subject return study drug on visits #3, #4, and #5; subject is to bring diary for review on visits #2, #3, #4, and #5.

[redacted] (b) (6) enrolled [redacted] (b) (6), on Visit #3 ([redacted] (b) (6)) subject forgot to bring in tube #1 and on Visit #4 [redacted] (b) (6) forgot to bring tube #2. The subject did not bring the study medications tube #1 and tube #2 on later visits. Subject did not bring diary on Visits #4 [redacted] (b) (6), and on visit #5 [redacted] (b) (6). The dairies after [redacted] (b) (6) were never brought in for review. Study compliance was noted on CRF visits #4 and #5 without review of subject diary. This subject remained enrolled through to study termination.

Subject [redacted] (b) (6) did not return the diaries for review by study personnel. Further, the subject did not return study medications as required by the protocol in visits #3 and #4. The practice of documenting study compliance in the absence of study diaries and test article accountability is unacceptable. This reviewer recommends that subject [redacted] (b) (6) be excluded from the bioequivalence evaluation because compliance with the study protocol cannot be confirmed.

2) **Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to drug administration. Specifically, the informed consent for subject [redacted] (b) (6) was signed by the subject and the person explaining the consent to the subject (A non-physician study-coordinator) on [redacted] (b) (6) The Clinical Investigator signed this form on [redacted] (b) (6), two days later.**

In his response, Dr. Dhawan acknowledged that the investigator signed the informed consent two days after the subject consented, as he inadvertently had not signed on the same day.

In the opinion of this DBGLPC reviewer, the observation is not likely to affect the outcome of the study as this was an isolated incident and there is no evidence that safety of the subject was compromised.

3) **Failure to store retain samples in accordance with labeled storage conditions. Specifically, the retain samples for TOL-AK.-2008-02 are labeled to be stored at controlled room temperature (15°C-30°C). The retains were stored in a location without climate control or temperature recording equipment."**

In his response, Dr. Dhawan acknowledged the observation and stated that the reserve samples were stored at labeled conditions for three years after study completion, until they were moved to the external storage in July 2012. The study clinical research coordinator provided an affidavit to this effect to the ORA investigator during the inspection. At the time of collection, the reserve samples were stored at a location without climate control or temperature recording equipment, making it impossible to confirm the storage conditions. The uncontrolled storage was in Freemont, CA, where summer temperatures could have resulted in degradation of reserves, such as gel separation, and compromising their testing by DPA.

In this reviewer’s opinion, integrity of the reported data can be assured only by positive identification of test and reference products by DPA. DGBGLP has contacted DPA for the testing results and will forward results of DPA's testing to DB2 as soon as it is available.

Clinical Site #3: Stephen Miller, MD, San Antonio, TX.

1) **An investigation was not conducted in accordance with the investigational plan. Specifically: TOL-AK-2008-02, Section 8.4 Treatment Assignment states: "A sealed randomization code will be stored at the study center at the conclusion of the study." You failed to retain a sealed randomization code; as a result I am unable to verify the randomization of subjects at your clinical site.**

In his response, Dr. Miller acknowledged the observation and stated that a sealed copy of randomization was never provided to him by the sponsor. He promised that for future studies, he would contact the sponsor to resolve any issues to comply with the Agency's requirements.

In the absence of randomization codes or the original drug product labels preserved at the clinical site, there is no assurance that subjects received their assigned treatments during the study.

2) **Investigational drug disposition records are *not* adequate with respect to dates, quantity, and use by subjects. Specifically: Protocol TOL-AK-2008-02 Investigational Product records show your receipt of Kits 4826-4830. The Investigational Product Return**

form does not account for Kits 4826-4830 as being used or returned unused.

A Clinsys Clinical Research Note-To-File dated 3-15-10 documents "Study drug kits 4826-4830 were returned to (b) (4) however it cannot be determined if these kits were used or unused as it was not indicated on the site's paperwork and the drug has been destroyed."

In his response, Dr. Miller stated that the Study Kits 4826-4830 were not opened, used, or dispensed during the study and were returned. He provided partial drug product accountability records that listed kits received and dispensed at the site. The last kit to be dispensed was numbered 4825. He promised to maintain accountability records of all used and unused kits for future studies.

In absence of complete drug accountability records for the use or disposition of study drugs provided to the clinical site by the sponsor, it cannot be confirmed if the subjects received their assigned treatments during the study as required by the protocol. In the opinion of this DBGLPC reviewer, integrity of the reported data cannot be assured.

3) **Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation, specifically:**
   a. **The CD-ROM received after completion of the study under study protocol TOL-AK-2008-02 does not include the capability to view details of audit trails.**

In his response, Dr. Miller acknowledged the observation and stated that audit trail records for the study were held by the sponsor. He stated that he reviewed data entered for each subject in the EDC (electronic data capture) system when the source data were transcribed. He also indicated that the sponsor had complete audit trail information in their archived database.

As the source data was available to the ORA investigator to compare to the submitted data to the agency during the inspection, in the opinion of this DBGLPC reviewer, the observation is not likely to affect the outcome of the study.

b. **Protocol TOL-AK-2008-02, Protocol Section 5.3, Concomitant and Prohibited Medication, states in part:"*** the following are prohibited during the study***the use of any actinic keratosis treatment, other than study drug, within the designated treatment area. However, ***cryodestruction*** are allowed on the face or scalp outside the designated treatment area.*"'*." Subjects [redacted] (b) (6) received cryodestruction treatment during their participation in the study however source records do not document whether cryodestruction occurred outside the designated treatment area.**

In his response, Dr. Miller acknowledged the observation and stated that although he did not document the location of the cryodestruction treatment, the treatment was outside the protocol treated areas. He promised to include more details in the clinical charts for future studies.

In the opinion of this DBGLCP reviewer, the above observation is not likely to impact the quality and integrity of study data.

Conclusions:

- Following our evaluation of the inspectional findings, this reviewer recommends excluding data from site #3 (Dr. Stephen Miller) from the bioequivalence evaluation. As the blinding code was not maintained at the study site by Dr. Miller, the test and reference drug products used at site #3 cannot be positively identified. The quality and integrity of the study data from site# 3 cannot be assured as the site did not main adequate drug accountability records (FDA-483, Observations 2).

- The data from site #1 (Dr. Sunil Dhawan) may be accepted for further agency review only when authenticity of the test and reference products used in the study can be positively identified by Division of Pharmaceutical Analysis (DPA) (FDA-483, Observation 3). The data from subject [redacted] (b) (6) are not reliable and should be excluded from the bioequivalence evaluation due to non-conformance with the protocol (FDA-483, Observations 1-c). The OGD reviewer should evaluate if the observations 1-a-1 and 1-a-2 have impact on the results of the study for subjects [redacted] (b) (6) .

- Data from site #2 (Dr. Marina Peredo) can be accepted for further agency review.

Arindam Dasgupta, Ph.D.

Final Classifications:

VAI – Sunil Dhawan, MD, Freemont, California (FEI:3008289735
NAI - Marina I. Peredo, MD, Smithtown, NY (FEI:3009936416)
OAI - Stephen Miller, MD, San Antonio, TX (FEI:3009787008)

cc:
CDER DSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Skelly/Dejernett/Dasgupta/CF
CDER/OPS/OGD/Nitin Patel
CDER/OPS/OGD/DCR/Peters
ORA/NE-FO/NYK-DO/NYK-DIB/LOIS-NY/Steyert
ORA/PA-FO/SAN-DO/SAN-IB/SANJO-CA/Grome
ORA/SW-FO/DAL-DO/DAL-IB/SAN-TX/Martinez
Draft: AD 02/19/2013,
Edit: MFS 2/27/13;SHH 3/01/2013
DSI: BE 6296; O:\Bioequiv\EIRCover\200936.tol.dic.doc
FACTS: 1425444

Attachment 1

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
1431 Harbor Bay Parkway Alameda, CA 94502-7070 (510) 337-6700 Fax:(510) 337-6702 Industry Information: www.fda.gov/oc/industry	08/10/2012 - 08/23/2012* FEI NUMBER 3008289735

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Sunil S. Dhawan, Principle Investigator

FIRM NAME	STREET ADDRESS
Sunil Dhawan, MD	2557 Mowry Ave. Suite 34 East Bay Dematology Medical Group, Inc.
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Fremont, CA 94538	Clinical Investigation Site

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

OBSERVATION 1

An investigation was not conducted in accordance with the investigational plan.

Specifically, for Protocol TOL-AK-2008-02

1. Enrolling subjects with documented and possible exclusion criteria (Protocol section 5.2.2)

(b) (6) enrolled on (b) (6)

"Chart Notes" included as medical history records on 2-2-09 "AKs upper extremity x 2, lower extremity x 2} tx c LN2: Exclusion #8 "Subjects who have been treated with the following in the past 60 days prior to study entry: ...cryodestruction..." E-mail sent to Clinical Study site on (b) (6) "clarification on exclusion #8: It refers to to treatment anywhere on the face scalp, back of the hands or forearms."

(b) (6), enrolled on (b) (6):

Medical History (b) (6) Peptic Ulcer onset (b) (6), Ongoing, concominant medications include cimetidine: Exclusion #6 "Subjects with active gastrointestinal ulceration..."

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Timothy C. Grome, Investigator	DATE ISSUED 08/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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1431 Harbor Bay Parkway Alameda, CA 94502-7070 (510) 337-6700 Fax:(510) 337-6702 Industry Information: www.fda.gov/oc/industry	08/10/2012 - 08/23/2012* FEI NUMBER 3008289735

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Sunil S. Dhawan, Principle Investigator

FIRM NAME	STREET ADDRESS
Sunil Dhawan, MD	2557 Mowry Ave. Suite 34 East Bay Dematology Medical Group, Inc.
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Fremont, CA 94538	Clinical Investigation Site

2. Persons other than enrolled subjects wrote on subject diaries (Protocol section 8.6 Assessment of Compliance)

The following subject diaries had cross-outs initialed and dated by study personnel RMA or CYE:

(b) (6) - days 1 to 28: 2 cross outs one for study day initialed by RMA dated (b) (6) (one week after visit 3) and another for date initialed by RMA on (b) (6) visit 2)

(b) (6) - Study Days card 1 to 28: date (b) (6) crossed and initialed by CYE (b) (6) (b) (6) Study Days 16 to 28 Date box (b) (6) crossed out initialed RMA (b) (6) Cross out on Study Days RMA (b) (6) (3 days after visit 1).

(b) (6) Study Days 56 to 84 date cross out for (b) (6) initialed CYE dated (b) (6)

(b) (6) - 1 to 28 AM checked (b) (6) note difference in style between AM and PM checks for (b) (6) Study Days 28 to 56 check crossed out initialed CYE dated (b) (6) (day of visit 4)

(b) (6) - Study Days 1 to 28: 6 dates were corrected "error RMA (b) (6)

(b) (6) - Study Days 1 to 28: 6 dates were corrected "error RMA (b) (6)

(b) (6) - Study days 1 to 28: check for AM on (b) (6) was crossed out and initialed CYE (b) (6) the repeated date (b) (6) was crossed out and changed to (b) (6) initialed CYE (b) (6) There is a check for (b) (6) PM that is scratched out without an initial or date. This subject was hospitalized in the afternoon on (b) (6) and was discharged from the study.

(b) (6) - Study Days 1 to 28: date crossed out and initialed CYE (b) (6)

3. Did not remove subjects from study for significant protocol deviations (Protocol section 7.0) Protocol requires that the subject return study drug on visits #3, #4, and #5; subject is to bring diary for review on visits #2, #3, #4, and #5.

(b) (6) enrolled (b) (6) on Visit #3 (b) (6) subject forgot to bring in tube #1 and on Visit #4 (b) (6) forgot to bring tube #2. The subject did not bring the study medications tube #1 and tube #2 on later visits. Subject did not bring diary on Visits #4 (b) (6), and on visit #5 (b) (6) The dairies after (b) (6) were never brought in for review. Study compliance was noted on CRF visits #4 and #5 without review of subject diary. This subject remained enrolled through to study termination.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Timothy C. Grome, Investigator	DATE ISSUED 08/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
1431 Harbor Bay Parkway Alameda, CA 94502-7070 (510) 337-6700 Fax:(510) 337-6702 Industry Information: www.fda.gov/oc/industry	08/10/2012 - 08/23/2012* FEI NUMBER 3008289735

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Sunil S. Dhawan, Principle Investigator

FIRM NAME	STREET ADDRESS
Sunil Dhawan, MD	2557 Mowry Ave. Suite 34 East Bay Dematology Medical Group, Inc.
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Fremont, CA 94538	Clinical Investigation Site

OBSERVATION 2

Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to drug administration .

Specifically, the informed consent for subject [redacted] (b) (6) was signed by the subject and the person explaining the consent to the subject (A non-physician study-coordinator) on [redacted] (b) (6) The Clinical Investigator signed thsi form on [redacted] (b) (6) two days later.

OBSERVATION 3

Failure to store retain samples in accordance with labeled storage conditions.

Specifically, the retain sample for TOL-AK-2008-02 are labeled to store at controlled room temperature (15°c-30°c) The retains were stored in a location without climate control or temperature recording equipment.

*** DATES OF INSPECTION:**
08/10/2012(Fri), 08/13/2012(Mon), 08/14/2012(Tue), 08/15/2012(Wed), 08/17/2012(Fri), 08/23/2012(Thu)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Timothy C. Grome, Investigator	DATE ISSUED 08/23/2012

Attachment 2

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
4040 North Central Expressway, Suite 300 Dallas, TX 75204 (214) 253-5200 Fax:(214) 253-5314 Industry Information: www.fda.gov/oc/industry	10/02/2012 - 10/10/2012*
	FEI NUMBER 3009787008

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Stephen Miller, M.D., Principal Investigator

FIRM NAME	STREET ADDRESS
Stephen Miller, M.D.	16110 Via Shavano
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
San Antonio, TX 78249	Clinical Investigator

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

OBSERVATION 1

An investigation was not conducted in accordance with the investigational plan.

Specifically,

TOL-AK-2008-02, Section 8.4, Treatment Assignment, states: "A sealed randomization code will be stored at the study center at the conclusion of the study." You failed to retain a sealed randiomization code, as a result, I am unable to veify the randomization of subjects at your clinical site.

OBSERVATION 2

Investigational drug disposition records are not adequate with respect to dates, quantity, and use by subjects.

Specifically,

Protocol TOL-AK-2008-02 Investigational Product records show your receipt of Kits 4826- 4830. The Investigational Product Return form does not account for Kits 4826- 4830 as being used or returned unused.

A Clinsys Clinical Research Not-To-File dated 3-15-10 documents "Study drug kits 4826- 4830 were returned to (b) (4) however, it can not be determined if these kits were used or unused as it was not indicated on the site's paperwork and the drug has been destroyed."

OBSERVATION 3

Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

Specifically,

a The CD-ROM received after completion of the study under study protocol TOL-AK-2008-02 does not include the capability to view details of audit trails.

b Protocol TOL-AK-2008-02, Protocol Section 5.3, Concomitant and Prohibited Medication, states in part:

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Joel Martinez, Investigator	10/10/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
4040 North Central Expressway, Suite 300 Dallas, TX 75204 (214) 253-5200 Fax:(214) 253-5314 Industry Information: www.fda.gov/oc/industry	10/02/2012 - 10/10/2012* FEI NUMBER 3009787008

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Stephen Miller, M.D., Principal Investigator

FIRM NAME	STREET ADDRESS
Stephen Miller, M.D.	16110 Via Shavano
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
San Antonio, TX 78249	Clinical Investigator

"*** the following are prohibited during the study *** The use of any actinic keratosis treatment, other than study drug, within the designated treatment area. However, *** cryodestruction *** are allowed on the face or scalp outside the designated treatment area. ***."

Subjects [redacted] (b) (6) received cryodestruction treatment during their participation in the study; however, source records do not document whether the cryodestruction occurred outside the designated treatment area.

*** DATES OF INSPECTION:**
10/02/2012(Tue), 10/03/2012(Wed), 10/04/2012(Thu), 10/10/2012(Wed)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Joel Martinez, Investigator	10/10/2012

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

/s/

ARINDAM DASGUPTA
03/03/2013

SAM H HAIDAR
03/03/2013

WILLIAM H TAYLOR
03/04/2013

MEMORANDUM
Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: December 15, 2011

TO: Sam H. Haidar, PhD
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
WO51, HFD-45

THROUGH: John R. Peters, MD
Acting Director, Division of Clinical Review
Office of Generic Drugs
MPNI, HFD-600

FROM: Nitin K. Patel, PharmD
Medical Affairs Coordinator, Division of Clinical Review
Office of Generic Drugs
MPNI, HFD-600
240-276-8887

SUBJECT: Compliance Program 7348.001 – In Vivo Bioequivalence

REQUEST FOR INSPECTION

REFERENCES:

ANDA#	200936
Product	Diclofenac Sodium Gel, 3%
Sponsor: full address	TOLMAR Inc. 701 Centre Avenue Fort Collins, CO 80526
Sponsor Contact Phone Fax	Michelle R. Ryder Director, Regulatory Affairs (970) 212-4901 (970) 212-4950
Submission Date	December 14, 2009

PRIORITY: **C**

A (highest) = ready for approval in the office
B = ready for approval, clinical study under review
C = pending clinical review

DUE DATE: March 15, 2012

REASON FOR REQUEST:

	Not inspected in the last three years
	For Cause/Violative History
X	New Sites
	Other

Clinical Endpoint Study

TITLE:	A Double-Blind, Randomized, Parallel-Group, Vehicle-Controlled, Multicenter Study to Evaluate the Safety and Bioequivalence of Diclofenac Sodium Gel, 3% (TOLMAR Inc.) and Solaraze™ (Diclofenac Sodium) Gel, 3% and both Active Treatments to a Vehicle Control in the Treatment of Actinic Keratosis
PROTOCOL #:	TOL-AK-2008-02
NUMBER OF STUDY SITES:	38
Medical Monitor:	Nermina Nakas, MD, MPH Director, Clinical Development and Drug Safety Clinsys Clinical Research, Inc. 5128 Reids Pointe Road, Glen Allen, VA 23060 Phone: 804-270-6074; (b) (6) Fax: 804-270-6075 nnakas@clinsys.com

SITES TO BE INSPECTED	
Site # 1	Center for Dermatology Clinical Research (Site 1)
Address	2557 Mowry Avenue, Suite 34 Fremont, CA 94538
Phone	510-797-4111
Investigator (Name/Contact Info)	Sunil S. Dhawan, MD
# of subjects	12
Site # 2	Marina I. Peredo, MD (Site 2)
Address	260 Middle County Road, Suite 208 Smithtown, NY 11787
Phone	631-863-3223
Investigator (Name/Contact Info)	Marina I. Peredo, MD
# of subjects	16
Site # 3	Stephen Miller, MD (Site 5)
Address	8431 Fredericksburg Rd., Suite 100 San Antonio, TX 78229
Phone	210-614-2662
Investigator (Name/Contact Info)	Stephen Miller, MD
# of subjects	15

COMMENTS/ADDITIONAL INFORMATION FOR INSPECTORS:

This ANDA is located in the Electronic Document Room (EDR).

CLINICAL STUDY STATUS:

X	Study under review
	Study review completed
	Decision:
	Other: Review not started.

CLINICAL REVIEWER/CONTACT INFORMATION: Brenda Gierhart, MD (240-276-8960)

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

/s/

NITIN K PATEL
12/15/2011

JOHN R PETERS
12/15/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 200936

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: I	Team: 13	PM: Trang Tran

Electronic ANDA: Yes ☒ No ☐

ANDA #:200936
Firm Name:Tolmar Inc
ANDA Name:Diclofenac Sodium Gel, 3%
RLD Name:Solaraze® (diclofenac sodium) Gel, 3%.

Electronic AP Routing Summary Located:
V:\Chemistry Division I\Team 13\Electronic AP Summary\200936.ARS.doc

AP/TA Letter Located:
V:\Chemistry Division I\Team 13\Approval Letters\200936.AP.doc

Project Manager Evaluation: **Date: 10/7/2013 Initials:** TT

☐ Previously reviewed and tentatively approved --- Date _____
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date 12/16/2009	Date of Application 12/14/2009	Date Acceptable for Filing 12/16/2009
Patent Certification (type) PIV	Date Patent/Excl. expires 11/16/2016	Citizens' Petition/Legal Case? Yes☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐ **DMF#:** (b) (4) (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☒ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☒ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

GDUFA User Fee Obligation Status: ☒ Met ☐ Unmet**:** ☐ Facility Fee not paid, ☐ Backlog fee not paid
EER Status: ☐ Pending ☒ Acceptable ☐ OAI *EES Date Acceptable: 7/10/13* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☒ Comment:
Date of Acceptable Quality (Chemistry) 1/8/2013 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 10/4/2013 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 10/18/2013 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) n/a

Methods Val. Samples Pending: Yes ☐ No ☒**;** Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☒ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: _____ REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: _____

☒ Division

☒ Bob West / Peter Rickman

☐ Kathleen Uhl

☐Filed AP Routing Summary in DARRTs	☐Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 10/18/2013**
Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD = Solaraze Gel 3% NDA# 21-005 Date Checked 10/27/13 Nothing Submitted ☒ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☒ No ☐ Has case been settled: Yes ☒ No ☐ Date settled: Is applicant eligible for 180 day NO Is a forfeiture memo needed: Yes ☐ No ☒ If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	

Date of latest Labeling Review/Approval Summary _____

Any filing status changes requiring addition Labeling Review Yes ☐ No ☒

Type of Letter:
☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP
☐ OTHER:

Comments:ANDA submitted on 12/16/2009, BOS=Solaraze NDA 21-005, PIV to '738, '753, '002, '322, '048, '850. ANDA ultimately ACK for filing with a PIV on 12/16/2009 (ANDA first ACK, then RTR, then RTR rescinded with Tolmar granted original filing date-first PIV ACK LO date 3/18/2010).
Patent Amendment rec'd on 4/12/2010-notice sent to SkyePharma PLC in London UK, SkyePharma U.S. Inc. in San Diego CA, Nycomed U.S. in Melville NY, SkyePharma A.G. in Muttenz Switzerland, Nycomed International Management GmbH in Zurich Switzerland, SkyePharma US Inc. in Cambridge MA, Jagotec AG in Muttenz Switzerland and PharmaDerm in Florham Park NJ via (b) (4) with all notices delivered between 4/9/2010 and 4/12/2010.
Patent Amendment rec'd on 11/8/2010-CA 10 CV 2635 filed in the D of NJ on 5/28/2010 for infringement of the '738, '753, '002, '322, '048 and '850 patents, as suit was filed within 45 days there is an automatic 30 month stay of approval that expired on 10/12/2012.
Patent Amendment rec'd on 4/28/2011-reiteration of 6 PIV certs as provided in original submission, this was done to acknowledge changes in the expiration dates of two patents.
Patent Amendment rec'd on 9/1/2011-Letter from Covington and Burling indicating that the 30 month stay of approval had been extended until 4/9/2013.
Patent Amendment rec'd on 9/17/2012-all claims and counterclaims of CA 10 CV 2635 dismissed on 9/13/2012.

With the dismissal of CA 10 CV 2635, none of the 6 listed patents represent a barrier to the approval of this ANDA. This applicant was the first to submit a substantially complete ANDA with a PIV certification. The applicant did not secure TA within 30 months of their submission date and therefore appear to have forfeited eligibility for 180 day exclusivity.

(b) (4)

ANDA is eligible for full approval while punting on the 180 day exclusivity forfeiture issue.

2. ***Labeling Endorsement***

Reviewer, Beverly Weitzman: Labeling Team Leader, John Grace:
Date10/21/13 Date10/21/13

REMS required? REMS acceptable?
☐Yes ☒No ☐Yes ☐No ☒n/a

Comments:

From: Grace, John F
Sent: Monday, October 21, 2013 3:02 PM
To: Weitzman, Beverly

Cc: Tran, Trang
Subject: Re: Request for Labeling Endorsement for ANDA 200936 - Diclofenac Sodium Gel 0.3% - 1st Generic

Concur.

From: Weitzman, Beverly
Sent: Monday, October 21, 2013 02:16 PM
To: Grace, John F
Cc: Tran, Trang
Subject: RE: Request for Labeling Endorsement for ANDA 200936 - Diclofenac Sodium Gel 0.3% - 1st Generic

The labeling review done by Beverly Weitzman and signed off by John Grace remains acceptable. There are no new changes to the RLD labeling at this time. No changes noted

From: Tran, Trang
Sent: Monday, October 21, 2013 10:35 AM
To: Weitzman, Beverly; Grace, John F
Cc: Mazza, Tania
Subject: Request for Labeling Endorsement for ANDA 200936 - Diclofenac Sodium Gel 0.3% - 1st Generic
Importance: High

Hi Beverly/John,

Could you provide the labeling endorsement for the above ANDA? Attached is the AP letter for your reference.

Thanks,

Trang

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 21Oct2013**
OGD Regulatory Counsel **InitialsDTR**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Changes to AP letter saved to the V drive. As Marty notes, being the only ANDA referencing RLD Solaraze, this ANDA is a prime candidate for a "punt" regarding forfeiture. It is noted, however, that disputes bwteen FDA and Tolmar regarding appropriate BE criteris extended over a couple of years at least, and perhaps even from the very day this ANDA was submitted and RTR'ed (RTR was rescinded, somewhat reluctantly). There were multiple dispute resolutions regarding the appropriate approval criteria, ending with our agreeing that Tolmar had submitted sufficient data to demonstrate BE without the in vitro skin permeation data we had been requesting. However, one of the reasons for punting is to avoid unnecessary work even when we are quite sure of the answer to the forfeiture question, and that would seem to be the case here.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 10/22/13**
Chemistry Div. **I (Raw)** **InitialsASR**
Comments:cmc acceptable.

OGD Office Management Evaluation
5. Peter Rickman **Date 10/27/13**
Director, DLPS **Initials rlw/for**
Para.IV Patent Cert: Yes☐ ☐ ☐ No☐
Pending Legal Action: Yes☐ ☐ No☐
Petition: Yes☐ No☐
Entered to APTrack database ☐
GDUFA User Fee Obligation Status Met☐ Unmet☐
Press Release Acceptable ☐

Date PETS checked for first generic drug _____

Comments: Bioequivalence established through clinical endpoint study. Statistical review found acceptable 6/6/13. OGD Clinical Division endorsement dated 10/4/13. DBE determined it would not pursue resolution of deficiencies associated with Tolmar's in-vitro skin permeation study for reasons detailed in review and memorandum filed in DARRTS. Study sites have acceptable OSI inspection histories. Office-level bio endorsed 10/4/13.

Final-printed labeling (FPL) found acceptable for approval 10/18/13, as endorsed 10/21/13. No REMS is required.

CMC found acceptable for approval (Chemistry Review #3) 1/8/13.

OR

6. Robert L. West **Date 10/27/13**
Deputy Director, OGD **Initials RLWest**
Para.IV Patent Cert: Yes☒ No☐
Pending Legal Action: Yes☐ No☒
Petition: Yes☐ No☒
Entered to APTrack database ☒
GDUFA User Fee Obligation Status Met☒ Unmet☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 7/10/13 (Verified 10/27/13). No "OAI" Alerts noted.

Tolmar provided a paragraph IV certification to the '738, '753, '002, '322, '048 and '850 patents and was sued within the 45-day period on each patent. All litigation was subsequently dismissed on 9/13/12. There are no additional patents or exclusivity currently listed in the "Orange Book" for this drug product.

This first-generic ANDA is recommended for approval. The approval letter will declare that Tolmar is eligible for 180-day generic drug exclusivity for this drug product (RLD = Solaraze Gel, 3%).

7. ***OGD Director Evaluation***
Kathleen Uhl
Comments: RLWest for Kathleen Uhl, M.D., Acting Director, Office of Generic Drugs 10/27/13.
First Generic Approval ☒
PD or Clinical for BE ☒
Special Scientific or Reg. Issue ☐
Press Release Acceptable ☐

Comments: No press release necessary - not top 100 drug product. IA forwarded to OGD communications team.

8. Project Manager **Date _____**
Initials _____

Comments:

Check Communication and Routing Summary into DARRTS

Establishment Evaluation System

File Edit Search Navigate Options Help Window

ORACLE

Application Drawer

Application | Establishments | Status | Milestones | Comments | Contacts | Product

Application: A 200936/000 Subtype: N/A Sponsor: TOLMAR

Drug Name: DICLOFENAC SODIUM

FEI / CFN	Establishment Name	Profile Code	Last Milestone Name	Last Compliance Date	Status	Date	OAI Alert	EER Re-eval Date
(b) (4)								
3006218434	TOLMAR, INC.	OIN	OC RECOMMENDATION	10-JUL-2013	AC	10-JUL-2013		07-SEP-2014
(b) (4)								

Overall Compliance:

Date	Recommendation	Overall Re-eval Date
10-JUL-2013	ACCEPTABLE	(b) (4)
01-JUL-2013	PENDING	

OAI Alert Comments

Save Close

Record: 1/5 ... <OSC>

Java Applet Window

start Inb... 4 I... 3 M. 3:16 PM

Reference ID: 3397098

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

- [1]
- [2]

- FDA Home[3]
- Drug Databases[4]
- Orange Book[5]

-

Patent and Exclusivity Search Results from query on Appl No 021005 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021005	001	5639738	Jun 17, 2014			U - 402	
N021005	001	5792753	Aug 11, 2015				
N021005	001	5852002	Jun 17, 2014			U - 402	
N021005	001	5914322	Aug 11, 2015				

Revised, Jun 2013

Reference ID: 3397098

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021005	001	5929048	Jun 17, 2014			U - 402	
N021005	001	5985850	Aug 11, 2015		Y		

Exclusivity Data

There is no unexpired exclusivity for this product.

7 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CHITRA MAHADEVAN
10/04/2013

ETHAN M STIER
10/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 200936

NOT ACCEPTED –
FORMAL DISPUTE RESOLUTION REQUEST

Tolmar Inc.
Attention: Michelle Ryder
Senior Director, Regulatory Affairs
701 Centre Avenue
Fort Collins, CO 80526

Dear Ms. Ryder:

Please refer to your Abbreviated New Drug Application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for diclofenac sodium gel, 3%.

We acknowledge receipt on August 9, 2013, of your August 8, 2013, request for formal dispute resolution concerning the complete response action on June 14, 2013. Specifically, the deficiency that bioequivalence was not established within the epidermis in the first stage of the in vitro study, and that a second stage test should be conducted to show bioequivalence between the test drug product and the reference drug.

In accordance with the procedures for dispute resolution described in the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level" *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM343101.pdf* the appropriate course of action for a sponsor that disagrees with a decision is to first request reconsideration of the matter by the division/original deciding authority before the issue may be appealed to the next higher management level. In instances where a sponsor disagrees with a complete response action, our practices have been that the sponsor requests a post-action meeting with the division/original deciding authority to discuss the sponsor's concerns with the decision. If a sponsor chooses not to take the advice that the division/original deciding authority provides at the post-action meeting, the sponsor may proceed with the formal dispute resolution process.

Since a post-action meeting has not been held between the Office of Generics Drug (OGD) and you following the complete response action on June 14, 2013, it would be inappropriate to consider this matter under formal dispute resolution at this time. We believe that there is value in your having a post-action meeting with OGD to discuss your concerns.

Please submit a meeting request for a post-action meeting to the ANDA administrative file. We will work to schedule this meeting as soon as a mutually agreed upon date can be found. If you have any questions, contact Trang Tran, Sr. Regulatory Health Project Manager, at (240) 276-8518.

If, after this reconsideration, the issue is still not resolved to your satisfaction, you may appeal the matter to the Director of the Office of Pharmaceutical Science (OPS).

If you have any questions about the formal dispute resolution process, please call me at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

Amy Bertha
Formal Dispute Resolution Project Manager
Office of New Drugs
Center for Drug Evaluation and Research

Cc: Hyman, Phelps & McNamara, P.C.
Attention: Roger Thies
700 Thirteenth Street N.W.
Suite 1200
Washington D.C. 20005

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/s/

AMY E BERTHA
08/13/2013

EASILY CORRECTABLE DEFICIENCY FAX

ANDA 200936

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: TOLMAR Inc, TEL: (970) 212-4901

ATTN: Michelle Ryder FAX: (970) 212-4950

FROM: Trang Q. Tran FDA CONTACT PHONE: (240) 276-8518

Dear Madam:

This facsimile is in reference to your abbreviated new drug application (ANDA) dated , submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Diclofenac Sodium Gel, 3%.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies with an "*EASILY CORRECTABLE DEFICIENCY AMENDMENT*" within ten (10) working days.

If you do not submit a complete response within ten (10) working days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments. In addition, please notify the Project Manager listed below.

A partial response to this fax will not be processed as an amendment and will not start a review. Please submit official archival copies of your response to the ANDA. Please notify the above Project Manager when your amendment has been submitted.

If you have questions regarding these deficiencies please contact the Project Manager, Trang Q. Tran at (240) 276-8518.

SPECIAL INSTRUCTIONS:

We have completed our review of this ANDA, as amended, and have the following comments:

PRODUCT QUALITY

(b) (4)

[redacted]

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/s/

RICHARD R CHANG
12/06/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 200936

Roger C. Thies, Esq.
Hyman, Phelps & McNamara, P.C.
700 Thirteenth St., N.W.
Suite 1200
Washington, D.C. 20005

Dear Mr. Thies:

This letter is in response to your letter of July 12, 2012, addressed to Dr. Keith O. Webber, then Acting Director of the Office of Generic Drugs (OGD). Your letter seeks assurance that OGD's review of the above captioned ANDA for Diclofenac Sodium Gel, 3%, is not further delayed.

In particular, you are concerned about OGD's review of the clinical endpoint bioequivalence study (Study No. TOL-AK-2008-02) and that "further review of the ANDA will be held in abeyance until OGD receives the report of the in vitro skin permeation study." Because the purpose of your letter is quite straightforward, i.e., that OGD not delay its review of ANDA 200936, it is not necessary for the agency to address the accuracy of every statement made in your letter except to note that we do not agree with some of what is said, or implied, in the letter.

The review of your ANDA has not and will not be delayed or "held in abeyance" pending the submission of the skin permeation study. I have spoken with key personnel involved with this ANDA, and its review continues in a normal manner.

I hope this provides the assurance you seek. If you have further questions about this matter, please contact Dave Read, Regulatory Counsel, Office of Generic Drugs, 240-276-9320.

Sincerely,

{See appended electronic signature page}

Gregory P. Geba, M.D., M.P.H.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

ROBERT L WEST

08/07/2012

Deputy Director, Office of Generic Drugs
for Gregory P. Geba, M.D., M.P.H.

QUALITY DEFICIENCY - MINOR

ANDA 200936

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: TOLMAR Inc.

TEL: (970) 212-4901

ATTN: Michelle Ryder

FAX: (970) 212-4950

FROM: Trang Q. Tran

FDA CONTACT PHONE: (240) 276-8518

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 14, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Diclofenac Sodium Gel, 3%.

Reference is also made to your amendments dated December 21, 2010; September 27, 2011; and March 23, 2012.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 200936 APPLICANT: Tolmar, Inc.

DRUG PRODUCT: Diclofenac Sodium Gel, 3%

The deficiencies presented below represent MINOR deficiencies

A. Deficiencies:

(b) (4)

1.

2.

3.

4.

5.

6.

7.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available drug product room temperature stability data.

2. All facilities referenced in your ANDA should be in compliance with cGMP at the time of approval. We have requested an evaluation from the Office of Compliance.
3. We encourage you to apply Quality by Design (QbD) principles to the pharmaceutical development of your future original ANDA product

submissions. A risk-based, scientifically sound submission would be expected to include the following:

- Quality target product profile (QTPP)
- Critical quality attributes (CQAs) of the drug product
- Product design and understanding including identification of critical attributes of excipients, drug substance(s), and/or container closure systems
- Process design and understanding including identification of critical process parameters and in-process material attributes
- Control strategy and justification

An example illustrating QbD concepts can be found online at FDA's **Generic Drugs: Information for Industry** webpage: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf

Sincerely yours,

{See appended electronic signature page}

Andre Raw, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

JAMES M FAN
07/30/2012
for Andre Raw

BIOEQUIVALENCE AMENDMENT

ANDA 200936

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Tolmar Inc. TEL: (970) 212-4901

ATTN: Michelle Ryder FAX: (970) 212-4950

FROM: Jerome Lee FDA CONTACT PHONE: (240) 276-8817

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on December 14, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Diclofenac Sodium Topical Gel, 3%.

Reference is also made to your amendment dated September 27, 2011 and March 23, 2012.

The Division of Bioequivalence II has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Other
Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence II, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCES

ANDA: 200936

APPLICANT: Tolmar Inc.

DRUG PRODUCT: Diclofenac Sodium Topical Gel, 3%

The Division of Bioequivalence II (DB II) has completed its review and the following deficiencies have been identified.

1. Your proposal to use human cadaver skin is acceptable. However, please repeat the in vitro permeation bioequivalence study using at least 6 skin sample replicates. The skin samples should preferably be obtained from the same region of the body of all donors (at least 6 donors in total).

2. Please validate the integrity of the human cadaver skin samples to be used in the in vitro permeation bioequivalence study to ensure that there are no areas of unusual permeability in the cadaver skin samples.

3. Please conduct your study using one lot each of your 'to be marketed' test product (ANDA formulation) and reference product.

4. Please repeat the in vitro permeation study, which consists of Distribution Release-rate study and Mass-balance study, comparing your test product with the reference listed drug (RLD). In order to support a finding of pharmaceutical equivalence between the test and reference product, the following comments are provided for future in vitro permeation studies:

   a. Appropriately validated specific and sensitive analytical procedure should be used to analyze the samples and to determine the drug concentration and the amount of drug release.

   b. For the Distribution Release-rate study, 5 or more time-points (at least 6 replicates per time-point) over an appropriate time period should be used per lot of test product and RLD. Mass-balance would be determined from the drug accumulation in the different skin layers (e.g. **stratum corneum, epidermis, dermis**). The Mass-balance study may be conducted at an appropriate time-point,

using at least 6 replicates per lot of test product and RLD.

c. The DB II also recommends randomization, using appropriate software, of the test product and the RLD in each run of the experiment. This approach of including both products in each run of the in vitro apparatus will help ensure an unbiased comparison in the event of a systematic difference between runs. Please follow the *Guidance for Industry: Nonsterile Semisolid Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation (SUPAC-SS)* for the study design, as well as setup and operation of the Vertical (Franz) Diffusion Cell.

d. Please provide full details of the method of extraction and recovery of the drug from the different layers of the skin samples, and how the skin was separated into different layers (stratum corneum, epidermis, dermis).

e. Please submit all your pre-study bioanalytical method validation (including reproducibility, evaluation of sink conditions, skin binding), and 20% of the chromatograms.

f. Please submit Distribution Release-rate study data and Mass-balance study data electronically as SAS (.xpt) data file(s). Data should be analyzed statistically using the approach outlined in the *SUPAC-SS guidance* referred in comment 4c above.

g. The final report of the study should include lot numbers, date of manufacture, expiration date, and batch size of the test product and RLD, as applicable.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

BARBARA M DAVIT
04/19/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 200936

ACKNOWLEDGE DISPUTE APPEAL

TOLMAR Inc.
Attention: Michelle R. Ryder
Director, Regulatory Affairs
701 Centre Avenue
Fort Collins, CO 80526

Dear Ms. Ryder:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 14, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Diclofenac Sodium Gel, 3%.

We acknowledge receipt on September 27, 2011, of your September 27, 2011, request for formal dispute resolution concerning the non-approval of Abbreviated New Drug Application No. 200936 for a generic version of Solaraze (diclofenac sodium) Gel, 3% by the Office of Generic Drugs.

Your appeal has been forwarded for review to Helen Winkle, Director, Office of Pharmaceutical Science, Center for Drug Evaluation and Research. We will contact you should we have any questions or require additional information.

If you have any questions, please call me at (301) 796-1773.

Sincerely,

{See appended electronic signature page}

Marilyn Welschenbach, Ph.D.
Regulatory Project Manager
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MARILYN A WELSCHENBACH
10/06/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 200936

TOLMAR Inc.
Attention: Michelle R. Boyer
Director, Regulary Affairs
701 Centre Avenue
Fort Collins, CO 80526

Dear Madam:

This letter is in reference to your Abbreviated New Drug Application (ANDA) dated December 14, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Diclofenac Sodium Gel, 3%.

Reference is also made to your amendments dated March 10, July 8, and December 21, 2010; and April 19, 2011.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form because: 1) one or more of the inactive ingredients of the proposed drug or its composition raise serious questions of safety or efficacy [21 CFR §314.127(a)(8)(ii)(A)], and 2) the bioequivalence study is not adequate to demonstrate that the test product is bioequivalent to the reference listed drug [21 CFR §314.127(a)(6)(i)].

The FDA has determined that one or more of the inactive ingredients of the proposed drug or its composition raise serious questions of safety or efficacy under 21 CFR 314.127(a)(8)(ii)(A), for the following reasons:

According to U.S. Patents listed for the RLD in the FDA Orange Book and a publication (M.B. Brown and S.A. Jones, "Hyaluronic Acid: a unique topical vehicle for the localized delivery of drugs to the skin", Journal European Academy of Dermatology and Venerology, 19, 308-318, 2005), hyaluronate sodium is a functional excipient. It not only imparts viscosity and gelling properties to the RLD, but also promotes the penetration of the drug through the stratum corneum and the retention of the drug in the epidermis of the skin. You have not demonstrated that your selected excipient performs similarly to hyaluronate sodium.

We notice that the viscosity of your drug product is (b) (4) compared to that of the RLD (b) (4) (b) (4) (b) (4) You

have not explained your reasoning for not matching the viscosity of the RLD. You also have not demonstrated that the gel retention on the skin and in the epidermis after application is similar to that of the RLD.

The FDA has determined that the bioequivalence study submitted for this application is unacceptable under 21 CFR 314.127(a)(6)(i), for the following reasons:

The design of TOL-AK-2008-02 is unacceptable because it may not be adequately sensitive to detect a difference in product performance. According to 21 CFR 320.24 (b)(4), well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for the purposes of demonstrating bioequivalence, are the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence. Clinical trials as an approach to demonstrate bioequivalence generally are considered insensitive.[1] To improve the sensitivity of comparative clinical trials, the dosing regimen and period of dosing must be carefully selected. If the doses chosen for both agents are too high then subjects may reach an upper threshold in response, leading to a false conclusion of equivalence.[2] We consider the same to be true of longer treatment durations.

The primary difference between the 3 pivotal Phase 3 clinical studies supporting approval of the RLD was the duration of treatment (i.e., 30, 60 or 90 days). The shortest treatment duration demonstrating a statistically significant difference between active drug and placebo was 60 days of treatment. Increasing the treatment duration to 90 days resulted in an overall higher complete clearance rate only for the vehicle. Thus, the 90 day treatment duration is more likely to capture only the maximum effect and not the rate and extent of drug delivery to the site of action. The OGD recommends that Diclofenac Sodium Gel/Topical 3% be administered twice daily for 60 days with the primary efficacy endpoint evaluation at the 30-day post-treatment assessment in the bioequivalence study with clinical endpoint. Thus, the study design of TOL-AK-2008-02 with an 84-day treatment duration and the primary efficacy endpoint evaluation at the 28-day post-treatment assessment is not acceptable. The longer, 84-day treatment duration is likely to minimize any differences between the test and reference treatment effects.

---

[1] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Bioavailability and bioequivalence studies for orally administered drug products-general considerations. March 2003; pg. 9.
[2] Jones B et al. Trials to assess equivalence: the importance of rigorous methods. *BMJ.* 1996; 313: 36-9.

In order to resolve these deficiencies, you will need to provide the following additional information:

1. Demonstrate that your selected excipient performs similarly to hyaluronate sodium. This may be accomplished through in vitro skin permeation studies and a well-designed comparative pharmacokinetic bioequivalence study.

2. Explain your rationale for not matching the viscosity of the RLD.

3. Demonstrate that the gel retention on the skin and in the epidermis after application is similar to that of the RLD.

4. Conduct a clinical endpoint study designed to have the maximum sensitivity for detecting differences in product performance between the test and reference products.

The Office of Generic Drugs will suspend any further review of this application until an amendment containing complete information and data necessary to support your chosen plan of action is submitted to the Agency.

The file for this ANDA is now closed. It is required that an action described under 21 CFR §314.120 and 21 CFR §314.96 be taken, which will either amend or withdraw this application. Should you decide to amend this ANDA, the amendment should respond to all the deficiencies stated above and to those presented in previous letters. In the event that reformulation of the test product is needed to meet the agency's bioequivalence requirements, revised chemistry, manufacturing, controls and labeling information should also be included in the amendment. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered as a **Major Amendment** and should be so designated in your cover letter. The cover letter should clearly state what information is being provided in the submission (i.e., Chemistry, Bioequivalence, Labeling). If there is substantial disagreement with our reasons for not approving this application, a hearing request can be submitted.

If you have any questions concerning this letter please contact: Trang Q. Tran, Project Manager, Office of Generic Drugs at 240-276-8518.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

ROBERT L WEST

07/11/2011

Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.