

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

***APPLICATION NUMBER:***  
**ANDA 208077**

**Name:** Diclofenac Sodium Topical Gel, 1%

**Sponsor:** Amneal Pharmaceuticals

**Approval Date:** March 18, 2016

**Indication:** For the relief of the pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands.

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:  
ANDA 208077Orig1s000  
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**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 208077Orig1s000**

**APPROVAL LETTER**



ANDA 208077

**ANDA APPROVAL**

Amneal Pharmaceuticals  
85 Adams Avenue  
Hauppauge, NY 11788  
Attention: Alpesh Patel  
Vice President - Global Regulatory Affairs

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Diclofenac Sodium Topical Gel, 1%.

Reference is also made to your amendment dated January 13, January 15, January 29, April 14, August 5, August 27, September 28, December 4, 2015; and February 4, 2016.

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 Office of Bioequivalence has determined your Diclofenac Sodium Topical Gel, 1% to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug product (RLD), Voltaren Gel, 1%, of GlaxoSmithKline Consumer Health.

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(s) 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,

**William P.  
Rickman -S**

For Carol A. Holquist, RPh  
Acting Deputy Director  
Office of Regulatory Operations  
Office of Generic Drugs  
Center for Drug Evaluation and Research

Digitally signed by William P. Rickman -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People,  
0.9.2342.19200300.100.1.1=1300043242,  
cn=William P. Rickman -S  
Date: 2016.03.18 14:16:15 -04'00'

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 208077Orig1s000**

**LABELING**



NDC 65162-833-66

# Diclofenac Sodium Topical Gel, 1%

**Use the Dosing Card Attached Inside the Carton**  
**See Medication Guide and Patient Instructions Inside of Carton**  
**For Topical Use Only**

**Rx only**

**Net Wt 100 g**

EXP  
LOT

Each gram contains 1% w/w diclofenac sodium, USP.

**Inactive Ingredients:** carbomer homopolymer Type C, cocoyl caprylocaprate, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water and strong ammonia solution.

For topical use only.  
Not for ophthalmic use.

**Keep out of reach of children.**

**DOSAGE:** Apply to skin over the affected area four times daily. Use the dosing card provided to measure the amount of diclofenac sodium topical gel to be applied. See accompanying prescribing information.

**To open tube:** Unscrew cap, puncture seal with pointed end of cap.

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

Store the dosing card with your diclofenac sodium topical gel, 1%.

Comments or Questions? Call toll free 1-877-835-5472

Manufactured by: **Amneal Pharmaceuticals**  
Piscataway, NJ 08854

Distributed by: **Amneal Pharmaceuticals**  
Glasgow, KY 42141

Rev. 08-2015-01



Diclofenac Sodium Topical Gel, 1%

Label Size: 5.375" x 4.1875"



Each gram contains 1% w/w diclofenac sodium, USP.

**Inactive Ingredients:** carbomer homopolymer Type C, cocoyl caprylocaprate, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water and strong ammonia solution.

For topical use only.  
Not for ophthalmic use.  
**Keep out of reach of children.**

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NDC 65162-833-66

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Net Wt 100 g

NDC 65162-833-66  
**Diclofenac Sodium  
Topical Gel, 1%**

Net Wt 100 g

(b) (4)

**Dosing card for Diclofenac Sodium Topical Gel 1%**



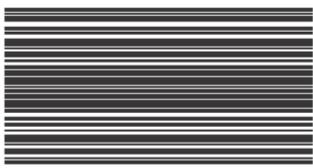
2 grams  
(2.25 inches)

4 grams  
(4.5 inches)

Please see instructions for use.



(b) (4)



8825 1814  
Rx Only  
Rev. 08-2015-00  
DICLOFENAC SODIUM topical gel, 1%

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DICLOFENAC SODIUM TOPICAL GEL safely and effectively. See full prescribing information for DICLOFENAC SODIUM TOPICAL GEL.

DICLOFENAC SODIUM topical gel, 1%, for topical use only  
Initial U.S. Approval: 1988

#### WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISK

See full prescribing information for complete boxed warning.

##### Cardiovascular Risk

- Non-steroidal anti-inflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. (5.1)
- Diclofenac sodium topical gel is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

##### Gastrointestinal Risk (4, 5.2)

- Non-steroidal anti-inflammatory drugs (NSAIDs), including diclofenac sodium topical gel, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. Elderly patients are at greater risk for serious gastrointestinal events. (5.2)

#### INDICATIONS AND USAGE

Diclofenac sodium topical gel, 1% is a non-steroidal anti-inflammatory drug indicated for the relief of the pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands. (1)

- Diclofenac sodium topical gel, 1% was not evaluated for use on joints of the spine, hip, or shoulder. (14.1)

#### DOSAGE AND ADMINISTRATION

Total dose should not exceed 32 g per day, over all affected joints. (2.3) Diclofenac sodium topical gel, 1% should be measured into the enclosed dosing card to the appropriate 2 g or 4 g designation. (2)

- Lower extremities: Apply the gel (4 g) to the affected area 4 times daily. Do not apply more than 16 g daily to any one affected joint of the lower extremities. (2.2)
- Upper extremities: Apply the gel (2 g) to the affected area 4 times daily. Do not apply more than 8 g daily to any one affected joint of the upper extremities. (2.3)

#### DOSAGE FORM AND STRENGTH

- 1% gel (3)

#### CONTRAINDICATIONS

- Known hypersensitivity to diclofenac, aspirin, or other NSAIDs. (4, 5.2)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. (4)
- Use during the peri-operative period in the setting of coronary artery bypass graft (CABG) surgery. (4)

#### WARNINGS AND PRECAUTIONS

- Serious and potentially fatal cardiovascular (CV) thrombotic events, myocardial infarction, and stroke can occur with NSAID treatment. The lowest possible dose of diclofenac sodium topical gel should be used in patients with known CV disease or risk factors for CV disease. (5.1)
- NSAIDs, including diclofenac, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation. Diclofenac sodium topical gel should be prescribed with caution in those with a prior history of ulcer disease or gastrointestinal bleeding. (5.2)
- Elevation of one or more liver tests may occur during therapy with diclofenac. Diclofenac sodium topical gel should be discontinued immediately if abnormal liver tests persist or worsen. (5.3)
- Long-term administration of NSAIDs can result in renal papillary necrosis and other renal injury. Diclofenac sodium topical gel should be used with caution in patients at greatest risk of this reaction, including the elderly, those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and ACE-inhibitors. (5.6)
- Hypertension can occur with NSAID treatment. Blood pressure should be monitored closely during treatment with diclofenac sodium topical gel. (5.4)
- Fluid retention and edema have been observed in some patients taking NSAIDs. Diclofenac sodium topical gel should be used with caution in patients with fluid retention or heart failure. (5.5)
- Anaphylactoid reactions may occur in patients with the aspirin triad or in patients without prior exposure to diclofenac sodium topical gel and should be discontinued immediately if an anaphylactoid reaction occurs. (5.7)
- NSAIDs can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Diclofenac sodium topical gel should be discontinued if rash or other signs of local skin reaction occur. (5.8)

#### ADVERSE REACTIONS

Most common adverse reactions (incidence >2% of patients treated with diclofenac sodium topical gel and greater than placebo) are application site reactions, including dermatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Anveel Pharmaceuticals at 1-877-835-5472 or www.anveel.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

#### DRUG INTERACTIONS

- Concomitant administration of diclofenac and aspirin is not generally recommended because of the potential of increased adverse effects including increased GI bleeding. (7.1)
- Concomitant use of anticoagulants and diclofenac have a risk of serious GI bleeding higher than users of either drug alone. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: August 2015

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Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke [see *Contraindications* (4)].

**5.2 Gastrointestinal Effects – Risk of GI Ulceration, Bleeding, and Perforation**  
NSAIDs, including diclofenac, can cause serious gastrointestinal (GI) events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAIDs therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. Physicians and patients should remain alert for signs and symptoms of GI ulceration and bleeding during diclofenac therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

##### 5.3 Hepatic Effects

Elevations of one or more liver tests may occur during therapy with diclofenac sodium. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (i.e. less than 3 times the ULN [ULN = the upper limit of normal range]) or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of AST (GOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5,700 patients at some time during diclofenac treatment. In a large, open-label, controlled trial of 3,700 patients treated for 2 to 6 months, patients were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4% of patients and included marked elevations (i.e., more than 8 times the ULN) in about 1% of the 3,700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3 to 8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

Almost all meaningful elevations in transaminases were detected before patients became symptomatic. Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations.

In postmarketing reports, cases of drug-induced hepatopathy have been reported in the first month, and in some cases, the first 2 months of therapy, but can occur at any time during treatment with diclofenac. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation. Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatopathy may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and postmarketing experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with diclofenac.

If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, abdominal pain, diarrhea, dark urine, etc.), diclofenac sodium should be discontinued immediately. To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatopathy (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms), and the appropriate action patients should take if they have signs and symptoms appear.

To minimize the potential risk for an adverse liver related event in patients treated with diclofenac sodium, the lowest effective dose should be used for the shortest duration possible. Caution should be exercised in prescribing diclofenac sodium with concomitant drugs that are known to be potentially hepatotoxic (e.g., antibiotics, anti-epileptics).

##### 5.4 Hypertension

NSAIDs, including diclofenac sodium topical gel, can lead to the onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of cardiovascular events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including diclofenac sodium topical gel should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with diclofenac sodium topical gel and throughout the course of therapy.

##### 5.5 Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients treated with NSAIDs, including diclofenac sodium topical gel. Diclofenac sodium topical gel should be used with caution in patients with fluid retention or heart failure.

##### 5.6 Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE-inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of diclofenac sodium topical gel in patients with advanced renal disease. Therefore, treatment with diclofenac sodium topical gel is not recommended in patients with advanced renal disease. If diclofenac sodium topical gel therapy is initiated, close monitoring of the patient's renal function is advisable.

##### 5.7 Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without prior exposure to diclofenac sodium topical gel. Diclofenac sodium topical gel should not be given to patients with the aspirin triad. This symptom complex 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 [see *Contraindications* (4), *Warnings and Precautions* (5.7)]. Emergency help should be sought in cases where an anaphylactoid reaction occurs.

##### 5.8 Skin Reactions

NSAIDs, including diclofenac sodium topical gel, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations, and the use of the drug should be discontinued at the first appearance of skin rash or any other signs of hypersensitivity.

Diclofenac sodium topical gel should not be applied to open skin wounds, infections, inflammations, or exfoliative dermatitis, as it may affect absorption and tolerability of the drug. Diclofenac sodium topical gel should not be allowed to come into contact with the eyes or with mucous membranes.

The effect of diclofenac sodium topical gel under occlusive dressings has not been evaluated, and should be avoided.

##### 5.9 Pregnancy

As with other NSAIDs, diclofenac sodium topical gel should be avoided in late pregnancy, because it may cause premature closure of the ductus arteriosus.

##### 5.10 Corticosteroid Treatment

Diclofenac sodium topical gel cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness.

Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

##### 5.11 Inflammation

The pharmacologic activity of diclofenac in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

##### 5.12 Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including diclofenac sodium topical gel, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients treated with diclofenac sodium topical gel who may be adversely affected by alteration in platelet function, such as those with coagulation disorders or patients receiving anticoagulants should be carefully monitored.

##### 5.13 Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other non-steroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, diclofenac sodium topical gel should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

##### 5.14 Sun Exposure

Patients should minimize or avoid exposure to natural or artificial sunlight on treated areas because studies in animals indicated topical diclofenac treatment resulted in an earlier onset of ultraviolet light induced skin damage. The potential effects of diclofenac sodium topical gel on skin response to ultraviolet damage in humans are not known.

##### 5.15 Eye Exposure

Contact of diclofenac sodium topical gel with eyes and mucosa, although not studied, should be avoided. Patients should be advised that if eye contact occurs, they should immediately wash out the eye with water or saline and consult a physician if irritation persists for more than an hour.

##### 5.16 Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs, should have a CBC and a chemistry profile checked periodically. If abnormal liver tests or renal tests persist or worsen, diclofenac sodium topical gel should be discontinued.

##### 6 ADVERSE REACTIONS

##### 6.1 Clinical Trials Experience

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

During clinical development, 913 patients were exposed to diclofenac sodium topical gel in randomized, double-blind, multicenter, vehicle-controlled, parallel-group studies in osteoarthritis of the superficial joints of the extremities. Of these, 513 patients received diclofenac sodium topical gel for osteoarthritis of the knee and 400 were treated for osteoarthritis of the hand. Additionally, 583 patients were exposed to diclofenac sodium topical gel in an uncontrolled, open-label, long-term safety trial in osteoarthritis of the knee. Of these, 355 patients were treated for osteoarthritis of 1 knee and 228 were treated for osteoarthritis of both knees. Duration of exposure ranged from 8 to 12 weeks for the placebo-controlled studies, and up to 12 months for the open-label safety trial.

##### Short-Term Placebo-Controlled Trials:

Adverse reactions observed in at least 1% of patients treated with diclofenac sodium topical gel:

Non-serious adverse reactions that were reported during the short-term placebo-controlled studies comparing diclofenac sodium topical gel and placebo (vehicle gel) over study periods of 8 to 12 weeks (16 g per day), were application site reactions. These were the only adverse reactions that occurred in > 1% of treated patients with a greater frequency in the diclofenac sodium topical gel group (7%) than the placebo group (2%).

Table 1 lists the types of application site reactions reported. Application site dermatitis was the most frequent type of application site reaction and was reported by 4% of patients treated with diclofenac sodium topical gel, compared to 1% of placebo patients.

Table 1. Non-serious Application Site Adverse Reactions (≥1% Diclofenac Sodium Topical Gel Patients)- Short-Term Controlled Trials			
Adverse Reaction†	Diclofenac sodium topical gel N=913	Placebo (vehicle) N=876	
	N (%)	N (%)	
<i>Any application site reaction</i>	62 (7)	19 (2)	
Application site dermatitis	32 (4)	6 (<1)	
Application site pruritus	7 (<1)	1 (<1)	
Application site erythema	6 (<1)	3 (<1)	
Application site paresthesia	5 (<1)	3 (<1)	
Application site dryness	4 (<1)	3 (<1)	
Application site vesicles	3 (<1)	0	
Application site irritation	2 (<1)	0	
Application site papules	1 (<1)	0	

†Preferred term according to MedDRA 9.1

In the placebo-controlled trials, the discontinuation rate due to adverse reactions was 5% for patients treated with diclofenac sodium topical gel, and 3% for patients in the placebo group. Application site reactions, including application site dermatitis, were the most frequent reason for treatment discontinuation.

##### Long-Term Open-Label Safety Trial:

In the open-label, long-term safety study, distribution of adverse reactions was similar to that in the placebo-controlled studies. In this study, where patients were treated for up to 1 year with diclofenac sodium topical gel up to 32 g per day, application site dermatitis was observed in 11% of patients. Adverse reactions that led to the discontinuation of the study drug were experienced in 12% of patients. The most common adverse reaction that led to discontinuation of the study was application site dermatitis, which was experienced by 6% of patients.

##### 7 DRUG INTERACTIONS

##### 7.1 Aspirin

When diclofenac is administered with aspirin, the binding of diclofenac to protein is reduced, although the clearance of free diclofenac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of diclofenac and aspirin is not generally recommended because of the potential of increased adverse effects.

##### 7.2 Anticoagulants

The effects of anticoagulants such as warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

##### 7.3 ACE-Inhibitors

NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

##### 7.4 Diuretics

Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. The response has been attributed to inhibition of renal prostaglandin synthesis. During concurrent therapy with NSAIDs, the patient should be observed closely for signs of renal failure [see *Warnings and Precautions* (5.6)], as well as to assure diuretic efficacy.

##### 7.5 Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs, including diclofenac, and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity.

##### 7.6 Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs, including diclofenac, are administered concomitantly with methotrexate.

##### 7.7 Cyclosporine

Diclofenac, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore concomitant therapy with diclofenac may increase cyclosporine's nephrotoxicity. Caution should be used when diclofenac is administered concomitantly with cyclosporine.

##### 7.8 Oral Non-steroidal Anti-inflammatory Drugs

Specific interaction studies of diclofenac sodium topical gel and oral NSAIDs were not performed. Also, the clinical trials of diclofenac sodium topical gel prohibited concomitant use of oral NSAIDs. There is systemic exposure to diclofenac following normal use of diclofenac sodium topical gel, up to 6% of the systemic levels of a single oral dose of diclofenac sodium [see *Clinical Pharmacology* (7.2.3)]. Therefore, concomitant administration of diclofenac sodium topical gel with oral NSAIDs or aspirin may result in increased adverse NSAID effects.

##### 7.9 Topical Treatments

Concomitant use of diclofenac sodium topical gel with other topical products, including topical medications, sunscreens, lotions, moisturizers, and cosmetics, on the same skin site has not been tested and should be avoided because of the potential to alter local tolerability and absorption.

##### 8 USE IN SPECIFIC POPULATIONS

##### 8.1 Pregnancy

The safety of diclofenac sodium topical gel has not been established during pregnancy. There are no well-controlled studies of diclofenac in pregnant women. Human and animal studies indicate that diclofenac crosses the placenta. In late pregnancy, as with other NSAIDs, diclofenac sodium topical gel should be avoided because it may cause premature closure of the ductus arteriosus.

##### Teratogenic Effects

Pregnancy Category C. Studies in mice, rats, and rabbits in which diclofenac was administered orally throughout gestation revealed no evidence of teratogenicity despite the induction of maternal toxicity and fetal toxicity corresponding to a human equivalent dose approximately 4.5-, 2-, and 9-fold (mouse, rat, rabbit, respectively) of

the maximum human topical dose of diclofenac sodium topical gel (based on bioavailability and body surface area comparison).

##### Nonteratogenic Effects



853-1814  
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DICLOFENAC SODIUM TOPICAL GEL, 1%

		Diclofenac sodium topical gel	Placebo (Vehicle)	Adjusted Difference (Placebo - Diclofenac sodium topical gel)
Study 1 (Knee) WOMAC Pain <sup>†</sup> at Week 12	Sample Size	127	119	
	Mean outcome	28	37	Δ=7† (1,12)
	95% confidence interval			
Study 2 (Hand) Pain Intensity <sup>†</sup> at Week 4	Sample Size	198	187	
	Mean outcome	43	50	Δ=7†† (2,12)
	95% confidence interval			
Study 2 (Hand) Pain Intensity <sup>†</sup> at Week 6	Sample Size	198	187	
	Mean outcome	40	47	Δ=7†† (1,13)
	95% confidence interval			

\* WOMAC = Western Ontario McMaster Osteoarthritis Index.

† Scale from 0 (best) to 100 (worst).

† Difference is adjusted using an analysis of covariance (ANCOVA) model with main effects of treatment and center and baseline covariate.

†† Difference is adjusted using an analysis of covariance (ANCOVA) model with main effects of treatment, center, indicator of pain in the CMC-1 joint, and baseline as a covariate, and the treatment-by-CMC-1 indicator interaction. Difference is weighted by size of CMC-1 strata.

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

Diclofenac sodium topical gel, 1% is available in tubes containing 100 g of the topical gel in each tube. Each tube contains diclofenac sodium in a gel base (10 mg of diclofenac sodium per gram of gel or 1%).

100 g tube NDC 65162-833-66

**Storage**  
Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Keep from freezing. Store the dosing card with your diclofenac sodium topical gel.

#### 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (NSAIDs Medication Guide and Instructions for Use) prior to using diclofenac sodium topical gel, 1%.

Inform patients of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy.

#### Cardiovascular Effects

Diclofenac sodium topical gel, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Advise patients of the importance of this follow-up [see Warnings and Precautions (5.1)].

#### Gastrointestinal Effects

Diclofenac sodium topical gel, like other NSAIDs, can cause GI discomfort and, rarely, more serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding. Instruct patients to ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up [see Warnings and Precautions (5.2)].

#### Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy with diclofenac sodium topical gel and seek immediate medical therapy [see Warnings and Precautions (5.3)].

#### Adverse Skin Reactions

Diclofenac sodium topical gel, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalization and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching. Instruct patients to ask for medical advice when observing any indicative signs or symptoms [see Warnings and Precautions (5.8)].

Advise patients to stop diclofenac sodium topical gel immediately if they develop any type of rash and contact their physicians as soon as possible.

Instruct patients not to apply diclofenac sodium topical gel to open skin wounds, infections, inflammations, or exfoliative dermatitis, as it may affect absorption and tolerability of the drug.

Instruct patients to avoid concomitant use of diclofenac sodium topical gel with other topical products, including sunscreens, cosmetics, lotions, moisturizers, and insect repellents. Concomitant use may result in skin reactions or change the absorption of diclofenac sodium topical gel.

Instruct patients to minimize or avoid exposure of treated areas to natural or artificial sunlight.

#### Weight Gain and Edema

Instruct patients to report to their physicians signs or symptoms of unexplained weight gain or edema following treatment with diclofenac sodium topical gel [see Warnings and Precautions (5.5)].

#### Anaphylactoid Reactions

Inform patients of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help [see Warnings and Precautions (5.7)].

#### Effects During Pregnancy

In late pregnancy, as with other NSAIDs, diclofenac sodium topical gel should be avoided because it will cause premature closure of the ductus arteriosus [see Warnings and Precautions (5.9)].

#### Eye Exposure

Instruct patients to avoid contact of diclofenac sodium topical gel with the eyes and mucosa, although not studied, should be avoided. Patients should be advised that if eye contact occurs, they should immediately wash out the eye with water or saline and consult a physician if irritation persists for more than an hour.

#### Proper Application

Instruct patients how to use the dosing card to measure the proper dose of diclofenac sodium topical gel, 1% to apply. If the patient loses their dosing card, instruct them that they can call 1-877-835-5472 to request a replacement dosing card or ask their pharmacist for a new dosing card. Instruct patients how to correctly measure the 2.25 inches (2 g) dose or 4.5 inches (4 g) dose while waiting for a replacement dosing card.

Comments or Questions?  
Call toll-free 1-877-835-5472

Manufactured by:

Anneal Pharmaceuticals

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Distributed by:

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Glasgow, KY 42141

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### Medication Guide For Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (See the end of this Medication Guide for a list of prescription NSAID medicines.)

**What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?**

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death.

This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

- can happen without warning symptoms
- may cause death

**The chance of a person getting an ulcer or bleeding increases with:**

- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

**What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?**

NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:

- different types of arthritis
- menstrual cramps and other types of short-term pain

**Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?**

**Do not take an NSAID medicine:**

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine

- for pain right before or after heart bypass surgery

**Tell your healthcare provider:**

- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**
- if you are breast-feeding. **Talk to your healthcare provider.**

**What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?**

**Serious side effects include:**

- heart attack
- stroke
- high blood pressure
- heart failure from body swelling (fluid retention)
- kidney problems including kidney failure
- bleeding and ulcers in the stomach and intestine
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- liver problems including liver failure
- asthma attacks in people who have asthma

**Other side effects include:**

- stomach pain
- constipation
- diarrhea
- gas
- heartburn
- nausea
- vomiting
- dizziness

**Get emergency help right away if you have any of the following symptoms:**

- shortness of breath or trouble breathing
- chest pain
- slurred speech
- weakness in one part or side of your body
- swelling of the face or throat

**Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:**

- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

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

**Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):**

- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some of these NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

#### NSAID medicines that need a prescription

Generic Name	Tradename
Celecoxib	Celebrex <sup>®</sup>
Diclofenac	Flector <sup>®</sup> , Cataflam <sup>®</sup> , Cambia <sup>®</sup> , Voltaren <sup>®</sup> , Voltaren gel <sup>®</sup> , Arthrotec <sup>®</sup> (combined with misoprostol), Pennsaid <sup>®</sup> , Zipsor <sup>®</sup> , Zorvolex <sup>™</sup>
Diflunisal	Dolobid <sup>®</sup>
Etodolac	Lodine <sup>®</sup> , Lodine <sup>®</sup> XL
Fenoprofen	Nalfon <sup>®</sup> , Nalfon <sup>®</sup> 200
Flurbiprofen	Ansaid <sup>®</sup>
Ibuprofen	Motrin <sup>®</sup> , Tab-Profen <sup>®</sup> , Vicoprofen <sup>®</sup> * (combined with hydrocodone), Combunox <sup>™</sup> (combined with oxycodone), Duexis <sup>®</sup> (combined with famotidine)
Indomethacin	Indocin <sup>®</sup> , Indocin <sup>®</sup> SR, Indo-Lemmon <sup>™</sup> , Indomethagan <sup>™</sup>
Ketoprofen	Oruvail <sup>®</sup> , Nexcede <sup>®</sup>
Ketorolac	Toradol <sup>®</sup> , Sprix <sup>®</sup>
Mefenamic Acid	Ponstel <sup>®</sup>
Meloxicam	Mobic <sup>®</sup>
Nabumetone	Relafen <sup>®</sup>
Naproxen	Naprosyn <sup>®</sup> , Anaprox <sup>®</sup> , Anaprox <sup>®</sup> DS, EC-Naproxyn <sup>®</sup> , Naprelan <sup>®</sup> , Naprapac <sup>®</sup> (co-packaged with lansoprazole), Treximet <sup>®</sup> (combined with sumatriptan succinate), and Vimovo <sup>®</sup> (combined with esomeprazole magnesium)
Oxaprozin	Daypro <sup>®</sup>
Piroxicam	Feldene <sup>®</sup>
Sulindac	Clinoril <sup>®</sup>
Tolmetin	Tolectin <sup>®</sup> , Tolectin <sup>®</sup> DS, Tolectin <sup>®</sup> 600

\* Vicoprofen<sup>®</sup> contains the same dose of ibuprofen as over-the-counter (OTC) NSAID, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long-term continuous use may increase the risk of heart attack or stroke.

**This Medication Guide has been approved by the U.S. Food and Drug Administration.**

#### Instructions for Use

**Diclofenac (dye-KLOE-fen-ak) Sodium Topical Gel, 1%**

**Important: Use the dosing card that is inside the diclofenac sodium topical gel carton to correctly measure each dose. The dosing card is re-usable. Do not throw the dosing card away. Before you use diclofenac sodium topical gel for the first time, your healthcare provider or pharmacist should show you how to correctly measure your dose using the dosing card.**

Read this Instructions for Use before you start using diclofenac sodium topical gel and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Your healthcare provider has prescribed diclofenac sodium topical gel to help relieve arthritis pain in some of your joints. Diclofenac sodium topical gel may be used to treat arthritis pain in the arms (hands, wrists, and elbows) and in the legs (feet, ankles, and knees). It is not known if diclofenac sodium topical gel is safe and effective if used on your spine, hips, or shoulders.

- Use diclofenac sodium topical gel exactly how your healthcare provider prescribes it for you. Do not apply diclofenac sodium topical gel anywhere other than where your healthcare provider tells you to.
- **Do not use more than a total of 32 grams of diclofenac sodium topical gel each day. If you add up the amount of diclofenac sodium topical gel as directed by your healthcare provider, it should not be more than 32 grams in one day.**

**The dose for your hands, wrists, or elbows is 2 grams of diclofenac sodium topical gel each time you apply it.**

- Apply diclofenac sodium topical gel 4 times a day (a total of 8 grams each day).

Do not apply more than 8 grams each day to any one of your affected hands, wrists, or elbows.

**The dose for your feet, ankles, or knees is 4 grams of diclofenac sodium topical gel each time you apply it.**

- Apply diclofenac sodium topical gel 4 times a day (a total of 16 grams each day).

Do not apply more than 16 grams each day to any one of your affected feet, ankles, or knees.

**Some examples of diclofenac sodium topical gel application include:**

- If you use 2 grams of diclofenac sodium topical gel on one hand, 4 times a day, your total dose for one day is 8 grams.
- If you use 4 grams of diclofenac sodium topical gel on one knee, 4 times a day, your total dose for one day is 16 grams.
- Your total dose for one day, treating one hand and one knee, is 8 grams plus 16 grams, which equals 24 grams of diclofenac sodium topical gel.

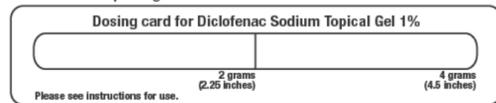


Figure A

- Before you use a new tube of diclofenac sodium topical gel for the first time, open the foil seal that covers the tube opening by using the spiked top of the cap. Remember to remove the dosing card from the carton to measure your dose (See Figure A).
- Apply diclofenac sodium topical gel to clean, dry skin that does not have any cuts, open wounds, infections, or rashes.
- Do not use heating pads or apply bandages to where you have applied diclofenac sodium topical gel.
- Avoid exposing skin where you apply diclofenac sodium topical gel to sunlight and artificial light, such as tanning booths.
- Do not use sunscreens, cosmetics, lotions, moisturizers, insect repellents, or other topical medicines on the same skin areas where you have applied diclofenac sodium topical gel.
- Do not get diclofenac sodium topical gel in your eyes, nose, or mouth. Diclofenac sodium topical gel is only to be used on your skin (topical use). If you get diclofenac sodium topical gel in your eyes, rinse your eyes right away with water or saline. Talk with your healthcare provider if eye irritation lasts for more than one hour.

**What if I miss a dose?**

- If you miss a dose of diclofenac sodium topical gel, continue with your next scheduled dose using the prescribed amount of diclofenac sodium topical gel. **Do not double the dose.**

**Applying 2 grams (2 g) of diclofenac sodium topical gel to hands, wrists, or elbows:**

**Step 1.** Remove the dosing card that is attached inside the diclofenac sodium topical gel carton. Use the dosing card to correctly measure each dose of diclofenac sodium topical gel. To measure the correct amount of diclofenac sodium topical gel, place the dosing card on a flat surface so that you can read the print. If the print is backwards, flip dosing card over (see Figure A). If you lose or misplace your dosing card, you can ask your pharmacist for a new one or call 1-877-835-5472. Ask your healthcare provider or pharmacist to show you how to correctly measure your dose of diclofenac sodium topical gel while you are waiting to receive your new dosing card.

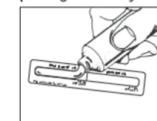


Figure B



Figure C



Figure D

**Step 2.** Squeeze diclofenac sodium topical gel onto the dosing card evenly, up to the 2 g line (a 2.25 inch length of gel). Make sure that the gel covers the 2 g area of the dosing card (see Figure B). Put the cap back on the tube of diclofenac sodium topical gel. Ask your healthcare provider or pharmacist if you are not sure how to correctly measure your dose of diclofenac sodium topical gel.

**Step 3.** Apply the gel to your hand, wrist, or elbow. You can use the dosing card to apply the gel (see Figure C). Then, use your hands to gently rub the gel into the skin (see Figure D). Do not share your dosing card with another person. Make sure to cover the entire affected hand, wrist, or elbow with the gel. Remember that the hand includes the palm of your hand, the top of your hand, and your fingers.

**Step 4.** After using the dosing card, hold end with fingertips, rinse and dry. **Store dosing card until next use.** Do not shower or bathe for at least 1 hour after applying diclofenac sodium topical gel. Do not wash your treated hands for at least 1 hour after applying the diclofenac sodium topical gel.

**Step 5.** After applying diclofenac sodium topical gel, wait 10 minutes before covering the treated skin with gloves or clothing.

**Applying 4 grams (4 g) of diclofenac sodium topical gel to feet, ankles, or knees:**

**Step 1.** Refer to **Step 1** above.

**Step 2.** Squeeze diclofenac sodium topical gel onto the dosing card evenly up to the 4 g line (a 4.5 inch length of gel), making sure the gel covers the 4 g area of the dosing card (see Figure E). Put the cap back on the tube of diclofenac sodium topical gel. Ask your healthcare provider or pharmacist if you are not sure how to correctly measure your dose of diclofenac sodium topical gel.

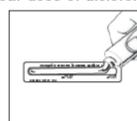


Figure E



Figure F



Figure G

**Step 3.** Apply diclofenac sodium topical gel to your foot, ankle, or knee. You can use the dosing card to apply the gel (see Figure F). Then, use your hands to gently rub the gel into the skin (see Figure G). Do not share your dosing card with another person. Make sure to cover your entire foot, ankle, or knee area with the gel. For example, cover the skin above, below, inside and outside the knee cap. Remember that the foot includes the sole of your foot, the top of your foot, and your toes.

**Refer to Steps 4 and 5 above.** Wash your hands after applying diclofenac sodium topical gel to your foot, ankle, or knee.

**What are the ingredients in diclofenac sodium topical gel?**

**Active ingredient:** diclofenac sodium, USP

**Inactive ingredients:** carbomer homopolymer Type C, cocoyl caprylocaprate, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, and strong ammonia solution.

**How should I store diclofenac sodium topical gel?**

Store at 20°C to 25°C (68°F to 77°F). Do not freeze diclofenac sodium topical gel. Store the dosing card with your diclofenac sodium topical gel.

**Keep diclofenac sodium topical gel, the dosing card, and all medicines out of the reach of children.**

This Medication Guide and Instructions for Use have been approved by the U.S. Food and Drug Administration.

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**Medication Guide For Non-Steroidal  
Anti-Inflammatory Drugs (NSAIDs)**  
(See the end of this Medication Guide  
for a list of prescription NSAID medicines.)

**What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?**

**NSAID medicines may increase the chance of a heart attack or stroke that can lead to death.**

This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

**NSAID medicines should never be used right before or after a heart surgery called a “coronary artery bypass graft (CABG).”**

**NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:**

- can happen without warning symptoms
- may cause death

**The chance of a person getting an ulcer or bleeding increases with:**

- taking medicines called “corticosteroids” and “anticoagulants”
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

**NSAID medicines should only be used:**

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

**What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?**

NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:

- different types of arthritis
- menstrual cramps and other types of short-term pain

**Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?**

**Do not take an NSAID medicine:**

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

**Tell your healthcare provider:**

- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**
- if you are breast-feeding. **Talk to your healthcare provider.**

**What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?**

<b>Serious side effects include:</b> <ul style="list-style-type: none"><li>• heart attack</li><li>• stroke</li><li>• high blood pressure</li><li>• heart failure from body swelling (fluid retention)</li><li>• kidney problems including kidney failure</li><li>• bleeding and ulcers in the stomach and intestine</li><li>• low red blood cells (anemia)</li><li>• life-threatening skin reactions</li><li>• life-threatening allergic reactions</li><li>• liver problems including liver failure</li><li>• asthma attacks in people who have asthma</li></ul>	<b>Other side effects include:</b> <ul style="list-style-type: none"><li>• stomach pain</li><li>• constipation</li><li>• diarrhea</li><li>• gas</li><li>• heartburn</li><li>• nausea</li><li>• vomiting</li><li>• dizziness</li></ul>
--	---

**Get emergency help right away if you have any of the following symptoms:**

- shortness of breath or trouble breathing
- chest pain
- slurred speech
- weakness in one part or side of your body
- swelling of the face or throat

**Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:**

- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

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

**Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):**

- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some of these NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

**NSAID medicines that need a prescription**

<b>Generic Name</b>	<b>Tradename</b>
Celecoxib	Celebrex®
Diclofenac	Flector®, Cataflam®, Cambia®, Voltaren®, Voltaren gel®, Arthrotec® (combined with misoprostol), Pennsaid®, Zipsor®, Zorvolex™
Diflunisal	Dolobid®
Etodolac	Lodine®, Lodine® XL
Fenoprofen	Nalfon®, Nalfon® 200
Flurbiprofen	Ansaid®
Ibuprofen	Motrin®, Tab-Profen®, Vicoprofen®* (combined with hydrocodone), Combunox™ (combined with oxycodone), Duexis® (combined with famotidine)
Indomethacin	Indocin®, Indocin® SR, Indo-Lemmon™, Indomethagan™
Ketoprofen	Oruvail®, Nexcede®
Ketorolac	Toradol®, Sprix®
Mefenamic Acid	Ponstel®
Meloxicam	Mobic®
Nabumetone	Relafen®
Naproxen	Naprosyn®, Anaprox®, Anaprox® DS, EC-Naproxyn®, Naprelan®, Naprapac® (co-packaged with lansoprazole), Treximet® (combined with sumatriptan succinate), and Vimovo® (combined with esomeprazole magnesium)
Oxaprozin	Daypro®
Piroxicam	Feldene®
Sulindac	Clinoril®
Tolmetin	Tolectin®, Tolectin® DS, Tolectin® 600

\* Vicoprofen® contains the same dose of ibuprofen as over-the-counter (OTC) NSAID, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long-term continuous use may increase the risk of heart attack or stroke.

**This Medication Guide has been approved by the U.S. Food and Drug Administration.**

Rev. 04-2015-00

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 208077Orig1s000**

**LABELING REVIEWS**

## LABELING REVIEW

Division of Labeling Review  
Office of Regulatory Operations  
Office of Generic Drugs (OGD)

Center for Drug Evaluation and Research (CDER)

<b>Date of This Review</b>	9/4/15
<b>ANDA Number(s)</b>	208077
<b>Review Number</b>	3
<b>Applicant Name</b>	Amneal Pharmaceuticals
<b>Established Name &amp; Strength(s)</b>	Diclofenac Sodium Topical Gel, 1%
<b>Proposed Proprietary Name</b>	NA
<b>Submission Received Date</b>	8/27/15 (amendment)
<b>Labeling Reviewer</b>	Esther Kim, Pharm.D.
<b>Labeling Team Leader</b>	Adolph Vezza
<b>Review Conclusion</b>	
<input type="checkbox"/> ACCEPTABLE – No Comments.	
<input checked="" type="checkbox"/> ACCEPTABLE – Include Post Approval Comments	
<input type="checkbox"/> Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.	
<small>*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.</small>	
<input type="checkbox"/> On Policy Alert List	

## **1. LABELING COMMENTS**

### **1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT**

None

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling 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](http://service.govdelivery.com/service/subscribe.html?code=USFDA_17)

### **1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE**

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated 8/27/15.

### **1.3 POST APPROVAL REVISIONS**

These comments will NOT be sent to the applicants at this time.

These comments will be addressed post approval (in the first labeling supplement review).

#### **1. PRESCRIBING INFORMATION**

- a. HIGHLIGHTS OF PRESCRIBING INFORMATION: Center the title of the WARNING box and the sentence beneath it [*“See full prescribing ...”*].
- b. FULL PRESCRIBING INFORMATION/12 CLINICAL PHARMACOLOGY/12.3 Pharmacokinetics: In the key under Table 2, revise “AUC<sub>024</sub>” to read “AUC<sub>0-24</sub>”.

**2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT**

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

APPEARS THIS WAY ON  
ORIGINAL

## LABELING HISTORY:

- **12/19/14:** Original ANDA 208077 received by FDA.
- **3/3/15:** Labeling Review #1 finalized with deficiencies for Container, Carton, Dosing Card, Prescribing Information, Medication Guide and Patient Instructions.

The comments below are from the labeling review C1 based on the submission date 12/19/14:

### 1. CONTAINER LABEL

- a. Please add “Use the dosing card attached inside carton” to the principal display panel (PDP).
- b. Please add “Store the dosing card with your diclofenac sodium topical gel, 1%.” after the storage statement in accordance with the reference listed drug (RLD).
- c. Please remove “w/w” from the established name.
- d. Please provide the space for the lot number and expiration date.

### 2. CARTON LABELING

- a. Please add “Use the dosing card attached inside the carton” to the PDP.
- b. Please add “Store the dosing card with your diclofenac sodium topical gel, 1%.” after the storage statement in accordance with the RLD.
- c. Please remove “w/w” from the established name on the PDP and back label.

### 3. DOSING CARD

- a. Please add “Dosing card for” prior to the established name.
- b. Please add “(2.25 inches)” and “(4.5 inches)” directly below “2 grams” and “4 grams”, respectively.
- c. Please revise “Please see patient medication guide for instructions.” to read “Please see instructions for use.”

### 4. PRESCRIBING INFORMATION

- a. Revise your labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Voltaren® Gel, NDA 022122/S-007, approved 11/25/14.
- b. HIGHLIGHTS OF PRESCRIBING INFORMATION: Please revise the first paragraph to read: “These highlights do not include all the information needed to use diclofenac sodium topical gel safely and effectively. See full prescribing information for diclofenac sodium topical gel.
- c. HIGHLIGHTS OF PRESCRIBING INFORMATION/Title: Please revise to read: “**DICLOFENAC sodium topical gel, 1%, for topical use only**”.
- d. HIGHLIGHTS OF PRESCRIBING INFORMATION/DOSAGE AND ADMINISTRATION: Please revise the first sentence to read: “Total dose should not exceed 32 g per day, over all affected joints.”
- e. HIGHLIGHTS OF PRESCRIBING INFORMATION/ Revision date: The date in this section does not correlate with the date at the end of the insert. Please comment and/or revise this date.
- f. FULL PRESCRIBING INFORMATION/5 WARNINGS AND PRECAUTIONS/5.6 Renal Effects: In the third paragraph of this subsection, please revise “...dosedependent...” to read “...dose-dependent...”.
- g. FULL PRESCRIBING INFORMATION/ 5 WARNINGS AND PRECAUTIONS/5.10 Corticosteroid Treatment: Please revise the second sentence of this subsection to read: “Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness.”
- h. FULL PRESCRIBING INFORMATION/ 5 WARNINGS AND PRECAUTIONS/5.13 Preexisting Asthma: Please revise the second sentence to read: “The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal.”
- i. FULL PRESCRIBING INFORMATION/12 CLINICAL PHARMACOLOGY/12.3 Pharmacokinetics: Directly below Table 2, please revise “...tmax time of Cmax...” to read “tmax = time of Cmax”.

- j. FULL PRESCRIBING INFORMATION/13 NONCLINICAL TOXICOLOGY/13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: Please revise the first sentence to read: “Carcinogenicity studies in mice and rats administered diclofenac sodium as a dietary constituent for 2 years at doses up to 2 mg/kg/day resulted in no significant increases in tumor incidence corresponding to a human equivalent dose approximately 0.5- and 1-fold (mouse and rat, respectively) of the maximum human topical dose of diclofenac sodium topical gel (based on bioavailability and body surface area comparison).”
- k. FULL PRESCRIBING INFORMATION/16 HOW SUPPLIED: Please add the following statement: “Store the dosing card with your diclofenac sodium topical gel.” after the storage statement.

5. MEDICATION GUIDE (MG)

- a. Revise your Medication Guide (MG) to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Voltaren® Gel, NDA 022122/S-007, approved 11/25/14.
- b. Ensure a sufficient number of Medication Guides is available for dispensing and distribution to patients receiving a prescription for your drug product, per 21 CFR 208.24.
- c. **Who should not take Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?/Tell your healthcare provider:** Please revise the third bullet to read: “if you are pregnant. NSAID medicines should not be used by pregnant women late in their pregnancy.”
- d. **NSAID medicines that need a prescription** chart: Please add “®” to Flector, Voltaren gel, Arthrotec, Zipsor, Duexis, Oruvail, Toradol, Treximet, and Vimovo. Please relocate the “®” placed after Tolectin DS to the space after Tolectin. Lastly, please add “™” to Zorvolex.
- e. Please submit final printed labeling of the stand-alone MG; and ensure the font size is at least 10 font type.

6. PATIENT INSTRUCTIONS FOR USE

Revise your patient labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Voltaren® Gel, NDA 022122/S-007, approved 11/25/14.

- **4/3/15:** An Easily Correctable Deficiency (ECD) communication as sent to the applicant.
- **4/14/15:** Resubmission in response to the ECD.
- **6/25/15:** Labeling Review #2 was finalized with deficiencies for Container, Carton, and Prescribing Information.

The comments below are from the labeling review C2 based on the submission date 4/14/15:

1. CONTAINER LABEL

Please revise “Each gram contains 1% diclofenac sodium, USP.” to read “Each gram contains 1% w/w diclofenac sodium, USP.”

2. CARTON LABELING

Please refer to comment 1 above.

3. PRESCRIBING INFORMATION

a. **HIGHLIGHTS OF PRESCRIBING INFORMATION:** Due to a recent change in policy, revise the presentation of the established name to appear in all upper case letters, in the following text as such: “These highlights do not include all the information needed to use DICLOFENAC SODIUM TOPICAL GEL safely and effectively. See full prescribing information for DICLOFENAC SODIUM TOPICAL GEL.”

b. **HIGHLIGHTS OF PRESCRIBING INFORMATION:** The product title, immediately above the

initial U.S. approval date, should be revised as below to comply with PLR format requirements.

DICLOFENAC SODIUM topical gel, 1%, for topical use only

c. HIGHLIGHTS OF PRESCRIBING INFORMATION: Revise the subsection title to read “DOSAGE FORM AND STRENGTH”.

d. FULL PRESCRIBING INFORMATION/CONTENTS: Please revise “3 DOSAGE FORMS AND STRENGTHS” to read “3 DOSAGE FORM AND STRENGTH”.

e. FULL PRESCRIBING INFORMATION/2 DOSAGE AND ADMINISTRATION/2.1 Dosing Card: Please revise “2.1 Dosing Card [See the Instructions for Use]” to read “2.1 Dosing Card [See the patient Instructions for Use]”.

f. FULL PRESCRIBING INFORMATION/3 DOSAGE FORM AND STRENGTH: Please revise to read “3 DOSAGE FORM AND STRENGTH”. [Note the revision of “FORMS” to read “FORM” and “STRENGTHS” to read “STRENGTH”.]

g. FULL PRESCRIBING INFORMATION/16 HOW SUPPLIED, first sentence: Please revise to read: “Diclofenac sodium topical gel 1% is available....”

- **8/21/15:** An ECD communication was sent to the applicant.
- **8/27/15:** Resubmission in response to the ECD. This amendment is the subject of this review.

From the 8/27/15 cover letter regarding labeling deficiencies and recommendations:

## **LABELING DEFICIENCIES:**

### **1. CONTAINER LABEL**

#### **FDA’s Comment # 1**

Please revise “Each gram contains 1% diclofenac sodium, USP.” to read “Each gram contains 1% w/w diclofenac sodium, USP.”

#### **Amneal’ Response:**

Amneal acknowledges the Agency’s comment.

As recommended by the agency, Amneal has revised the container label to read as “*Each gram contains 1% w/w diclofenac sodium, USP.*” Please refer to **Module 1.14.2.1** for the revised final container label.

### **2. CARTON LABELING**

#### **FDA’s Comment # 2:**

Please refer to comment 1 above.

#### **Amneal’ Response:**

Amneal acknowledges the Agency’s comment.

As recommended by the agency, Amneal has revised the carton label to read as “*Each gram contains 1% w/w*”

*diclofenac sodium, USP*". Please refer to **Module 1.14.2.1** for the revised final carton label.

### 3. PRESCRIBING INFORMATION

#### FDA's Comment # 3a, 3b and 3c :

**a. HIGHLIGHTS OF PRESCRIBING INFORMATION:** Due to a recent change in policy, revise the presentation of the established name to appear in all upper case letters, in the following text as such: "These highlights do not include all the information needed to use DICLOFENAC SODIUM TOPICAL GEL safely and effectively. See full prescribing information for DICLOFENAC SODIUM TOPICAL GEL."

**b. HIGHLIGHTS OF PRESCRIBING INFORMATION:** The product title, immediately above the initial U.S. approval date, should be revised as below to comply with PLR format requirements. **DICLOFENAC SODIUM topical gel, 1%, for topical use only**

**c. HIGHLIGHTS OF PRESCRIBING INFORMATION:** Revise the subsection title to read "DOSAGE FORM AND STRENGTH".

#### Amneal' Response:

Amneal acknowledges the Agency's comment.

As recommended by the agency, Amneal has revised the "HIGHLIGHTS OF PRESCRIBING INFORMATION" section as follows:

- The presentation of the established name in the first paragraph of HIGHLIGHTS OF PRESCRIBING INFORMATION is revised to read as *"These highlights do not include all the information needed to use DICLOFENAC SODIUM TOPICAL GEL safely and effectively. See full prescribing information for DICLOFENAC SODIUM TOPICAL GEL."*
- The product title, immediately above the initial U.S. approval date is revised as *'DICLOFENAC SODIUM topical gel, 1%, for topical use only'* to comply as per the requirements of PLR format.
- The subsection title has been revised to read as "DOSAGE FORM AND STRENGTH".

#### FDA's Comment # 3d-3g:

**d. FULL PRESCRIBING INFORMATION/CONTENTS:** Please revise "3 DOSAGE FORMS AND

**STRENGTHS” to read “3 DOSAGE FORM AND STRENGTH”.**

- e. **FULL PRESCRIBING INFORMATION/2 DOSAGE AND ADMINISTRATION/2.1 Dosing Card: Please revise “2.1 Dosing Card [See the Instructions for Use]” to read “2.1 Dosing Card [See the patient Instructions for Use]”.**
- f. **FULL PRESCRIBING INFORMATION/3 DOSAGE FORM AND STRENGTH: Please revise to read “3 DOSAGE FORM AND STRENGTH”. [Note the revision of “FORMS” to read “FORM” and “STRENGTHS” to read “STRENGTH”.]**
- g. **FULL PRESCRIBING INFORMATION/16 HOW SUPPLIED, first sentence: Please revise to read: “Diclofenac sodium topical gel 1% is available....”**

**Amneal’ Response:**

Amneal acknowledges the Agency’s comments.

As recommended by the Agency, Amneal has revised the FULL PRESCRIBING INFORMATION as per the above agency’s comments from (#3d, #3e, #3f & #3g) to reflect all the changes.

**Reviewer Comments:**

The applicant has satisfactorily addressed the deficiencies and recommendations for Container, Carton, and Prescribing Information.

**2.1 CONTAINER AND CARTON LABELS**

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?  
**NO**

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

**Reviewer Comments:**

None

**2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW**

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

**Reviewer Comments:**

None

**3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT**

**3.1 REGULATORY INFORMATION**

**Are there any pending issues in DLR's [Repository](#) files? NO**

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

**Is the drug product listed in the Policy Alert Tracker on [OGD's SharePoint](#)? NO**

If Yes, please explain.

**3.2 MODEL PRESCRIBING INFORMATION**

**Table 1: Review Model Labeling for Prescribing Information and Patient Labeling  
(Check the box used as the Model Labeling)**

**MOST RECENTLY APPROVED NDA MODEL LABELING**

*(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)*

**NDA# /Supplement# (S-000 if original):** NDA 022122/S-009

**Supplement Approval Date:** 5/11/15

**Proprietary Name:** Voltaren Gel

**Established Name:** diclofenac sodium topical gel

**Description of Supplement:** This supplement proposes to maintain the currently primary packaging of (b) (4)

The cartons will match the current existing cartons.

**MOST RECENTLY APPROVED ANDA MODEL LABELING**

**ANDA#/Supplement# (S-000 if original):** 41T

**Supplement Approval Date:** 41T

**Proprietary Name:** 41T

**Established Name:** 41T

**Description of Supplement:**

**TEMPLATE (e.g., BPCA, PREA, Carve-out):** 41T

**OTHER (Describe):**

S-007 is a labeling supplement approved 11/25/14 and is the model for the Prescribing Information.

**Reviewer Assessment:**

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **YES**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

**Reviewer Comments:**

**HIGHLIGHTS OF PRESCRIBING INFORMATION:**

We will request the applicant center the title of the WARNING box and the sentence beneath it ["See full prescribing ..."].

**FULL PRESCRIBING INFORMATION:**

12 Pharmacokinetics: In the key under Table 2, we will request the applicant revise “AUC<sub>0-24</sub>” to read “AUC<sub>0-24</sub>” as a post approval revision.

### 3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: DARRTS 1/18/15 submission]

For (b) (4) tube:

Each gram contains 1% w/w diclofenac sodium.  
**Inactive ingredients:** carbomer homopolymer Type C, cocoyl caprylocaprate, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, and strong ammonia solution.  
 For topical use only. Not for ophthalmic use. **Keep out of reach of children.**  
**Dosage:** Apply to skin over the affected area four times daily. Use the dosing card provided to measure the amount of Voltaren® Gel to be applied. See accompanying prescribing information.  
**To open tube:** Unscrew cap, puncture seal with pointed end of cap.

Store at 20°C to 25°C (68°F to 77°F). Keep from freezing. Store the dosing card with your Voltaren® Gel.  
 Comments or Questions? Call toll free 1-800-452-0051

**Endo** Pharmaceuticals Inc. Malvern, PA 19355  
 Manufactured for: Novartis Consumer Health, Inc. Parsippany, NJ 07054  
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**NOVARTIS** NOVARTIS  
 Manufactured by: Novartis Pharma Produktions GmbH Wehr, Germany

3 63481 68447 4

See Medication Guide and Patient Instructions Inside of Carton  
 NDC 63481-684-47

**Voltaren® Gel**  
 (diclofenac sodium topical gel) 1%  
 For Topical Use Only Rx only

Net Wt 100 g Use the Dosing Card Attached Inside Carton

LOT / EXP

From DARRTS (6/7/14) for (b) (4) tubes, carton, and dosing card:

See Medication Guide and Patient Instructions Inside of Carton  
 NDC 63481-684-47

**Voltaren® Gel**  
 (diclofenac sodium topical gel) 1%  
 For Topical Use Only Rx only

Net Wt 100 g Use the Dosing Card Attached Inside Carton

Each gram contains 1% w/w diclofenac sodium.  
**Inactive ingredients:** carbomer homopolymer Type C, cocoyl caprylocaprate, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, and strong ammonia solution.  
 For topical use only. Not for ophthalmic use. **Keep out of reach of children.**  
**Dosage:** Apply to skin over the affected area four times daily. Use the dosing card provided to measure the amount of Voltaren® Gel to be applied. See accompanying prescribing information.  
**To open tube:** Unscrew cap, puncture seal with pointed end of cap.

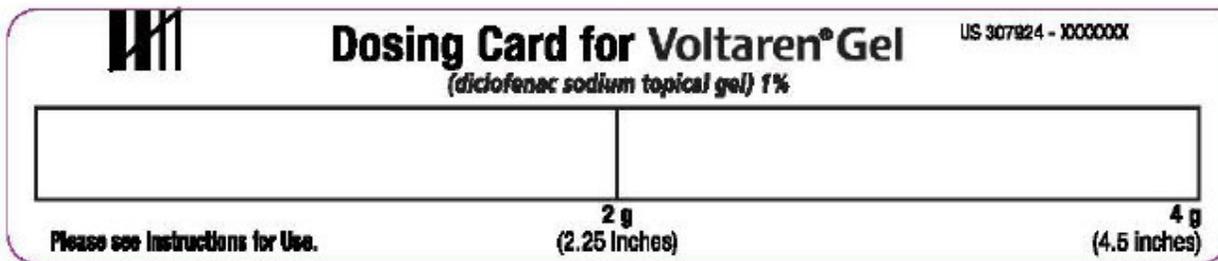
Store at 20°C to 25°C (68°F to 77°F). Keep from freezing. Store the dosing card with your Voltaren® Gel.  
 Comments or Questions? Call toll free 1-800-452-0051

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**NOVARTIS** NOVARTIS  
 Manufactured by: Novartis Pharma Produktions GmbH Wehr, Germany

3 63481 68447 4

LOT / EXP



### 3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	9/4/2015	NO	NA	NA
PF	9/4/2015	NO	NA	NA

**Reviewer Comments:**

None

### 3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 9/4/2015.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
NA						

**Reviewer Assessment:**

Is the applicant's "patent carve out" acceptable? **NA**

**Reviewer Comments:**

There are no unexpired patents for this product in the Orange Book Database.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA					

**Reviewer Assessment:**

Is the applicant's "exclusivity carve out" acceptable? **NA**

**Reviewer Comments:**

There is no unexpired exclusivity for this product.

### 4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

**Reviewer Assessment:**

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**

Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**

Are there changes to the manufacturer/distributor/packer statements? **NO**

If yes, then comment below in Tables 5, 6, and 7.

**Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)**

Previous Labeling Review	Currently Proposed	Assessment
Diclofenac sodium topical gel, 1% also contains carbomer homopolymer Type C, cocoyl caprylocaprates, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, and strong ammonia solution.	Diclofenac sodium topical gel, 1% also contains carbomer homopolymer Type C, cocoyl caprylocaprates, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, and strong ammonia solution.	No change

**Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products**

Previous Labeling Review	Currently Proposed	Assessment
Diclofenac sodium topical gel, 1% w/w is available in tubes containing 100 g of the topical gel in each tube. Each tube contains diclofenac sodium in a gel base (10 mg of diclofenac sodium per gram of gel or 1%). 100 g tube NDC 65162-833-66 Storage Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Keep from freezing. Store the dosing card with your diclofenac sodium topical gel.	Diclofenac sodium topical gel, 1% is available in tubes containing 100 g of the topical gel in each tube. Each tube contains diclofenac sodium in a gel base (10 mg of diclofenac sodium per gram of gel or 1%). 100 g tube NDC 65162-833-66 Storage Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Keep from freezing. Store the dosing card with your diclofenac sodium topical gel.	The applicant has revised the first sentence as requested in Labeling Review #2. This is acceptable.

**Table 7: Manufacturer/Distributor/Packer Statements**

Previous Labeling Review	Currently Proposed	Assessment
Manufactured by: Amneal Pharmaceuticals Piscataway, NJ 08854 Distributed by: Amneal Pharmaceuticals Glasgow, KY 42141	Manufactured by: Amneal Pharmaceuticals Piscataway, NJ 08854 Distributed by: Amneal Pharmaceuticals Glasgow, KY 42141	No change

## 5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

### Reviewer Comments:

None

## 6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

### Reviewer Comments:

None

## 7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item “Final, Draft, or “NA”. If you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	100 g	8/27/15	Satisfactory
Blister	NA			
Carton	Final	1 tube	8/27/15	Satisfactory
(Other – specify)	Final	NA	8/27/15	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Final	08-2015-00	8/27/15	Satisfactory*
Medication Guide	Final	04-2015-00	8/27/15	Satisfactory
Patient Information	Final	08-2015-00	8/27/15	Satisfactory
SPL Data Elements		8/2015	8/27/15	Satisfactory

\*Post approval revision

## LABELING REVIEW

Division of Labeling Review  
Office of Regulatory Operations  
Office of Generic Drugs (OGD)

Center for Drug Evaluation and Research (CDER)

<b>Date of This Review</b>	6/25/15
<b>ANDA Number(s)</b>	208077
<b>Review Number</b>	2
<b>Applicant Name</b>	Amneal Pharmaceuticals
<b>Established Name &amp; Strength(s)</b>	Diclofenac Sodium Topical Gel, 1%
<b>Proposed Proprietary Name</b>	NA
<b>Submission Received Date</b>	4/14/15 (amendment)
<b>Labeling Reviewer</b>	Esther Kim, Pharm.D.
<b>Labeling Team Leader</b>	Adolph Vezza
<b>Review Conclusion</b>	
<input type="checkbox"/> ACCEPTABLE – No Comments.	
<input type="checkbox"/> ACCEPTABLE – Include Post Approval Comments	
<input checked="" type="checkbox"/> <b>Minor Deficiency*</b> – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.	
<small>*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.</small>	

## 1. LABELING COMMENTS

### 1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

#### 1. CONTAINER LABEL

Please revise “Each gram contains 1% diclofenac sodium, USP.” to read “Each gram contains 1% w/w diclofenac sodium, USP.”

#### 2. CARTON LABELING

Please refer to comment 1 above.

#### 3. PRESCRIBING INFORMATION

- a. HIGHLIGHTS OF PRESCRIBING INFORMATION: Due to a recent change in policy, revise the presentation of the established name to appear in all upper case letters, in the following text as such: **“These highlights do not include all the information needed to use DICLOFENAC SODIUM TOPICAL GEL safely and effectively. See full prescribing information for DICLOFENAC SODIUM TOPICAL GEL.”**
- b. HIGHLIGHTS OF PRESCRIBING INFORMATION: The product title, immediately above the initial U.S. approval date, should be revised as below to comply with PLR format requirements. **DICLOFENAC SODIUM topical gel, 1%, for topical use only**
- c. HIGHLIGHTS OF PRESCRIBING INFORMATION: Revise the subsection title to read **“DOSAGE FORM AND STRENGTH”**.
- d. FULL PRESCRIBING INFORMATION/CONTENTS: Please revise “3 DOSAGE FORMS AND STRENGTHS” to read “3 DOSAGE FORM AND STRENGTH”.
- e. FULL PRESCRIBING INFORMATION/2 DOSAGE AND ADMINISTRATION/2.1 Dosing Card: Please revise “2.1 Dosing Card [*See the Instructions for Use*]” to read “2.1 Dosing Card [*See the patient Instructions for Use*]”.
- f. FULL PRESCRIBING INFORMATION/3 DOSAGE FORM AND STRENGTH: Please revise to read “3 DOSAGE FORM AND STRENGTH”. [Note the revision of “FORMS” to read “FORM” and “STRENGTHS” to read “STRENGTH”.]
- g. FULL PRESCRIBING INFORMATION/16 HOW SUPPLIED, first sentence: Please revise to read: “Diclofenac sodium topical gel 1% is available....”

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling 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](http://service.govdelivery.com/service/subscribe.html?code=USFDA_17)

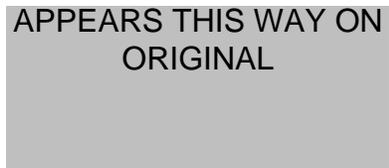
### 1.2 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.

These comments will be addressed post approval (in the first labeling supplement review).

None

APPEARS THIS WAY ON  
ORIGINAL



**2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT**

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment. Include the previous review(s) finalized date(s).

APPEARS THIS WAY ON  
ORIGINAL

## **LABELING HISTORY:**

- **12/19/14:** Original ANDA 208077 received by FDA.
- **3/3/15:** Labeling Review #1 finalized with deficiencies for Container, Carton, Dosing Card, Prescribing Information, Medication Guide and Patient Instructions.
- **4/3/15:** An Easily Correctable Deficiency (ECD) communication as sent to the applicant.
- **4/14/15:** Resubmission in response to the ECD. This amendment is the subject of this review.

From the 4/14/15 cover letter regarding labeling deficiencies and recommendations:

## **LABELING DEFICIENCIES:**

### **1. CONTAINER LABEL**

#### **FDA's Comment # 1a**

**a. Please add "Use the dosing card attached inside carton" to the principal display panel (PDP).**

#### **Amneal' Response:**

Amneal acknowledges the Agency's comment.

As recommended by the agency, Amneal has revised the container label to reflect the "Use the dosing card attached inside carton" to the principal display panel (PDP). Please refer to **Module 1.14.2.1** for the revised final container label.

For side-by-side comparison of Amneal's revised container label vs. Amneal's previously submitted container label, please refer to **Module 1.14.1.2**.

#### **FDA's Comment # 1b**

**b. Please add "Store the dosing card with your diclofenac sodium topical gel, 1%." after the storage statement in accordance with the reference listed drug (RLD).**

#### **Amneal' Response:**

Amneal acknowledges the Agency's comment.

As recommended by the agency, Amneal has included "Store the dosing card with your diclofenac sodium topical gel, 1%" after the storage statement in accordance with the reference listed drug (RLD). Please refer to **Module 1.14.2.1** for the revised final container label.

For side-by-side comparison of Amneal's revised container label vs. Amneal's previously submitted container label, please refer to **Module 1.14.1.2**.

#### **FDA's Comment # 1c and 1d**

**c. Please remove "w/w" from the established name.**

**d. Please provide the space for the lot number and expiration date.**

#### **Amneal' Response:**

Amneal acknowledges the Agency's comments.

As recommended by the agency, Amneal has revised the container labels to remove the "w/w" from the established name and provided the space for the Lot number and expiration date. Please refer to **Module 1.14.2.1** for the revised final container label.

For side-by-side comparison of Amneal's revised container label vs. Amneal's previously submitted container label, please refer to **Module 1.14.1.2**.

### **2. CARTON LABELING**

#### **FDA's Comment # 2a:**

**a. Please add "Use the dosing card attached inside the carton" to the PDP.**

#### **Amneal' Response:**

Amneal acknowledges the Agency's comment.

As recommended by the agency, Amneal has revised the carton label to reflect the "Use the dosing card attached inside carton" to the principal display panel (PDP). Please refer to **Module 1.14.2.1** for the revised final carton label.

For side-by-side comparison of Amneal's revised carton label vs. Amneal's previously submitted carton label, please refer to **Module 1.14.1.2**.

#### **FDA's Comment # 2b:**

**b. Please add “Store the dosing card with your diclofenac sodium topical gel, 1%.” After the storage statement in accordance with the RLD.**

#### **Amneal' Response:**

Amneal acknowledges the Agency's comment.

As recommended by the agency, Amneal has included “Store the dosing card with your diclofenac sodium topical gel, 1%” after the storage statement in accordance with the reference listed drug (RLD). Please refer to **Module 1.14.2.1** for the revised final carton label.

For side-by-side comparison of Amneal's revised carton label vs. Amneal's previously submitted carton label, please refer to **Module 1.14.1.2**.

#### **FDA's Comment # 2c:**

**c. Please remove “w/w” from the established name on the PDP and back label.**

#### **Amneal' Response:**

Amneal acknowledges the Agency's comment and accordingly revised the carton labels to remove “w/w” from the established name on the PDP and on the back label. Please refer to **Module 1.14.2.1** for the revised final carton labels.

For side-by-side comparison of Amneal's revised carton labels vs. Amneal's previously submitted carton labels, please refer to **Module 1.14.1.2**.

### **3. DOSING CARD**

#### **FDA's Comment # 3:**

**a. Please add “Dosing card for” prior to the established name.**

**b. Please add “(2.25 inches)” and “(4.5 inches)” directly below “2 grams” and “4 grams”, respectively.**

**c. Please revise “Please see patient medication guide for instructions.” to read “Please see instructions for use.”**

#### **Amneal' Response:**

Amneal acknowledges the Agency's comments (**#3a, #3b & #3c**) and accordingly revised the Dosing Card to add “Dosing Card for” prior to the established name and to reflect “(2.25 inches)” and “(4.5 inches)” directly below “2 grams” and “4 grams” respectively. Amneal has also revised the dosing card to read “Please see instructions for use” instead of “Please see patient medication guide for instructions”.

Please refer to **Module 1.14.2.1** for final Dosing Card label for Diclofenac Sodium Topical Gel, 1% and refer to **Module 1.14.1.2** for side-by-side comparison of Amneal's revised dosing card vs. Amneal's previously submitted dosing card.

### **4. PRESCRIBING INFORMATION**

#### **FDA's Comment # 4a:**

**a. Revise your labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Voltaren® Gel, NDA 022122/S-007, approved 11/25/14.**

#### **Amneal' Response:**

Amneal acknowledges the Agency's comment and revised the prescribing information according to the most recently approved labeling of the RLD, VOLTAREN®, NDA 022122/S-007, approved on 11/25/2014.

Please refer to **Module 1.14.2.3 (WORD, FPL and SPL formats)** for the final package insert of Diclofenac Sodium Topical Gel, 1%. A side-by-side labeling comparison of the Amneal's currently revised package insert versus Amneal's previously submitted package insert is provided in **Module 1.14.3.1**.

#### **FDA's Comment # 4b:**

**b. HIGHLIGHTS OF PRESCRIBING INFORMATION: Please revise the first paragraph to read: “These highlights do not include all the information needed to use diclofenac sodium topical gel safely and effectively. See full prescribing information for diclofenac sodium topical gel.”**

#### **Amneal' Response:**

Amneal acknowledges the Agency's comment. As recommended by the agency, Amneal has updated the first paragraph of HIGHLIGHTS OF PRESCRIBING INFORMATION to read “*These highlights do not include all*”

*the information needed to use diclofenac sodium topical gel safely and effectively. See full prescribing information for diclofenac sodium topical gel.”*

Please refer to **Module 1.14.2.3 (WORD, FPL and SPL formats)** for the final package insert of Diclofenac Sodium Topical Gel, 1%. A side-by-side labeling comparison of the Amneal’s currently revised package insert versus Amneal’s previously submitted package insert is per **FDA’s Comment # 4c**:

**c. HIGHLIGHTS OF PRESCRIBING INFORMATION/Title: Please revise to read: “DICLOFENAC sodium topical gel, 1%, for topical use only”.**

**Amneal’ Response:**

Amneal acknowledges the Agency’s comment and revised the HIGHLIGHTS OF PRESCRIBING INFORMATION/Title section of package insert to read “DICLOFENAC sodium topical gel, 1%, for topical use only.”

Please refer to **Module 1.14.2.3 (WORD, FPL and SPL formats)** for the final package insert of Diclofenac Sodium Topical Gel, 1%. A side-by-side labeling comparison of the Amneal’s currently revised package insert versus Amneal’s previously submitted package insert is provided in **Module 1.14.3.1**.

**FDA’s Comment # 4d:**

**d. HIGHLIGHTS OF PRESCRIBING INFORMATION/DOSAGE AND ADMINISTRATION: Please revise the first sentence to read: “Total dose should not exceed 32 g per day, over all affected joints.”**

**Amneal’ Response:**

Amneal acknowledges the Agency’s comment and revised the first sentence of the HIGHLIGHTS OF PRESCRIBING INFORMATION/ DOSAGE AND ADMINISTRATION section of package insert to read “Total dose should not exceed 32 g per day, over all affected joints.”

Please refer to **Module 1.14.2.3 (WORD, FPL and SPL formats)** for the final package insert of Diclofenac Sodium Topical Gel, 1%. A side-by-side labeling comparison of the Amneal’s currently revised package insert versus Amneal’s previously submitted package insert is provided in **Module 1.14.3.1**.

**FDA’s Comment # 4e:**

**e. HIGHLIGHTS OF PRESCRIBING INFORMATION/ Revision date: The date in this section does not correlate with the date at the end of the insert. Please comment and/or revise this date.**

**Amneal’ Response:**

Amneal acknowledges the Agency’s comments.

As recommended by the Agency, Amneal has updated the Revision Date provided in the HIGHLIGHTS OF PRESCRIBING INFORMATION/ Revision date section to be consistent with the date at the end of the insert. Please refer to **Module 1.14.2.3 (WORD, FPL and SPL formats)** for the final package insert of Diclofenac Sodium Topical Gel, 1%. A side-by-side labeling comparison of the Amneal’s currently revised package insert versus Amneal’s previously submitted package insert is provided in **Module 1.14.3.1**.

**FDA’s Comment # 4f-4k:**

**f. FULL PRESCRIBING INFORMATION/5 WARNINGS AND PRECAUTIONS/5.6 Renal Effects: In the third paragraph of this subsection, please revise “...dose dependent...” to read “...dose-dependent...”.**

**g. FULL PRESCRIBING INFORMATION/ 5 WARNINGS AND PRECAUTIONS/5.10 Corticosteroid Treatment: Please revise the second sentence of this subsection to read: “Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness.”**

**h. FULL PRESCRIBING INFORMATION/ 5 WARNINGS AND PRECAUTIONS/5.13 Preexisting Asthma: Please revise the second sentence to read: “The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal.”**

**i. FULL PRESCRIBING INFORMATION/12 CLINICAL PHARMACOLOGY/12.3 Pharmacokinetics: Directly below Table 2, please revise “...tmax time of Cmax...” to read “tmax = time of Cmax”.**

**j. FULL PRESCRIBING INFORMATION/13 NONCLINICAL TOXICOLOGY/13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: Please revise the first sentence to read: “Carcinogenicity studies in mice and rats administered diclofenac sodium as a dietary constituent for 2 years at doses up to 2**

mg/kg/day resulted in no significant increases in tumor incidence corresponding to a human equivalent dose approximately 0.5- and 1-fold (mouse and rat, respectively) of the maximum human topical dose of diclofenac sodium topical gel (based on bioavailability and body surface area comparison).”

**k. FULL PRESCRIBING INFORMATION/16 HOW SUPPLIED:** Please add the following statement: “Store the dosing card with your diclofenac sodium topical gel.” after the storage statement.

**Amneal’ Response:**

Amneal acknowledges the Agency’s comments.

As recommended by the Agency, Amneal has revised the FULL PRESCRIBING INFORMATION as per the above agency’s comments from (#4f, #4g, #4h, #4i, #4j & #4k) to reflect all the changes. Please refer to **Module 1.14.2.3 (WORD, FPL and SPL formats)** for the final package insert of Diclofenac Sodium Topical Gel, 1%. A side-by-side labeling comparison of the Amneal’s currently revised package insert versus Amneal’s previously submitted package insert is provided in **Module 1.14.3.1**.

**5. MEDICATION GUIDE**

**FDA’s Comment # 5a:**

**a. Revise your Medication Guide (MG) to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Voltaren® Gel, NDA 022122/S-007, approved 11/25/14.**

**Amneal’ Response:**

Amneal acknowledges the Agency’s comments. Amneal has updated the medication guide according to the most recently approved medication guide of the RLD, VOLTAREN®, NDA 022122/S-007 approved on 11/25/2014.

Please refer to **Module 1.14.2.3 (WORD, FPL and SPL formats)** for the medication guide as a part of final package insert of Diclofenac Sodium Topical Gel, 1%. To facilitate the Agency’s review, we have provided the stand-alone medication guide in **Module 1.14.2.3**. Please refer to **Module 1.14.3.1** for the side-by-side comparison of Amneal’s revised package insert vs. Amneal’s previously submitted package insert with medication guide for Diclofenac Sodium Topical Gel, 1%.

**FDA’s Comment # 5b:**

**b. Ensure a sufficient number of Medication Guides is available for dispensing and distribution to patients receiving a prescription for your dug product, per 21 CFR 208.24.**

**Amneal’ Response:**

Amneal acknowledges the Agency’s comment and would like to inform to the Agency that “*Each bottle will be affix with the package insert, which includes the Medication Guide. The Medication Guide will also be printed in pads of 25 count and provided to distributors in each shipper box. Amneal will provide distributors with electronic copies of the Medication Guide so that each individual pharmacy can provide a copy as the medication is dispensed.*”

Please refer to **Module 1.14.2.3** for the stand-alone medication guide for Diclofenac Sodium Topical Gel, 1%. Please refer to **Module 1.14.3.1** for the side-by-side comparison of Amneal’s revised package insert vs. Amneal’s previously submitted package insert with medication guide for Diclofenac Sodium Topical Gel, 1%.

**FDA’s Comment # 5c-5e:**

**c. Who should not take Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?/Tell your healthcare provider:** Please revise the third bullet to read: “if you are pregnant. NSAID medicines should not be used by pregnant women late in their pregnancy.”

**d. NSAID medicines that need a prescription chart:** Please add “®” to Flector, Voltaren gel, Arthrotec, Zipsor, Duexis, Oruvail, Toradol, Treximet, and Vimovo. Please relocate the “®” placed after Tolectin DS to the space after Tolectin. Lastly, please add “™” to Zorvolex.

**e. Please submit final printed labeling of the stand-alone MG; and ensure the font size is at least 10 font type.**

**Amneal’ Response:**

Amneal acknowledges the Agency’s comment and would like to inform to the Agency that Amneal have revised the proposed package insert for Diclofenac Sodium Topical Gel, 1% to reflect all the above recommendations in above Agency’s comment # 5c, 5d, & 5e.

Please refer to **Module 1.14.2.3** for the stand-alone medication guide and **Module 1.14.2.3 (WORD, FPL and SPL formats)** for the final package insert of Diclofenac Sodium Topical Gel, 1%. Please refer to **Module 1.14.3.1** for the side-by-side comparison of Amneal’s revised package insert vs. Amneal’s previously submitted package insert with medication guide for Diclofenac Sodium Topical Gel, 1%.

## **6. PATIENT INSTRUCTIONS FOR USE**

### **FDA’s Comment # 6:**

**Revise your patient labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Voltaren® Gel, NDA 022122/S-007, approved 11/25/14.**

### **Amneal’ Response:**

Amneal acknowledges the Agency’s comments. Amneal has updated the Amneal’s proposed Patient Instructions for Use labeling according to the most recently approved labeling of the RLD, VOLTAREN®, NDA 022122/S-007, approved on 11/25/2014. Please refer to **Module 1.14.2.3 (WORD, FPL and SPL formats)** for the final package insert of Diclofenac Sodium Topical Gel, 1%. A side-by-side labeling comparison of the Amneal’s currently revised package insert versus Amneal’s previously submitted package insert is provided in **Module 1.14.3.1**.

### **Reviewer Comments:**

The applicant has satisfactorily revised the deficiencies and recommendations for Container, Carton, Dosing Card, Prescribing Information, Medication Guide and Instructions for Use.

Container and Carton:

We will request the applicant revise “Each gram contains 1% diclofenac sodium, USP.” to read “Each gram contains 1% w/w diclofenac sodium, USP.”

### **2.1 CONTAINER AND CARTON LABELS**

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?  
**NO**

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

### **Reviewer Comments:**

None

### **2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW**

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s).

### **Reviewer Comments:**

None

## **3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT**

### **3.1 REGULATORY INFORMATION**

**Are there any pending issues in DLR’s SharePoint Repository files? NO**

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

**Is the drug product listed in the Policy Alert Tracker on OGD’s SharePoint? NO**

If Yes, please explain.

### 3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling  
(Check the box used as the Model Labeling)

**MOST RECENTLY APPROVED NDA MODEL LABELING**

*(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)*

NDA#/Supplement# (S-000 if original): NDA 022122/S-009

Supplement Approval Date: 5/8/15

Proprietary Name: Voltaren Gel

Established Name: diclofenac sodium topical gel

Description of Supplement:

(b) (4)

The cartons will match the current existing cartons.

**MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): 41T

Supplement Approval Date: 41T

Proprietary Name: 41T

Established Name: 41T

Description of Supplement: 41T

**TEMPLATE (e.g., BPCA, PREA, Carve-out): 41T**

**OTHER (Describe): 41T**

#### ***Reviewer Assessment:***

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **YES**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

#### **Reviewer Comments:**

HIGHLIGHTS OF PRESCRIBING INFORMATION:

We will request the applicant revise the limitations to read:

Revise the presentation of the established name to appear in all upper case letters, in the following text as such: **“These highlights do not include all the information needed to use DICLOFENAC SODIUM TOPICAL GEL safely and effectively. See full prescribing information for DICLOFENAC SODIUM TOPICAL GEL.”**

We will request the applicant revise the title to read: **DICLOFENAC SODIUM topical gel, 1%, for topical use only**

We will request the applicant revise the subsection title to read **“DOSAGE FORM AND STRENGTH”**.

FULL PRESCRIBING INFORMATION:

CONTENTS: We will request the applicant revise “3 DOSAGE FORMS AND STRENGTHS” to read “3 DOSAGE FORM AND STRENGTH”.

2 DOSAGE AND ADMINISTRATION/2.1 Dosing Card: We will request the applicant to revise “2.1 Dosing Card [See the Instructions for Use]” to read “2.1 Dosing Card [See the patient Instructions for Use]”.

3 DOSAGE FORM AND STRENGTH: We will request the applicant revise to read “3 DOSAGE FORM AND

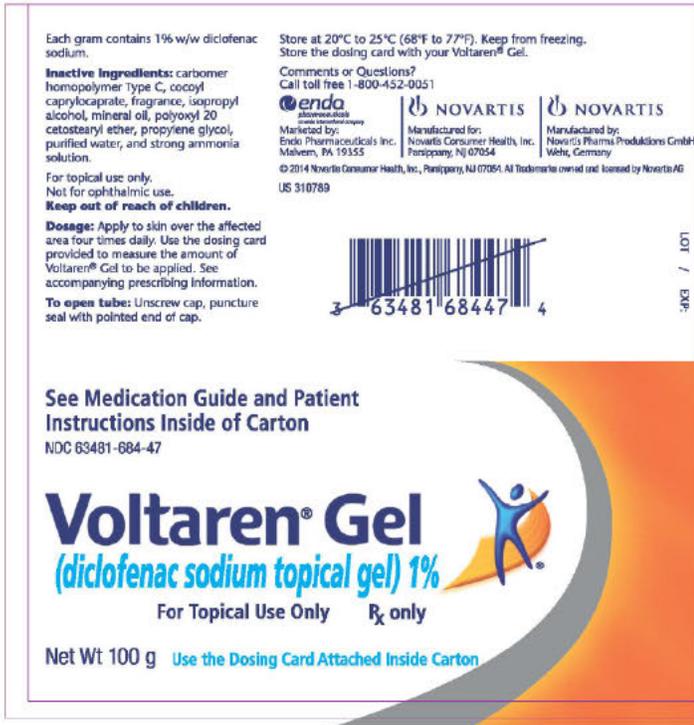
STRENGTH”.

16 HOW SUPPLIED, first sentence: We will request the applicant to revise to read: “Diclofenac sodium topical gel 1% is available....”

### 3.3 MODEL CONTAINER LABELS

Model labels and carton labeling. [Insert or paste images below]

From DARRTS (1/8/15) for (b) (4) tube



From DARRTS (6/7/14) for (b) (4) tubes, carton, and dosing card

Tube:

See Medication Guide and Patient Instructions Inside of Carton  
NDC 63481-684-47

# Voltaren® Gel

(diclofenac sodium topical gel) 1%



For Topical Use Only    **R<sub>x</sub>** only

Net Wt 100 g    Use the Dosing Card Attached Inside Carton

EXP: / LOT:

Each gram contains 1% w/w diclofenac sodium.

**Inactive ingredients:** carbomer homopolymer Type C, cocoyl caprylocaprate, fragrance, isopropyl alcohol, mineral oil, polyoxy 20 cetostearyl ether, propylene glycol, purified water, and strong ammonia solution.

For topical use only.

Not for ophthalmic use.

**Keep out of reach of children.**

**Dosage:** Apply to skin over the affected area four times daily. Use the dosing card provided to measure the amount of Voltaren® Gel to be applied. See accompanying prescribing information.

**To open tube:** Unscrew cap, puncture seal with pointed end of cap.

Store at 20°C to 25°C (68°F to 77°F). Keep from freezing. Store the dosing card with your Voltaren® Gel.

Comments or Questions?  
Call toll free 1-800-452-0051



Marketed by:  
Endo Pharmaceuticals Inc.  
Malvern, PA 19355



Manufactured for:  
Novartis Consumer Health, Inc.  
Parsippany, NJ 07054



Manufactured by:  
Novartis Pharma Produktions GmbH  
Wehr, Germany

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US 307925



3 63481-684-47 4

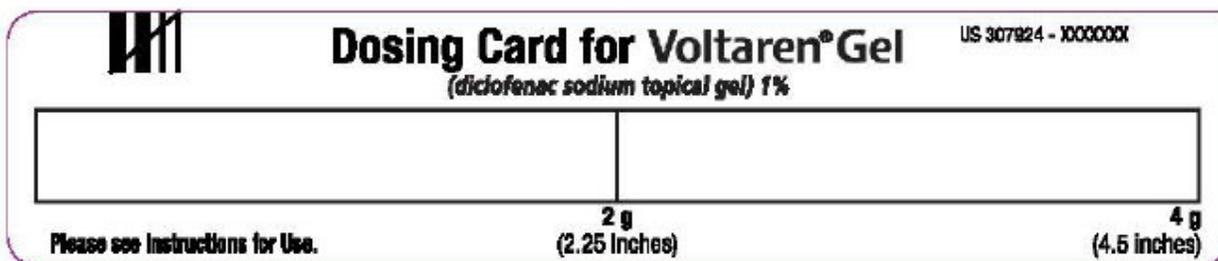


XXXXXXXX

Carton:



**Dosing Card:**



### 3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	6/26/2015	NO	NA	NA
PF	6/26/2015	NO	NA	NA

**Reviewer Comments:**

None

### 3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 6/26/2015.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
NA						

**Reviewer Assessment:**

Is the applicant's "patent carve out" acceptable? **NA**

**Reviewer Comments:**

There are no unexpired patents for this product in the Orange Book Database.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA					

**Reviewer Assessment:**

Is the applicant's "exclusivity carve out" acceptable? **NA**

**Reviewer Comments:**

There is no unexpired exclusivity for this product.

### 4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the DESCRIPTION section, HOW SUPPLIED section and manufacturing statements of the Prescribing Information when compared to the previous labeling review.

**Reviewer Assessment:**

Are there changes to the inactives in the DESCRIPTION section? **NO**

Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED? **NO**

Are there changes to the manufacturing statements? **NO**  
 If yes, then comment below in Tables 5, 6, and 7.

**Table 5: Comparison of DESCRIPTION Section**

Previous Labeling Review	Currently Proposed	Assessment
Diclofenac sodium topical gel, 1% also contains carbomer homopolymer Type C, cocoyl caprylocaprate, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, and strong ammonia solution.	Diclofenac sodium topical gel, 1% also contains carbomer homopolymer Type C, cocoyl caprylocaprate, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, and strong ammonia solution.	No change.

**Table 6: Comparison of HOW SUPPLIED Section**

Previously Labeling Review	Currently Proposed	Assessment
Diclofenac sodium topical gel, 1% w/w is available in tubes containing 100 g of the topical gel in each tube. Each tube contains diclofenac sodium in a gel base (10 mg of diclofenac sodium per gram of gel or 1%). 100 g tube NDC 65162-833-66 Storage Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Keep from freezing.	Diclofenac sodium topical gel, 1% w/w is available in tubes containing 100 g of the topical gel in each tube. Each tube contains diclofenac sodium in a gel base (10 mg of diclofenac sodium per gram of gel or 1%). 100 g tube NDC 65162-833-66 Storage Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Keep from freezing. Store the dosing card with your diclofenac sodium topical gel.	The applicant added "Store the dosing card with your diclofenac sodium topical gel." as requested in labeling review #1. This is acceptable.

**Table 7: Manufactured by statement**

Previously Labeling Review	Currently Proposed	Assessment
Manufactured by: Amneal Pharmaceuticals Piscataway, NJ 08854 Distributed by: Amneal Pharmaceuticals Glasgow, KY 42141	Manufactured by: Amneal Pharmaceuticals Piscataway, NJ 08854 Distributed by: Amneal Pharmaceuticals Glasgow, KY 42141	No change.

**5. COMMENTS FOR CHEMISTRY REVIEWER**

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

**Reviewer Comments:**

None

## 6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

### Reviewer Comments:

None

## 7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for each material analyzed in this review.

If this review is acceptable, then all pertinent labeling pieces must be entered for both tables.

For each row, if you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Date	Recommendation
Container	Final	100 g	4/14/15	Revise
Blister	NA			
Carton	Final	1 tube	4/14/15	Revise
Dosing Card	Final	NA	4/14/15	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Date	Recommendation
Prescribing Information	Final	Rev. 04-2015-00	4/14/15	Revise
Medication Guide	Final	Rev. 04-2015-00	4/14/15	Satisfactory
Patient Information	Final	Rev. 04-2015-00	4/14/15	Satisfactory
SPL Data Elements		4/2015	4/14/15	Satisfactory

\* Post-approval revision

## LABELING REVIEW

Division of Labeling Review  
Office of Regulatory Operations  
Office of Generic Drugs (OGD)  
Center for Drug Evaluation and Research (CDER)

<b>Date of This Review</b>	2/20/15
<b>ANDA Number(s)</b>	208077
<b>Review Cycle Number</b>	1
<b>Applicant Name</b>	Amneal Pharmaceuticals
<b>Established Name &amp; Strength(s)</b>	Diclofenac Sodium Topical Gel, 1%
<b>Proposed Proprietary Name</b>	NA
<b>Submission Received Date</b>	12/19/14
<b>Labeling Reviewer</b>	Esther Kim, Pharm.D.
<b>Labeling Team Leader</b>	Jeanne Skanchy, R.Ph.

### Review Conclusion

- ACCEPTABLE – No Comments
- ACCEPTABLE – Include Post Approval Comments
- Minor Deficiency\* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

\*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

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## 1. LABELING COMMENTS

### 1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

#### 1. CONTAINER LABEL

- a. Please add “Use the dosing card attached inside carton” to the principal display panel (PDP).
- b. Please add “Store the dosing card with your diclofenac sodium topical gel, 1%.” after the storage statement in accordance with the reference listed drug (RLD).
- c. Please remove “w/w” from the established name.
- d. Please provide the space for the lot number and expiration date.

#### 2. CARTON LABELING

- a. Please add “Use the dosing card attached inside the carton” to the PDP.
- b. Please add “Store the dosing card with your diclofenac sodium topical gel, 1%.” after the storage statement in accordance with the RLD.
- c. Please remove “w/w” from the established name on the PDP and back label.

#### 3. DOSING CARD

- a. Please add “Dosing card for” prior to the established name.
- b. Please add “(2.25 inches)” and “(4.5 inches)” directly below “2 grams” and “4 grams”, respectively.
- c. Please revise “Please see patient medication guide for instructions.” to read “Please see instructions for use.”

#### 4. PRESCRIBING INFORMATION

- a. Revise your labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Voltaren® Gel, NDA 022122/S-007, approved 11/25/14.
- b. HIGHLIGHTS OF PRESCRIBING INFORMATION: Please revise the first paragraph to read: “These highlights do not include all the information needed to use diclofenac sodium topical gel safely and effectively. See full prescribing information for diclofenac sodium topical gel.
- c. HIGHLIGHTS OF PRESCRIBING INFORMATION/Title: Please revise to read: “**DICLOFENAC sodium topical gel, 1%, for topical use only**”.
- d. HIGHLIGHTS OF PRESCRIBING INFORMATION/DOSAGE AND ADMINISTRATION: Please revise the first sentence to read: “Total dose should not exceed 32 g per day, over all affected joints.”
- e. HIGHLIGHTS OF PRESCRIBING INFORMATION/ Revision date: The date in this section does not correlate with the date at the end of the insert. Please comment and/or revise this date.
- f. FULL PRESCRIBING INFORMATION/5 WARNINGS AND PRECAUTIONS/5.6 Renal Effects: In the third paragraph of this subsection, please revise “...dosedependent...” to read “...dose-dependent...”.
- g. FULL PRESCRIBING INFORMATION/ 5 WARNINGS AND PRECAUTIONS/5.10 Corticosteroid Treatment: Please revise the second sentence of this subsection to read: “Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness.”
- h. FULL PRESCRIBING INFORMATION/ 5 WARNINGS AND PRECAUTIONS/5.13 Preexisting Asthma: Please revise the second sentence to read: “The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal.”
- i. FULL PRESCRIBING INFORMATION/12 CLINICAL PHARMACOLOGY/12.3 Pharmacokinetics: Directly below Table 2, please revise “...tmax time of Cmax...” to read “tmax = time of Cmax”.

- j. FULL PRESCRIBING INFORMATION/13 NONCLINICAL TOXICOLOGY/13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: Please revise the first sentence to read: “Carcinogenicity studies in mice and rats administered diclofenac sodium as a dietary constituent for 2 years at doses up to 2 mg/kg/day resulted in no significant increases in tumor incidence corresponding to a human equivalent dose approximately 0.5- and 1-fold (mouse and rat, respectively) of the maximum human topical dose of diclofenac sodium topical gel (based on bioavailability and body surface area comparison).”
- k. FULL PRESCRIBING INFORMATION/16 HOW SUPPLIED: Please add the following statement: “Store the dosing card with your diclofenac sodium topical gel.” after the storage statement.

#### 5. MEDICATION GUIDE (MG)

- a. Revise your Medication Guide (MG) to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Voltaren® Gel, NDA 022122/S-007, approved 11/25/14.
- b. Ensure a sufficient number of Medication Guides is available for dispensing and distribution to patients receiving a prescription for your drug product, per 21 CFR 208.24.
- c. **Who should not take Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?/Tell your healthcare provider:** Please revise the third bullet to read: “if you are pregnant. NSAID medicines should not be used by pregnant women late in their pregnancy.”
- d. **NSAID medicines that need a prescription** chart: Please add “®” to Flector, Voltaren gel, Arthrotec, Zipsor, Duexis, Oruvail, Toradol, Treximet, and Vimovo. Please relocate the “®” placed after Tolectin DS to the space after Tolectin. Lastly, please add “™” to Zorvolex.
- e. Please submit final printed labeling of the stand-alone MG; and ensure the font size is at least 10 font type.

#### 6. PATIENT INSTRUCTIONS FOR USE

Revise your patient labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Voltaren® Gel, NDA 022122/S-007, approved 11/25/14.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling 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](http://service.govdelivery.com/service/subscribe.html?code=USFDA_17)

### 1.2 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.

These comments will be addressed post approval (in the next supplement review).

None

## 2. LABELING REVIEW INFORMATION

### 2.1 REGULATORY INFORMATION

Has the ANDA been accepted for filing? YES

Are there any pending issues in SharePoint Repository files? NO

If Yes, please explain.

### 2.2 MODEL LABELING

#### 2.2.1 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check all that apply)

MOST RECENTLY APPROVED MODEL LABELING – NDA

*(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)*

NDA#/Supplement# (S-000 if original): NDA 022122/S-007

Supplement Approval Date: 11/25/14

Proprietary Name: Voltaren Gel

Established Name: diclofenac sodium topical gel

Description of Supplement: This "Changes Being Effected" supplemental new drug application provides for changes to product labeling, including the prescribing information, instructions for use, and carton and container labeling, intended to alert the consumer to look for the dosing card inside the carton, and utilize the dosing card to properly administer an accurate dose of the topical gel.

MOST RECENTLY APPROVED MODEL LABELING – ANDA

ANDA#/Supplement# (S-000 if original): 41T

Supplement Approval Date: 41T

Proprietary Name: 41T

Established Name: 41T

Description of Supplement: [Click here to enter text.](#)

BPCA or PREA TEMPLATE (Describe): 41T

OTHER (Describe):

S-008 was approved 9/29/14. This "Changes Being Effected in 30 Days" supplemental new drug application provides for revision to the drug product specification.

S-009 is a pending supplement. This prior approval supplement is for alternate primary packaging.

#### 2.2.2 MODEL CONTAINER LABELS

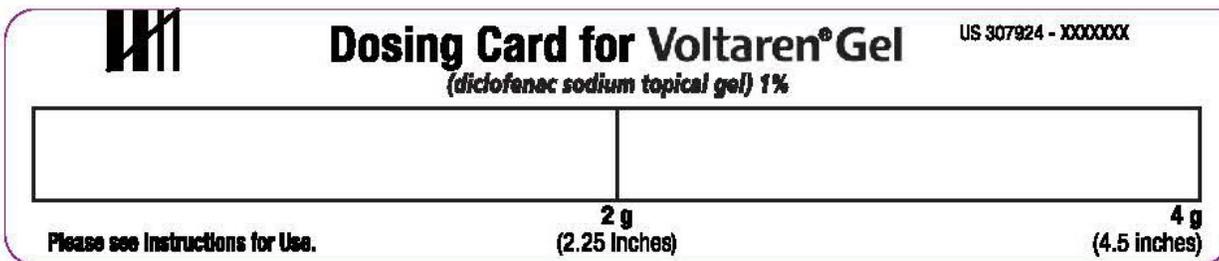
Tube:

<p>See Medication Guide and Patient Instructions Inside of Carton NDC 63481-684-47</p> <h1>Voltaren® Gel</h1> <p>(diclofenac sodium topical gel) 1%</p> <p>For Topical Use Only    <b>Rx only</b></p> <p>Net Wt 100 g    Use the Dosing Card Attached Inside Carton</p>		<p>EXP: / LOT:</p>
<p>Each gram contains 1% w/w diclofenac sodium.</p> <p><b>Inactive ingredients:</b> carbomer homopolymer Type C, cocoyl caprylocaprate, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, and strong ammonia solution.</p> <p>For topical use only. Not for ophthalmic use. <b>Keep out of reach of children.</b></p> <p><b>Dosage:</b> Apply to skin over the affected area four times daily. Use the dosing card provided to measure the amount of Voltaren® Gel to be applied. See accompanying prescribing information.</p> <p><b>To open tube:</b> Unscrew cap, puncture seal with pointed end of cap.</p>	<p>Store at 20°C to 25°C (68°F to 77°F). Keep from freezing. Store the dosing card with your Voltaren® Gel.</p> <p>Comments or Questions? Call toll free 1-800-452-0051</p> <p> <b>NOVARTIS</b> </p> <p>Marketed by: Endo Pharmaceuticals Inc. Malvern, PA 19355</p> <p>Manufactured for: Novartis Consumer Health, Inc. Parsippany, NJ 07054</p> <p>Manufactured by: Novartis Pharma Produktions GmbH Wehr, Germany</p> <p>© 2014 Novartis Consumer Health, Inc., Parsippany, NJ 07054. All Trademarks owned and licensed by Novartis AG US 307925</p> <p>XXXXXXXX</p>  3 63481-684-47 4	

**Carton:**



**Dosing Card:**



### 2.3 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	2/20/2015	NO	NA	NA
PF	2/20/2015	NO	NA	NA

### 2.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 2/20/2015.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
NA						

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA					

### 2.5 MANUFACTURING FACILITY

Table 5 provides a description of the drug product manufacturing facility.

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of Facility ANDA Manufactured (Cite Source)	Name and Address on ANDA Container/Carton	Name and Address on ANDA Prescribing Information
<p>From 2.3.P.3 QOS:</p> <p><b>Amneal Pharmaceuticals</b> 1 New England Avenue Piscataway, NJ 08854 (Building A)</p> <p>FEI # 3008861605</p> <p>DUNS # 053542455</p>	<p>Tube:</p> <p>Manufactured by: <b>Amneal Pharmaceuticals</b> Piscataway, NJ 08854</p> <p>Distributed by: <b>Amneal Pharmaceuticals</b> Glasgow, KY 42141</p>	<p>Carton:</p> <p>Manufactured by: <b>Amneal Pharmaceuticals</b> Piscataway, NJ 08854</p> <p>Distributed by: <b>Amneal Pharmaceuticals</b> Glasgow, KY 42141</p> <p>Insert:</p> <p>Manufactured by: <b>Amneal Pharmaceuticals</b> Piscataway, NJ 08854</p> <p>Distributed by: <b>Amneal Pharmaceuticals</b> Glasgow, KY 42141</p>

### **3. ASSESSMENT OF ANDA LABELING AND LABELS**

The results for each material reviewed in this section provide the basis for the labeling comments to the applicant.

**Is this product Rx or OTC? Please check one.**

- Rx Product (If Rx, complete sections 3.1, 3.3, 3.4 and 3.5.)  
 OTC Product (If OTC, complete sections 3.2, 3.3, 3.4 and 3.5.)

#### **3.1 RX (PRESCRIPTION) DRUG PRODUCT**

##### **3.1.1 RX: PRESCRIBING INFORMATION**

***Reviewer Assessment:***

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **NO**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **YES**

Is the established name for this ANDA acceptable? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Are the required USP recommendations reflected in the labeling? **NA**

Is the applicant's "patent carve out" acceptable? **NA**

Is the applicant's "exclusivity carve out" acceptable? **NA**

Is the Manufacturer statement acceptable? **YES**

## **Reviewer Comments:**

We will request the applicant update their labeling to be in accordance with the RLD, Voltaren® Gel, NDA 022122/S-007, approved 11/25/14.

**HIGHLIGHTS OF PRESCRIBING INFORMATION:** We will request the applicant revise the first paragraph to read: “These highlights do not include all the information needed to use diclofenac sodium topical gel safely and effectively. See full prescribing information for diclofenac sodium topical gel.

**HIGHLIGHTS OF PRESCRIBING INFORMATION/Title:** We will request the applicant revise to read: “DICLOFENAC sodium topical gel, 1% for topical use only”.

**HIGHLIGHTS OF PRESCRIBING INFORMATION/DOSAGE AND ADMINISTRATION:** We will request the applicant revise the first sentence to read: “Total dose should not exceed 32 g per day, over all affected joints.”

**HIGHLIGHTS OF PRESCRIBING INFORMATION/ Revision date:** The date in this section does not correlate with the date at the end of the insert. We will ask the applicant to comment and/or revise this date.

**5 WARNINGS AND PRECAUTIONS/5.6 Renal Effects:** In the third paragraph of this subsection, we will request the applicant to revise “...dosedependent...” to read “...dose-dependent...”.

**5 WARNINGS AND PRECAUTIONS/5.10 Corticosteroid Treatment:** We will request the applicant revise the second sentence of this subsection to read: “Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness.”

**5 WARNINGS AND PRECAUTIONS/5.13 Preexisting Asthma:** We will request the applicant revise the second sentence to read: “The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal.”

**12 CLINICAL PHARMACOLOGY/12.3 Pharmacokinetics:** Directly below Table 2, we will request the applicant revise “...tmax time of Cmax...” to read “tmax = time of Cmax”.

**13 NONCLINICAL TOXICOLOGY/13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility:** We will request the applicant the first sentence to read: “Carcinogenicity studies in mice and rats administered diclofenac sodium as a dietary constituent for 2 years at doses up to 2 mg/kg/day resulted in no significant increases in tumor incidence corresponding to a human equivalent dose approximately 0.5- and 1-fold (mouse and rat, respectively) of the maximum human topical dose of diclofenac sodium topical gel (based on bioavailability and body surface area comparison).”

The following issues should be corrected when the applicant updates their insert (not all inclusive):

**HIGHLIGHTS OF PRESCRIBING INFORMATION/CONTENTS/6 ADVERSE REACTIONS:** We will request the applicant to revise “6.1 Clinical Studies Experience” to read “6.1 Clinical Trials Experience”.

**HIGHLIGHTS OF PRESCRIBING INFORMATION/CONTENTS/17 PATIENT COUNSELING INFORMATION:** We will request the applicant remove all subsections listed in accordance with the RLD.

### **FULL PRESCRIBING INFORMATION:**

**2 DOSAGE AND ADMINISTRATION/2.1 Dosing Card:** We will request the applicant revise the title of this subsection to read: “Dosing Card [See the Patient Instructions for Use]”. Additionally, we will request the applicant add the following statement as the first sentence in this subsection: “The dosing card can be found attached to the inside of the carton.” We will also request the applicant add the following statements as the fifth and sixth sentences of this subsection: “The 2 g line is 2.25 inches long. The 4 g line is 4.5 inches long.” in accordance with the RLD. Lastly, we will request the applicant revise the last sentence of this subsection to read: “If treatment site is the hands, patients should wait at least one (1) hour to wash their hands.”

**2 DOSAGE AND ADMINISTRATION/2.4 Special Precautions:** We will request the applicant revise the sixth bullet to read: “Avoid concomitant use of diclofenac sodium topical gel, 1% on the treated skin site with other topical products, including sunscreens, cosmetics, lotions, moisturizers, insect repellants, or other topical medications [see Drug Interactions (7.9)].”

5 WARNINGS AND PRECAUTIONS/5.3 Hepatic Effects: We will request the applicant to revise the last sentence of this subsection to read: “Caution should be exercised in prescribing diclofenac sodium with concomitant drugs that are known to be potentially hepatotoxic (e.g., antibiotics, anti-epileptics).”

6 ADVERSE REACTIONS: We will request the applicant revise “6.1 Clinical Studies Experience” to read “6.1 Clinical Trials Experience”.

17 PATIENT COUNSELING INFORMATION:

We will request the applicant to remove: “See Medication Guide.”, 17.1 Medication Guide as well as all subsection numbers in accordance with the RLD. remove

We will request the applicant to add the following statements as the first two sentence of this section: “Advise the patient to read the FDA-approved patient labeling (NSAIDs Medication Guide and Instructions for Use) prior to using diclofenac sodium topical gel, 1%. Inform patients of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy”

17 PATIENT COUNSELING INFORMATION/Cardiovascular Effects: We will request the applicant to revise the last sentence to read: “Advise patients of the importance of this follow-up [see Warnings and Precautions (5.1)].”

17 PATIENT COUNSELING INFORMATION/Gastrointestinal Effects: We will ask the applicant to revise the second to read: “Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding. Instruct patients to ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis.”

17 PATIENT COUNSELING INFORMATION/Hepatotoxicity: We will request the applicant revise the first sentence to read: “Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms).”

### **3.1.1.1 RX: DESCRIPTION**

We reviewed the DESCRIPTION section for accuracy (with input from the chemistry review, if appropriate) and acceptability from a Labeling perspective. We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

**Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section**

<b>Model Labeling Inactive Ingredients</b>	<b>ANDA Labeling Inactive Ingredients</b>
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<p>VOLTAREN®GEL also contains carbomer homopolymer Type C, cocoyl caprylocaprate, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, and strong ammonia solution.</p>	<p>Diclofenac sodium topical gel, 1% also contains carbomer homopolymer Type C, cocoyl caprylocaprate, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, and strong ammonia solution.</p> <p>From 3.2.P.1 QOS:</p>							
	Ingredients	Quantity in %w/w	Quantity mg/g	Quantity in mg/unit	Quantity in mg/2 g <sup>h</sup>	Quantity in mg/4 g <sup>h</sup>	Quantity mg/day <sup>1</sup>	Function
	Diclofenac Sodium USP	1.00	10.00	1000.00	20.00	40.00	320.00	Active
	Isopropyl Alcohol USP	(b) (4)						(b) (4)
	Carbomer Homopolymer Type C USP/NF							(b) (4)
	Strong Ammonia Solution NF							(b) (4)
	Cocoyl Caprylocaprate							(b) (4)
	Mineral Oil USP							(b) (4)
								(b) (4)
	Polyoxyl 20 Cetostearyl							(b) (4)
Propylene Glycol USP	(b) (4)							
Purified Water USP	(b) (4)							

**Reviewer Assessment:**

Does the chemistry review follow the [Chemistry/Labeling Memorandum of Understanding](#) (MOU)?

**YES, chemistry review pending**

(Note: The MOU became effective on November 1, 2014. MOU does not apply to amendment reviews for ANDAs originally reviewed before November 1, 2014.)

If the chemistry review follows the MOU, labeling reviewer is not responsible for reviewing for accuracy of the DESCRIPTION section for chemical properties, system components of the drug product, etc. Please refer to the MOU, Appendix A, DESCRIPTION section for delineation of responsibilities. If chemistry review does NOT follow the MOU, labeling reviewer will follow the traditional review approach of reviewing the entire DESCRIPTION section.)

Is the DESCRIPTION section of the labeling acceptable? **YES**

Are the inactive ingredients information consistent with “Components and Composition” information as provided in Module 3.2.P.1? (If Chemistry follows the MOU, refer to the Labeling section of Chemistry review. Enter PENDING if the Chemistry review is pending. **YES**

For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**

If the labeling includes a “Does not contain...” statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

**Reviewer Comments:**

None

**3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING**

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 7 and will be referred to the appropriate review discipline for evaluation.

Table 7: Comparison of Model Labeling to ANDA Labeling	
<b>Model Labeling</b>	<p>VOLTAREN® GEL is available in tubes containing 100 g of the topical gel in each tube. Each tube contains diclofenac sodium in a gel base (10 mg of diclofenac sodium per gram of gel or 1%).</p> <p>100 g tube.....NDC 63481-684-47</p> <p>3 Pack (3 Tubes containing 100 g each).....NDC 63481-684-03</p> <p>5 Pack (5 Tubes containing 100 g each).....NDC 63481-684-05</p> <p>Storage</p> <p>Store at 20°C to 25°C (68°F to 77°F). Keep from freezing. Store the dosing card with your VOLTAREN® GEL.</p>
<b>ANDA Labeling</b>	<p>Diclofenac sodium topical gel, 1% w/w is available in tubes containing 100 g of the topical gel in each tube. Each tube contains diclofenac sodium in a gel base (10 mg of diclofenac sodium per gram of gel or 1%).</p> <p>100 g tube NDC 65162-833-66</p> <p>Storage</p> <p>Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].</p> <p>Keep from freezing.</p> <p>From 3.2.P.1.5QOS:</p> <p style="text-align: center;"><b>Amneal's –</b> <b><i>Diclofenac Sodium Topical Gel, 1% w/w</i></b></p> <p>An opaque, white to off white gel base free from any foreign particles.</p>

**Reviewer Assessment:**

Does the chemistry review follow the Chemistry/Labeling MOU? **YES, chemistry review pending**

If the chemistry review does NOT follow the MOU, is the description ([scoring](#), color and [imprint](#)) of the finished product in the HOW SUPPLIED section consistent with the information in Module 3.2.P.5.1 for Drug Product Specification? **NA**

Does the ANDA require the same color coding as the Model Labeling? **NO**

Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**

Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **YES**

If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**

Is the storage or dispensing statement acceptable as compared to the Model Labeling? **NO**

Is the storage or dispensing statement acceptable as compared to the USP? **YES**

Does the temperature statement conform to the OGD format for controlled room temperature? **YES**

**Reviewer Comments:**

We will request the applicant add the following statement: “Store the dosing card with your diclofenac sodium topical gel.” in accordance with the RLD.

**3.1.2 RX: MEDICATION GUIDE**

Is Medication Guide required? **YES**

If YES go to Reviewer Assessment below, if NO go to section 3.1.3.

**Reviewer Assessment:**

Was Medication Guide submitted? **YES**  
Is the Medication Guide same as the model labeling, except for allowable differences? **YES**  
Does the format meet the requirements of [21 CFR 208.20](#)? **YES**  
Has the Applicant committed to provide a sufficient number of medication guides? **NO**  
Is the phonetic spelling of the proprietary or established name present? **NA**  
Is FDA 1-800-FDA-1088 phone number included? **YES**

**Reviewer Comments:**

The Medication Guide is NSAID class specific.  
Who should not take Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?/Tell your healthcare provider: In the third bullet, we will request the applicant revise to read: “if you are pregnant. NSAID medicines should not be used by pregnant women late in their pregnancy.”  
NSAID medicines that need a prescription chart: We will ask the applicant to add “®” to Flector, Voltaren gel, Arthrotec, Zipsor, Duexis, Oruvail, Toradol, Treximet, and Vimovo. We will request the applicant relocate the “®” placed after Tolectin DS to the space after Tolectin. We will request the applicant add “™” to Zorvolex. We will request the applicant ensure a sufficient number of Medication Guides is available for dispensing and distribution to patients receiving a prescription for your dug product, per 21 CFR 208.24.

**3.1.3 RX: OTHER PATIENT LABELING**

Are other patient labeling required? **YES**  
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.

**Reviewer Assessment:**

Was other patient labeling submitted? **YES**  
Is the patient labeling the same as the model labeling, except for allowable differences? **NO**

**Reviewer Comments:**

We will request the applicant update their patient labeling in accordance with the RLD, Voltaren® Gel, NDA 022122/S-007 approved 11/25/14.

**3.1.4 RX: CONTAINER LABEL**

Was container label (other than Blisters) submitted? **YES**  
(For BLISTER labels go to section 3.1.5.)

We evaluated the container labels for the inclusion of all required statements and safety considerations.

**Reviewer Assessment:**

Is the established name acceptable? **YES**  
Is title case used in expressing the established name? **YES**  
Does labeling comply with Tall Man lettering recommendations found on FDA webpage? **NA**  
Is container label too small to contain all required information? **NO** If yes, does the container meet the “too small” exemption found in [21 CFR 201.10\(i\)](#)? **NA**  
Does the following information appear as the most prominent information on the Principal Display Panel?  
Proprietary name: **NA**  
Established name: **YES**  
Product strength: **YES**  
Is the following information properly displayed?  
Net quantity statement: **YES**  
Route(s) of administration (other than oral): **YES**  
Warnings (if any) or cautionary statements (if any): **YES**  
Medication Guide Pharmacist instructions per 21 CFR 208.24(d): **YES**

Controlled substance symbol: **NA**

Usual Dosage statement: **YES**

Product strength equivalency statement: **NA**

NDC: **YES**

Bar code per 21 CFR 201.25(c)(2): **YES**

Is the Manufacturer statement acceptable? **YES**

For foreign manufacturers, does the labeling have the country of origin? **NA**

Are the required USP recommendations reflected on the label(s)? **NA**

Is the storage or dispensing statement consistent with the How Supplied section of the insert? **YES**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**

Are all abbreviations acceptable? (e.g., mg, mcg, HCl)? **YES**

Are the recommendations for leading and terminal zeroes, decimals, and commas followed? **YES**

Are multiple strengths differentiated by use of different color or other acceptable means? **NA**

Are the labels of related products differentiated to avoid selection errors? **YES**

Does the ANDA require the same color coding as the Model Labeling? **NO**

Are the requirements of 21 CFR 201.15 met for all required label statements? **YES**

Are the requirements of 21 CFR 201.100 met for all required label statements? **YES**

**Reviewer Comments:**

We will request the applicant remove “w/w” from the established name.

We will request the applicant add “Use the dosing card attached inside carton” to the PDP. Additionally, we will request the applicant add “Store the dosing card with your diclofenac sodium topical gel, 1%.” after the storage statement in accordance with the RLD.

We will request the applicant provide the space for the lot number and expiration date.

The applicant has two pending ANDAs for topical forms of diclofenac sodium; however, both are topical solutions. (b) (4). Both forms are topical; (b) (4)  
(b) (4)

Pending ANDA 208198

(b) (4)







### **3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS**

Is container for parenteral solution? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.4.2.

#### ***Reviewer Assessment:***

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **NA**

If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **NA**

Is the quantity or proportion of all inactive ingredients listed on label as required under [21 CFR 201.100\(b\)\(5\)\(iii\)](#)? **NA**

#### **Reviewer Comments:**

None

### **3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE**

Is container for solid injectable? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.4.3.

#### ***Reviewer Assessment:***

Is the strength in terms of the total amount of drug per vial? **NA**

Are instructions for reconstitution and resultant concentration provided, if space permits? **NA**

Is the quantity or proportion of all inactive ingredients listed on label as required under [21 CFR 201.100\(b\)\(5\)\(iii\)](#)? **NA**

#### **Reviewer Comments:**

None

### **3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE**

Is container a Pharmacy Bulk Package (parenteral preparations for admixtures)? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.5.

#### ***Reviewer Assessment:***

Is there a prominent, boxed declaration reading “Pharmacy Bulk Package – Not for Direct Infusion” on the principal display panel following the expression of strength? **NA**

Does the container label include graduation marks? **NA**

Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **NA**

Is the quantity or proportion of all inactive ingredients listed on label as required under [21 CFR 201.100\(b\)\(5\)\(iii\)](#)? **NA**

#### **Reviewer Comments:**

None

### **3.1.5 RX: UNIT DOSE BLISTER LABEL**

Is container a Unit Dose Blister Pack? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.6.

#### ***Reviewer Assessment:***

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **NA**

Do proprietary name, established name, strength, bar code, and manufacturer appear on each blister cell? **NA**

Does the established name describe only one unit (e.g. “tablet” rather than “tablets”)? **NA**

**Reviewer Comments:**

None

**3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING**

Was carton labeling submitted? **YES**

If YES go to Reviewer Assessment below, if NO go to section 3.3.

***Reviewer Assessment:***

Is the established name acceptable? **YES**

Is title case used in expressing the established name? **YES**

Does labeling comply with Tall Man lettering recommendations found on FDA webpage? **NA**

If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **NA**

Does the following information appear as the most prominent information on the Principal Display Panel?

Proprietary name: **NA**

Established name: **YES**

Product strength: **YES**

Is the following information properly displayed?

Net quantity statement: **YES**

Route(s) of administration (other than oral): **YES**

Warnings (if any) or cautionary statements (if any): **YES**

Medication Guide Pharmacist instructions per 21 CFR 208.24(d): **YES**

Controlled substance symbol: **NA**

Usual Dosage statement: **YES**

Product strength equivalency statement: **NA**

NDC: **YES**

Bar code per 21 CFR 201.25(c)(2): **YES**

Is the Manufacturer statement acceptable? **YES**

Are the required USP recommendations reflected in the labeling? **NA**

Is the storage or dispensing statement consistent with the How Supplied section of the insert? **YES**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**

Are all abbreviations acceptable? (e.g., mg, mcg, HCl)? **YES**

Are the recommendations for leading and terminal zeroes, decimals, and commas followed? **YES**

Are multiple strengths differentiated by use of different color or other acceptable means? **NA**

Are the labels of related products differentiated to avoid selection errors? **YES**

Does the ANDA require the same color coding as the Model Labeling? **NO**

If country of origin is not on Container, does it appear on outer packaging labeling? **NA**

Are the requirements of 21 CFR 201.15 met for all required label statements? **YES**

Are the requirements of 21 CFR 201.100 met for all required label statements? **YES**

**Reviewer Comments:**

We will request the applicant remove “w/w” from the established name on the PDP and back label.

We will request the applicant add “Store the dosing card with your diclofenac sodium topical gel, 1%.” after the storage statement.

Dosing Card:

We will request the applicant add “Dosing card for” prior to the established name. Additionally, we will request the applicant add “(2.25 inches)” and “(4.5 inches)” directly below “2 grams” and “4 grams”, respectively.

### **3.2 OTC (OVER THE COUNTER) DRUG PRODUCT**

#### **3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION**

**Reviewer Assessment:**

Is the patient labeling the same as the model labeling, except for allowable differences? **NA**

Is Drug Facts Labeling format acceptable per [21 CFR 201.66](#)? **NA**

Does “Questions?” have a toll-free number no less than 6 pt. font size [per 21 CFR 201.66\(c\)\(9\)](#) or “1-800-FDA-1088” per [21 CFR 201.66 \(c\)\(5\)\(vii\)](#)? **NA**

Did firm submit a Labeling Format Information Table to evaluate the font size? **NA**

Is the applicant’s “patent carve out” acceptable? **NA**

Is the applicant’s “exclusivity carve out” acceptable? **NA**

Is the established name for this ANDA acceptable? **NA**

Is title case used in expressing the established name? **NA**

Does the following information appear as the most prominent information on the Principal Display Panel?

Proprietary name: **NA**

Established name: **NA**

Product strength: **NA**

Is the following information properly displayed?

Therapeutic category: **NA**

Net quantity statement: **NA**

Route(s) of administration (other than oral): **NA**

Warnings (if any) or cautionary statements (if any): **NA**

NDC: **NA**

Bar code per [21 CFR 201.25\(c\)\(2\)](#): **NA**

Is the Manufacturer statement acceptable? **NA**

For foreign manufacturers, does the labeling have the country of origin? **NA**

Are the required USP recommendations reflected in the labeling? **NA**

Is the storage statement acceptable? **NA**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**

Are all abbreviations acceptable? (e.g., mg, mcg, HCl)? **NA**

Are the recommendations for leading and terminal zeroes, decimals, and commas followed? **NA**

Are multiple strengths differentiated by use of different color or other acceptable means? **NA**

Are the labels of related products differentiated to avoid selection errors? **NA**

**Reviewer Comments:**

NA

**3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON**

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling Inactive Ingredients	ANDA Inactive Ingredients
NA	NA

**Reviewer Assessment:**

Are the inactive ingredients information consistent with “Components and Composition” information as provided in Module 3.2.P.1? **NA**

Are the inactive ingredients listed in alphabetical order? **NA**

For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**

If the labeling includes a “Does not contain...” statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

**Reviewer Comments:**

NA

**3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION**

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 9 and will be referred to the appropriate review discipline for evaluation.

Table 9: Comparison of Model Labeling to ANDA finished product	
Model Labeling	NA
ANDA (enter source of information of product description on the right hand column; e.g. chemistry Review & date, Module 3.2.P.5.1)	NA

**Reviewer Assessment:**

Is the description ([scoring](#), color and [imprint](#)) of the finished product consistent with the Drug Product Quality submission? **NA**

Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**

Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **NA**

If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**

Is the storage or dispensing statement acceptable as compared to the Model Labeling? **NA**

**Reviewer Comments:**

NA

**3.2.2 OTC: OTHER PATIENT LABELING**

Are other patient labeling required? **CLICK HERE**

If YES go to Reviewer Assessment below, if NO go to section 3.3.

**Reviewer Assessment:**

Was other patient labeling submitted? **NA**

Is the patient labeling the same as the model labeling, except for allowable differences? **NA**

**Reviewer Comments:**

NA

**3.3 CONTAINER/CLOSURE**

We evaluated the container/closure system of this product to determine if special child-resistant packaging is required based on packaging configuration. Additionally, we evaluated other aspects of the container closure that relate to the dosage form, product formulation, and product class. Below is a description of the container/closure for the ANDA product.

**Reviewer Assessment:**

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.

Does the container require a child-resistant closure (CRC) as described in the [Poison Prevention Act and regulations](#)? **NO**

Are the tamper evident requirements met for [OTC](#) and [Controlled Substances](#)? (If quality review follows the chemistry-labeling MOU, obtain answer from Appendix D of chemistry review; if quality review does not follow the MOU, labeling reviewer is responsible for assessing for tamper evidence.) **NA**

**For ophthalmic products:**

Does this ophthalmic products cap color match [the American Academy of Ophthalmology \(AAO\) packaging color-coding](#) scheme? **NA**

**For parenteral products:**

Is there text on the cap/ferrule overseal of this injectable product? **NA**

If YES, does text comply with the recommendations in USP General Chapter <1>? **NA**

What is the cap and ferrule color? **NA**

**NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.**

**Reviewer Comments:**

This product is non CRC.

**3.4 CALCULATIONS FOR CONTENTS IN LABELING**

Is calculation of ingredient(s) required? **NO**

If YES, go to Table 10 and Reviewer Assessment below, if NO go to section 3.5.

We verified the calculation on the following content.

Table 10: Ingredients		
Ingredient	Stated Content	Location of the Information
NA		

(Note: For Rx products, if chemistry review follows the MOU, chemistry reviewer will verify the accuracy of the active and inactive ingredient amount(s) if information is in the DESCRIPTION and HOW SUPPLIED sections for all products, and additionally, DOSAGE AND ADMINISTRATION section for parenteral

products. See Chemistry-Labeling MOU, Appendix A, Miscellaneous section for discussion on calculations.)

**Reviewer Assessment:**

Does the chemistry review follow the Chemistry/Labeling MOU? **CLICK HERE**

Are the stated contents in the table above acceptable? **CLICK HERE**

(b) (4)

Are the labeling requirements met per 21 CFR 201.323? **CLICK HERE**

**Reviewer Comments:**

NA

**3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS**

We evaluated the [SPL data elements](#) to ensure they are consistent with the information submitted in the ANDA.

Table 11: ANDA Tablet/Capsule Size and Imprint

Tablet/Capsule Strength	ANDA Tablet/Capsule Size (mm) and imprint code from SPL	ANDA Tablet/Capsule Size (mm) and imprint code (Cite source of information such as the chemistry review that follows the MOU, Product Specification in 3.2.P.5.1, Commercial Batch Record in 3.2.P.3.3. etc.)
41T	41T	41T
41T	41T	41T

**Reviewer Assessment:**

For solid oral dosage forms: Do size and imprint code from the SPL data elements match the information provided in the quality submission? **CLICK HERE**

Are all the other data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **YES**

**Reviewer Comments:**

This drug product is a gel. Thus, there is no tablet/capsule size and imprint information.

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 208077Orig1s000**

**MEDICAL REVIEW(S)**

### Addendum to Review of a Clinical Endpoint Bioequivalence Study Following OSIS Inspection Results

<b>ANDA number</b>	208077
<b>Drug Product</b>	Diclofenac Sodium Topical Gel, 1%
<b>Applicant Name</b>	Amneal Pharmaceuticals
<b>Treatment Indications</b>	Topical treatment for the relief of the pain of osteoarthritis of joints, such as the knees and those of the hands.
<b>Reference Listed Drug (RLD)</b>	Voltaren <sup>®</sup> Gel, 1%
<b>NDA for RLD</b>	022122, approved on 10/17/07
<b>RLD Applicant Name</b>	Novartis
<b>Date of Original Submission</b>	12/19/2014
<b>Materials Reviewed</b>	Original submission: 12/19/2014 Amendment(s): SAS.xpt files and a data definition file: 01/13/2015 Response to ECD: 08/05/2015  FDA statistical review report prior to OSIS inspection result: 05/28/2015 FDA statistical Addendum post OSIS “For-Cause” inspection result: 02/19/2016 OSIS Routine Inspection Result: 08/10/2015 OSIS “For Cause” Inspection Results: 1/27/16 and 02/19/16 (addendum) Draft Guidance of this product posted in March 2011
<b>Primary Reviewer</b>	Joe Zhang, MD, Ph.D. Clinical Reviewer, Division of Clinical Review (DCR) Office of Bioequivalence (OB) Office Generic Drugs (OGD)
<b>Secondary Reviewer</b>	Carol Y. Kim, Pharm. D. Acting Team Leader, ANDA Team DCR/OB/OGD
<b>Tertiary Reviewer</b>	Lesley-Anne Furlong, MD Director, DCR/OB/OGD
<b>Date of Completion</b>	02/25/2016
<b>Conclusion</b>	The final FDA statistical analysis results, following subject adjustments based on OSIS findings, show that the clinical endpoint BE study AM-DCG-001 is adequate to demonstrate bioequivalence between the products. Thus, DCR recommends approval of the application.

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## **Addendum to Review of a Clinical Endpoint Bioequivalence Study for ANDA 208077 Following OSIS Inspection Findings**

### **1 Executive Summary**

#### **1.1 Approval Recommendation**

DCR recommends approval of this application, contingent on approval recommendations from the other disciplines on the review team. Following the Office of Study Integrity and Surveillance (OSIS) inspection reports on 8/10/15, 1/27/16, and 2/19/16 and the final FDA statistical analysis results, DCR's conclusion remains the same.

#### **1.2 Summary of Clinical Findings**

This addendum review evaluates the information provided in the OSIS inspection reports dated 8/10/15, 1/27/16, and 2/19/16 for the study #AM-DCG-001. For the routine inspection, OSIS inspected 3 clinical sites (Malpani Multispecialty Hospital, GMERS Medical College and Hospital, and Rathi Orthopedic Research Centre) in India. Three additional sites (B.J Medical College & Hospital, Andhra Medical College, and Centre for Knee Surgery, Vadodara, Gujarat, India) were inspected for "For-Cause" as requested by DCR for the potential data fraud. Following the routine inspection, clinical data from 3 inspected sites were acceptable for the review. Based on the result of "For-Cause" inspection, clinical data from 1 site (B.J Medical College & Hospital) were not acceptable and 14 subjects from one site (Andhra Medical College) were excluded from the final FDA statistical analysis due to lack of proper verification of inclusion/exclusion criteria. The clinical data from the remaining one site (Centre for Knee Surgery, Vadodara, Gujarat, India) were accepted for the review.

In the original DCR review dated 8/13/15, DCR concluded that the clinical endpoint bioequivalence study (#AM-DCG-001) is adequate to support approval of the application pending OSIS inspection result.

After excluding those subjects based on OSIS recommendation, the conclusion of the final FDA statistical analysis result remains the same. According to the FDA statistical analysis in the new per protocol (PP) population, the 90% CI for the test/reference ratio of mean change from baseline to week 4 in WOMAC pain score is [0.977, 1.204], within the bioequivalence limits of [0.80, 1.25]. Both the test and reference products are shown to be superior ( $p$ -value  $< 0.0001$ ) to the vehicle in the FDA new modified intent-to-treat (MITT) population. A total of 1062 subjects were included in the FDA's final MITT population and 1036 subjects were included in the FDA's final PP population. Therefore, the applicant's study is **adequate** to support the bioequivalence between the products.

## 2 Clinical Review

### 2.1 Introduction and Background

This addendum review focuses on the information provided by the Office of Study Integrity and Surveillance (OSIS) and the final FDA statistical review following subject adjustments based on OSIS recommendation.

On 7/17/15, DCR requested “For-Cause” inspection on sites 24 (Andhra Medical College), 28 (B.J Medical College & Hospital), and 33 (Centre for Knee Surgery) for the potential data fraud because all subjects in the RLD group had the change from baseline in WOMAC pain score of “-1”.

On 7/22/15, DCR sent an ECD requesting clarification of data from 14 clinical sites (#5, #17, #19, #20, #22, #24, #26, #27, #28, #29, #30, #31 #32 and #33) out of 19 clinical sites for the study #AM-DCG-001.<sup>1</sup> Majority of subjects in the RLD group had a constant change in Western Ontario McMaster Osteoarthritis (WOMAC)<sup>2</sup> pain score equals to “-1” from the baseline with lack of variability in these 14 clinical sites. In 6 (#22, 24, 26, 28, 30, and 31) of these 14 clinical sites, all subjects in the RLD group had the change from baseline in WOMAC pain score of “-1” for the potential data fraud.

On 8/5/15, in response to DCR ECD request, the applicant stated as follows:<sup>3</sup> “Although this observation on the total WOMAC pain scores appears to be unusual, it can only be ascribed to chance. Additionally, it has no impact on the accuracy of the results and the fact that bioequivalence was demonstrated in this clinical study.”

On 8/10/15, OSIS provided routine inspection results from 3 clinical sites (Rathi Orthopedic and Research Centre, Ahmedabad, India (#19), Malpani Multispecialty Hospital, Jaipur, India (#20), and GMERS Medical College and Hospital, Ahmedabad, India (#32).<sup>4</sup> Based on their findings, OSIS recommended “data from these three study sites, Malpani Multispecialty Hospital, GMERS Medical College and Hospital, and Rathi Orthopedic Research Centre, be accepted for further agency review.”

On 1/27/16, OSIS provided “For Cause” inspection results. Following OSIS “For Cause” inspection findings at all three inspected clinical sites, #28 (B.J Medical College & Hospital, Ahmedabad, India), #24 (Andhra Medical College, Visakhapatnam, India), and #33 (Centre for Knee Surgery, Vadodara, India), OSIS recommended as follows:<sup>5</sup>

1. Clinical data from the site #28 are not acceptable. OSIS was not able to confirm whether 101 of 103 subjects enrolled in this site met inclusion/exclusion criteria prior to randomization.

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<sup>1</sup> DCR asked the applicant to provide the explanation why its study data lack variability for the change from baseline in WOMAC pain score for most subjects in the reference listed drug (RLD) group.

<http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880b2f662>

<sup>2</sup> WOMAC pain score ranges 1 to 20. “-1” means WOMAC pain score reduced 1 from baseline after treatment.

<sup>3</sup> [\\cdsesub1\evsprod\anda208077\0005\m1\us\1-2-cover-letter-seq-0005-20150805-word.doc](http://cdsesub1\evsprod\anda208077\0005\m1\us\1-2-cover-letter-seq-0005-20150805-word.doc)

<sup>4</sup> <http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880b48208>

<sup>5</sup> <http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880c7116b> and

<http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880c80f73>

2. Fourteen (14) subjects from the site 24 should be excluded due to lack of personal verification to confirm eligibility to meet inclusion/exclusion criteria.
3. Clinical data from the site #33 are acceptable. Although a protocol violation was noted for one subject who did not meet inclusion/exclusion criteria, data from this subject was not included in the efficacy assessment. Thus, OSIS stated that “data integrity will not be affected by this protocol violation”.

OSIS also noted that inspections of “two additional sites were to be arranged soon”. These sites were not related to the clinical endpoint BE study for ANDA 208077. They were from sites for two different ANDAs (ANDAs 202559 and 204272).<sup>6</sup>

On 02/02/16, based on OSIS inspection findings, DCR requested that all subjects from the site 28 and 14 subjects from the site 24 be excluded for the final FDA statistical analysis.

On 2/19/16, OSIS provided addendum report clarifying the missing subject (b)(6) from the site 24. In the original OSIS “for cause” inspection report dated 1/27/16, only 13 subject numbers were provided. In this OSIS addendum report, the OSIS included a list of subject numbers and randomization numbers for those 14 subjects from the site 24 to be excluded from the FDA statistical analysis.

On 2/19/2016, FDA statistician provided the final statistical result excluding all subjects from the site 28 and 14 subjects from the site 24. The FDA statistician concludes as follows: “The test product was bioequivalent to the reference product for the mean change from baseline to week 4 in WOMAC pain score in the FPP population with the 90% CI on the ratio of two means being (97.7%, 120.4%). This is within the range of 80% to 125%, demonstrating equivalence. The least squares mean of reference group (-1.84) in this re-analysis was slightly smaller than that (-1.77) in the original analysis by Dr. Fan. This numerical difference shifts the confidence interval but the overall conclusion remains the same. The test and reference products were both statistically significantly better than the vehicle control for the mean change from baseline to week 4 in WOMAC pain score in the FMITT population with p-value<0.05.”

Based on the OSIS inspection findings and FDA statistical re-analysis excluding all subjects from site 28 and 14 subjects from site 24, the study #AM-DCG-001 is adequate to demonstrate bioequivalence between products.

## 2.2 Summary of OSIS Inspection Report

### A. Review of the OSIS Report: Routine Inspection (8/10/15)<sup>7</sup>

Site no.	Site Name and Location	OSIS Findings	Comment
32	GMERS Medical College and Hospital	“Two-observation FDA Form-483” was issued at the conclusion of inspection.	VAI (Voluntary Action)

<sup>6</sup> <http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880c80fbc>

<sup>7</sup> <http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880b48208>

Site no.	Site Name and Location	OSIS Findings	Comment
		<p>Observation 1: An investigation was not conducted in accordance with the investigational plan.</p> <p>“The following subjects were screened and randomized prior to receipt of laboratory results for exclusion/inclusion criteria:</p> <p>a. Subject (b) (6) – randomized on 23/Jun/2014 and IP dispensed (Kit #2117) prior to obtaining laboratory results reported on 26/Jun/2014 and reviewed on 28/Jun/2014 by the principal investigator</p> <p>b. Subject (b) (6) – randomized on 24/Jun/2014 and IP dispensed (Kit #2122) prior to obtaining laboratory results reported on 27/Jun/2014 and reviewed on 30/Jun/2014 by the principal investigator</p> <p>c. Subject (b) (6) – randomized on 24/Jun/2014 and IP dispensed (Kit #2119) prior to obtaining laboratory results reported on 26/Jun/2014 and reviewed on 30/Jun/2014 by the principal investigator”</p> <p><i>OSIS found the firm’s response acceptable. The principal investigator contacted the laboratory by telephone to request the results and verified that laboratory results were acceptable for enrollment. A note to file was added for these subjects documenting why these subjects were randomized prior to review of lab reports.</i></p> <p>2. “The Site Staff Signature and Responsibility Log, Version 01, Effective 19MAR2014 does not identify the tasks and duties performed and documented in the case history records for the following study participants:</p> <p>a. CRC-1 performed UPT tests for 11 subjects (Subjects (b) (6) [redacted])</p> <p>b. CRC-2 performed physical procedures such as height and weight on five (5) subjects (b) (6) [redacted] and processed laboratory samples for two (2) subjects (b) (6) [redacted]</p> <p>c. CRC-3 performed physical procedures such as height and weight on 15 subjects (including (b) (6) [redacted]) and processed laboratory samples for 13 subjects (b) (6) [redacted]</p> <p><i>OSIS concluded that “these observations do not affect subject safety or data integrity”. The principal</i></p>	<p>Indicated)</p>

Site no.	Site Name and Location	OSIS Findings	Comment
		<p><i>investigators performed the entire physical examinations and laboratory samples were performed by Metropolis contract lab phlebotomists as recorded in the subjects' narrative sources.</i></p> <p>3. "There is no "File Note" in the Master File to document that phlebotomy procedures not identified on the Site Staff Signature and Responsibility Log, Version 01, Effective 19MAR2014, will be conducted on-site by off-site phlebotomists from the contract laboratory assigned to conduct laboratory analysis for subject samples collected during the screening visit as required by the investigational plan."</p> <p><i>OSIS concluded that "this observation doesn't affect data integrity". A note to file was added to clarify the phlebotomy and processing of blood samples.</i></p> <p>Observation 2: "Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. Specifically, the original color copy of the "Test Requisition Form (TRF)" was not maintained in the case history records for subject's (b) (6)</p> <p><i>OSIS concluded that "this observation doesn't impact data integrity". Because the lab reports were not provided in a timely manner, "a print of the "soft" copy of the TRF from the lab was included in several patient files".</i></p>	
20	Malpani Multispecialty Hospital	<p>FDA Form-483 was issued at the conclusion of inspection.</p> <p>Observation 1: "Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation and informed consent. Specifically, the following records were not adequate:</p> <p>a. Source documents for subjects (b) (6) note subjects obtained the Informed Consent Form, completed screening visit, completed physical exam and blood test conducted. However, the case history file does not document reason why subjects were not randomized and lost to follow up.</p> <p>b. Case report forms for subjects (b) (6)</p>	VAI

Site no.	Site Name and Location	OSIS Findings	Comment
		<p>(b) (6) do not indicate correct date of birth for the subjects according to source data.”</p> <p><i>OSIS concluded that “neither observation affects study data”. The firm explained that those subjects were not randomized “because enrollment targets were met”. For data clarification, forms were prepared to correct subject information.</i></p> <p>Observation 2: “Failure to assure that an IRB complying with applicable regulatory requirements was responsible for the initial and continuing review and approval of a clinical study. Specifically, the Protocol Deviation Log notes three (3) deviations pertaining to randomized subjects identified as (b) (6). However, there is no correspondence between the site and the Institutional Ethics Committee regarding these protocol deviations.”</p> <p><i>OSIS concluded that “this observation does not affect subject safety or data integrity”. The firm provided protocol deviations to the Institutional Ethics Committee.</i></p> <p>Observation 3: “An adequate final report was not provided to the sponsor shortly after completion of the investigator’s participation in the investigation. Specifically, a letter dated 11/Dec/2014 regarding Protocol No. AM-DCG-001 regarding study closure status EC notification indicates that there were 10 screen failures and 02 patients screened but could not be randomized as recruitment target met. However, the Subject Screening and Enrollment Log documents that there are nine (9) screening failures and (3) subjects that signed ICF and were screened but not randomized.”</p> <p><i>OSIS concluded that “there is no impact on data integrity”. Per OSIS, the firm’s explanation and corrective action were acceptable.</i></p>	
19	Rathi Orthopedic Research Centre	FDA Form-483 was not issued at the conclusion of the inspection.	VAI

**Overall Conclusion**

OSIS concluded as follows: “After evaluation of the EIRs, the Form-483 Observations, and the Firm’s responses, we recommend that data from these three study sites, Malpani Multispecialty

Hospital, GMERS Medical College and Hospital, and Rathi Orthopedic Research Centre, be accepted for further agency review.”

**Reviewer’s Comment:** *This reviewer agrees with the OSIS conclusion.*

B. Review of OSIS Report: For Cause inspection (1/27/16 and 2/19/16)<sup>8</sup>

At the conclusion of the For Cause inspection of three clinical sites (1. B.J Medical College & Hospital, Ahmedabad, Gujarat, India, 2. Andhra Medical College, Visakhapatnam, Andhra Pradesh, India, and 3. Centre for Knee Surgery, Vadodara, Gujarat, India), no form FDA 483 was issued at Andhra Medical College and Centre for Knee Surgery. A one-item FDA 483 was issued at B.J Medical College & Hospital, Ahmedabad, Gujarat, India.

Based on the inspection findings, OSIS recommended that data from B.J Medical College & Hospital clinical site are **not acceptable for review** because they were unable to confirm whether 101 of 103 study subjects enrolled in this study met the inclusion/exclusion criteria prior to randomization. The OSIS also recommended exclusion of 14 subjects from the Andhra Medical College due to insufficient verification of personal identification such as age of subjects to confirm eligibility to meet inclusion/exclusion criteria.

OSIS inspection findings specific to each site are shown below.

1. Site 28: B.J Medical College & Hospital, Ahmedabad, Gujarat, India

Site (#28)	OSIS findings	Comment
B.J Medical College & Hospital, Ahmedabad, Gujarat, India	<p>Observation 1: Form FDA 483 was issued for failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specific comments are as follows:</p> <p>a) Subject (b) (6) did not have target X-ray record as indicated in source document. As a corrective action, a “Note to File” was created for this subject and it described that the copy of knee x-ray taken at another facility was used during screening visit. <i>Per OSIS, their response was acceptable.</i></p> <p>b) Per source document, one subject (b) (6) was randomized with a subject (b) (6) at visit 2. But, this same subject was randomized with subject ID (b) (6) at visits 3 and visit 4. This was a typographical error and the corrected randomization for subject (b) (6) <i>Per OSIS, their response was acceptable.</i></p>	<ul style="list-style-type: none"> <li>• VAI (Voluntary Action Indicated)</li> <li>• OSIS concluded that data from this site is not acceptable for review.</li> </ul> <p>All subjects from this site were recommended to be excluded from the final FDA analysis.</p>

<sup>8</sup> <http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880c7116b> and <http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880c80f73>

	<p>c) Of 103 subjects screened, “all 99 subjects completed the study with each subject missing 1 application dose in this 4-week study trial as noted in the “Patient Diary Part 1 and Part 2” booklets provided to the subjects upon enrollment into the study”. The OSIS inspector observed that the diaries showed similarity in handwriting raising suspicion that the diaries may have been completed by a single person. The inspector also noted that no application dose was missing by any subject, except the first application, which was missing for all 99 subjects. <i>Per OSIS, the occurrence of one missing application dose during the course of the study didn’t violate study protocol and since it applies to all treatment categories (vehicle, test, and reference), its impact to the study outcome is “negligible”. The inspector also commented that they found “no strong evidence of record falsification to recommend rejection of data from these subjects”.</i></p> <p>Observation 2: In addition to the FDA 483 observations noted above, two discussed items were noted with the management at the close-out meeting on the site.</p> <p>Discussion item 1. “Inadequate documentation of “Note to File” regarding late laboratory reports for enrolled subjects”.</p> <ul style="list-style-type: none"><li>• <i>The laboratory report results of 15 subjects (b) (6) [redacted] were dated a month or longer from when the subject was randomized into the study.</i></li><li>• <i>Per OSIS, lab reports for these 15 subjects couldn’t be verified by source documents.</i></li></ul> <p>Discussion item 2. “Inadequate identification of the X-rays for all 103 subjects enrolled in the study. X-rays were labeled using “hospital” tape or “post-it” sticky notes with the subject number. The X-rays did not include a date it was taken and subjects who provided third party X-rays, the information was not adequately documented in the subject’s study record”.</p> <ul style="list-style-type: none"><li>• <i>Per OSIS, subject identification and date the x-rays were taken couldn’t be confirmed.</i></li><li>• <i>OSIS couldn’t confirm whether proper assessment</i></li></ul>	
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	<p><i>was conducted to ensure 101 or 103 subjects enrolled in the study met the inclusion/exclusion criteria prior to randomization.</i></p> <ul style="list-style-type: none"> <li>• <i>OSIS recommends that data from this site are NOT acceptable for Agency’s review.</i></li> </ul>	
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2. Sites 24 and 33: Andhra Medical College and Centre for Knee Surgery

Site 24	OSIS findings	Comment
<p>Andhra Medical College, Visakhapatnam, Andhra Pradesh, India</p>	<p>No FDA 483 was issued. The following items were discussed with the management at the close-out meeting.</p> <p>Discussion item 1. “Subject (b) (6) dispensing log was a copy and not able to be un-blinded. A “Note to File” documented that the dispensing log for this subject was inadvertently lost and a copy of the blinded dispense log previously submitted to the sponsor was obtained to remain in the Master File.”</p> <p><i>OSIS concluded that this was “an isolated incident and inclusion of this subject’s data is unlikely to affect the overall study outcome”. The applicant sent the copy of the original blinded record.</i></p> <p>Discussion item 2. “Source documents for 13 subjects did not contain identification records and a “Note to File” dated 02/SEP/2014 indicated repeated attempts to obtain subject id’s. However, subjects completed the study but no documentation of how or when subjects were asked to provide id’s for any of the 4 visits. In addition, subject (b) (6) was enrolled in the study and ID provided states (b) (6) and (b) (6) and there were no other documents to verify this discrepancy in the subject’s age. A “Note to File” dated 02/SEP/2014 states that date of birth recorded in signed ICF was considered the actual date of birth for the purpose of the study.”</p> <p><i>OSIS concluded that “the absence of source document to verify the personal identification information is a major concern as it is not possible to ascertain a large number of study subjects at this site indeed met the inclusion criteria”.</i></p> <p>Discussion item 3. “Three subjects enrolled in the study</p>	<p>VAI</p> <p>OSIS recommends exclusion of 14 subjects from the site 24 due to lack of proper verification of age of subjects to confirm eligibility to meet inclusion/exclusion criteria.</p>

	<p>were illiterate and signed the ICF with a thumbprint. However, the Patient Diaries were completed and source documents did not indicate how or who completed the diaries.”</p> <p>Discussion item 4. “Three subjects (b) (6) were enrolled in the study and completed the Patient Diaries. These subjects were enrolled on the same day (07/17/2014) and after reviewing the Patient Diaries all six diaries had similar handwriting.”</p> <p><i>For items 3 &amp; 4, OSIS noted that the diaries of 6 subjects noted above may have been completed by a person other than the study subjects which raises concern about the authenticity of the diaries. However, OSIS concluded that “the authenticity of the diaries doesn’t necessarily impact the efficacy determination”. No further subject adjustment was recommended by OSIS for these findings.</i></p>	
<p>Site 33, Centre for Knee Surgery, Vadodara, Gujarat, India</p>	<p>No Form FDA 483 was issued.</p> <p>Discussion item 1: A protocol violation occurred for one subject (b) (6) that did not meet inclusion/exclusion criteria but completed the study. The event was documented as a protocol deviation and it was due to laboratory findings received late by the study site.</p> <p><i>Per OSIS, data integrity will not be affected by this protocol violation because this subject wasn’t included in the efficacy assessment.</i></p>	<p>NAI (No Action Indicated)</p>

In conclusion, OSIS recommended as follows:

1. Data from site 28 (BJ Medical College & Hospital) are not acceptable for further Agency review because it is not possible to confirm whether 101 of 103 study subjects enrolled in the study met the inclusion/exclusion criteria prior to randomization.
2. Data for fourteen subjects (14) from site 24 (Andhra Medical College) should be excluded due to lack of proper verification of age of subjects to confirm eligibility to meet inclusion/exclusion criteria.

**Reviewer's Comments:**

*Based on the “For Cause” inspection findings, DCR recommended FDA statistician to exclude all subjects (103) from B.J Medical College & Hospital site and 14 subjects from Andhra Medical College. Following subject adjustments based on OSIS findings, the test product is shown to be bioequivalent to the RLD. Therefore, DCR’s conclusion in the original review remains the same.*

### 2.3 Review of the FDA Statistical Report (02/19/2016)

Based on the OSIS inspection findings, DCR recommended all subjects (103) from B.J Medical College & Hospital site and 14 subjects from Andhra Medical College be excluded for the final FDA statistical analysis.

Following subject adjustments based on OSIS findings, the final FDA statistical analysis results are shown below:<sup>9</sup>

	Sponsor			FDA		
	Test	Reference	Vehicle	Test	Reference	Vehicle
<b>PP Population</b>						
N	383	388	376	345	352	339
LSMean (WOMAC pain score)	-2.0050	-1.7762		-1.9977	-1.8430	
Point estimate of ratio and 90% CI for Test and Reference (%)	112.88(102.5, 124.56)			108.4 (97.7, 120.4)		
<b>MITT Population</b>						
N	389	391	386	352	357	352
LSMean (WOMAC pain score)	-2.2332	-2.0287	0.6387	-2.25	-2.109	0.524
(Test or Reference) vs. Vehicle	<0.0001	0.0001		<0.0001	<0.0001	

**Reviewer’s Comment:** *The final FDA statistical results indicate that the 90% CI for the test/reference ratio of mean change from baseline to week 4 in WOMAC pain score is [0.977, 1.204], within the bioequivalence limits of [0.80, 1.25] and the test and RLD products are also shown to be superior to the vehicle. Thus, the test product is shown to be bioequivalent to the RLD.*

### 2.4 Conclusion and Recommendation

#### 2.4.1 Conclusion

Based on the OSIS inspection findings dated 8/10/2015, 1/27/2016 and 2/19/2016, the clinical data from the study (AM-DCG-001) are acceptable except for the followings: all subjects (103) from B.J Medical College & Hospital site and 14 subjects from Andhra Medical College. Following exclusion of these subjects based on OSIS findings, the final FDA statistical analysis results show that the study AM-DCG-001 is adequate to demonstrate bioequivalence between products.

<sup>9</sup> <http://panorama.fda.gov/task/view?ID=5495280c0038c72f7aaf3ace8f0f0540>

#### **2.4.2 Recommendation**

DCR recommends approval of this application, contingent on approval recommendations from the other disciplines on the review team.

APPEARS THIS WAY ON  
ORIGINAL

**CLINICAL BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT**

The Division of Clinical Review has completed its review and has no comments at this time.

APPEARS THIS WAY ON ORIGINAL

### Review of a Clinical Endpoint Bioequivalence Study

<b>ANDA number</b>	208077
<b>Drug Product</b>	Diclofenac Sodium Topical Gel, 1%
<b>Applicant Name</b>	Amneal Pharmaceuticals
<b>Treatment Indication</b>	Topical treatment for the relief of the pain of osteoarthritis of joints, such as the knees and those of the hands.
<b>Reference Listed Drug (RLD)</b>	Voltaren <sup>®</sup> Gel, 1%
<b>NDA for RLD</b>	022122 , approved 10/17/07
<b>RLD Applicant Name</b>	Novartis
<b>Original Submission Date</b>	12/19/2014
<b>Materials Reviewed</b>	Original submission: 12/19/2014 Amendment(s): 01/13/2015: SAS.xpt files and a data definition file 01/15/2015: The placebo information 01/29/2015 :None requiring clinical review 08/05/2015:Response to ECD for data accuracy question OSIS inspection report: Routine inspection has been completed but the report is still pending. For Cause Inspection result is pending. FDA statistical review report prior to OSIS inspection result: 05/28/2015 Draft Guidance of this product posted in March 2011
<b>Primary Reviewer</b>	Zhuo Joe Zhang, MD, Ph.D., Clinical Reviewer Division of Clinical Review (DCR) Office of Bioequivalence (OBE) Office of Generic Drugs (OGD)
<b>Secondary Reviewer</b>	Carol Y. Kim, Pharm. D. Acting Team Leader, ANDA Team DCR/OBE/OGD
<b>Tertiary Reviewer</b>	Lesley-Anne Furlong, MD Acting Director, DCR OBE/OGD
<b>Date of Completion</b>	08/13/2015
<b>DCR Conclusion</b>	DCR concludes that the clinical endpoint bioequivalence study (#AM-DCG-001) is adequate to support approval of the application, contingent on approval recommendations from the other disciplines on the review team. This conclusion is based on clinical data prior to a routine OSIS inspection and For Cause Inspection reports.

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# Review of a Clinical Endpoint Bioequivalence Study for ANDA 208077

## 1 Executive Summary

The applicant, Amneal Pharmaceuticals, submitted an Abbreviated New Drug Application (ANDA) 208077 for Diclofenac Sodium Topical Gel 1%. The reference listed drug (RLD) is Voltaren® (diclofenac sodium) Topical Gel, 1% (NDA 022122, approved on 10/17/07). To support approval of Amneal Pharmaceuticals' Diclofenac Sodium Topical Gel 1%, the applicant submitted a randomized, double-blind, parallel-group, vehicle-controlled, multicenter clinical endpoint bioequivalence study (#AM-DCG-001) in subjects with knee pain due to osteoarthritis (OA) and a PK study (#ARL/12/443). This review focuses on the study (#AM-DCG-001) submitted to ensure that the test product is no worse than the reference listed drug (RLD) for pain relief in the treatment of subjects with osteoarthritis of the knee.

The primary endpoint of the study is the mean change from baseline to week 4 in the Western Ontario McMaster Osteoarthritis Index (WOMAC) pain score (pain score = 0 to 20). According to the applicant's statistical analysis in the per protocol (PP) population, the 90% CI for the test/reference ratio of mean change from baseline to week 4 in WOMAC pain score was [1.025, 1.2456], within the bioequivalence limits of [0.80, 1.25]. Both the test and reference products were superior (p-value < 0.0001) to the vehicle in the applicant modified intent-to-treat (MITT) population. A total of 1166 subjects were included in the applicant's MITT population and 1147 subjects were included in the applicant's PP population.

Based on the FDA statistical analysis of the PP population including all subjects who took rescue medications during the treatment period, the 90% CI for the test/reference ratio of mean change from baseline to week 4 in WOMAC pain score is [1.0194, 1.2400], within the bioequivalence limits of [0.80, 1.25]. Both test and reference products were shown to be superior (p-value < 0.0001) to the vehicle in the FDA MITT population<sup>1</sup>, consistent with the Applicant's study outcome. A total of 1175 subjects were included in the FDA MITT population and 1148 subjects were included in the FDA PP population.<sup>2</sup>

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<sup>1</sup> The FDA MITT population is defined as all subjects randomized and received at least one dose of assigned study treatment. The applicant MITT population definition is slightly different from the FDA MITT. The applicant MITT population is defined as all randomized subjects who met all inclusion/exclusion criteria, received study treatment, and returned for at least one post-baseline visit, which is the same as MITT population defined in the draft guidance of this product.

<sup>2</sup> The FDA PP population is defined as all randomized subjects who met all inclusion/exclusion criteria, were compliant with the assigned study treatment (used at least 75% and no more than 125% of study treatment doses), returned to the study site for the primary endpoint visit within the specified window (+/- 4 days) or discontinued from the study as a treatment failure, and did not have any protocol violations. The applicant PP population is the same as the FDA PP population.

However, this reviewer has concerns about data integrity for 14 clinical sites (#5, #17, #19, #20, #22, #24, #26, #27, #28, #29, #30, #31 #32 and #33). Most subjects in the RLD group had a constant change from the baseline in WOMAC pain score equals to “-1” with lack of variability. In six study sites (#22, #24, #26, #28, #30, and #31), all subjects (n=72) in reference drug group had a constant change from the baseline of WOMAC pain score equals -1 with no variability.

On July 22, 2015, an easily correctable deficiency (ECD) was sent to the applicant requesting an explanation for this lack of variability in the reduction of WOMAC pain score from baseline for most subjects in the reference listed drug (RLD) group. According to the applicant’s ECD response dated August 5, 2015, the applicant concluded that the lack of variability can only be ascribed to chance. The applicant stated that they reviewed the original source subject questionnaires, which were used by the subjects to record their individual pain scores at each visit and compared the subjects’ responses on the WOMAC 1-5 subscales to the Case Report Form. The applicant also reviewed the transcription of the raw data from the Case Report Form to the database which was used by the CRO to calculate the efficacy endpoints. Based on the applicant’s review of these data, no irregularities were found in the source data.

In order to confirm the data accuracy, a For Cause Inspection was requested for site #28 on July 17, 2015 and For Cause Inspections addendum was requested for two additional sites #24 and #33 on July 28, 2015. The results of the For Cause Inspections are pending.

There is a lower number of adverse events (less than 1%) reported in the applicant’s data compared to studies submitted for the approval of the RLD. It is unclear whether it is due to cultural/geographic factors (100% enrollment in India) differences in study design, or inadequate collection of adverse event data. Nine adverse events were reported during the study #AM-DCG-001 in 1175 subjects. All 9 AEs were classified as mild to moderate in severity (3=test, 2=RLD and 4=vehicle). One application site related AE occurred in the test group (subject (b) (6) and 2 application site related AEs occurred in the RLD group (b) (6) subjects). One subject (b) (6) from the test group was discontinued from the study due to mild itching and rashes. The study showed no clinically significant difference between the test and reference products with regard to reported adverse events.

## 1.1 Approval Recommendation

DCR recommends that the clinical endpoint bioequivalence study (#AM-DCG-001) is adequate to support approval of the application, contingent on approval recommendations from the other disciplines on the review team. This conclusion is based on clinical data prior to a routine OSIS inspection and the For Cause Inspection reports.

## 2 Clinical Review

### 2.1 Introduction and Background

#### 2.1.1 Summary of RLD Drug Information

<b>Reference Listed Drug</b>	Voltaren® Gel, 1%
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<b>RLD Applicant name</b>	Novartis
<b>NDA #</b>	022122
<b>Date of RLD Approval</b>	10/17/07
<b>Approved Indication(s)</b>	Topical treatment for the relief of the pain of osteoarthritis of joints, such as the knees and those of the hands.
<b>Recommended Dosing Regimens/dosing considerations for the topic treatment of pain of knees</b>	<p>For lower extremities: apply the gel (4 g) to the affected area 4 times daily. Do not apply more than 16 g daily to any one affect joint of the lower extremities.</p> <p>For upper extremities: apply the gel (2 g) to the affected area 4 times daily. Do not apply more than 8 g daily to any one affected joint of the upper extremities.</p> <p>Total dose should not exceed 32 g per day.</p>
<b>Absorption</b>	The amount of diclofenac sodium that is systemically absorbed from Voltaren <sup>®</sup> Gel is on average 6% of the systemic exposure from an oral form of diclofenac sodium. (Basis: treatment with Voltaren <sup>®</sup> Gel of 1 knee, 4 times a day versus 50 mg, 3 times a day of oral diclofenac tablets.)
<b>Mechanism of Action</b>	The mechanism of action of diclofenac is similar to that of other non-steroidal anti-inflammatory drugs. Diclofenac inhibits the enzyme, cyclooxygenase (COX), an early component of the arachidonic acid cascade, resulting in the reduced formation of prostaglandins, thromboxanes and prostacylin. It is not completely understood how reduced synthesis of these compounds results in therapeutic efficacy.
<b>Boxed Warnings</b>	<p><b><i>Cardiovascular Risk</i></b> Non-steroidal anti-inflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal.</p> <p>Voltaren<sup>®</sup> Gel is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.</p> <p><b><i>Gastrointestinal Risk</i></b> Non-steroidal anti-inflammatory drugs (NSAIDs), including Voltaren<sup>®</sup> Gel, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. Elderly patients are at greater risk for serious gastrointestinal events.</p>

<b>Use in specific populations</b>	Safety and effectiveness in pediatric patients have not been established
<b>Warnings and Precautions</b>	<p>The following special precautions were noted in the RLD labeling:</p> <ul style="list-style-type: none"> <li>• Showering/bathing should be avoided for at least 1 hour after the application. Patient should wash his/her hands after use, unless the hands are the treated joint. If Voltaren® Gel is applied to the hand(s) for treatment, patient should not wash the treated hand(s) for at least 1 hour after the application.</li> <li>• Voltaren® Gel should not be applied to open wounds.</li> <li>• Contact of Voltaren® Gel with eyes and mucous membranes should be avoided.</li> <li>• External heat and/or occlusive dressings should not be applied to treated joints.</li> <li>• Exposure of the treated joint(s) to sunlight should be avoided.</li> <li>• Voltaren® Gel should not be used concomitantly with sunscreens, cosmetics, lotions, moisturizers, insect repellants, or other topical medications on the same skin sites.</li> <li>• Concomitant use of Voltaren® Gel with oral non-steroidal anti-inflammatory drugs (NSAIDs) has not been evaluated, and may increase adverse NSAIDs effects. Wearing of clothing or gloves should be avoided for at least 10 minutes after applying Voltaren® Gel.</li> </ul>
<b>Commonly reported Adverse Events</b>	Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy.

### 2.1.2 Regulatory Background

<b>Draft Guidance</b>	The Draft Guidance for establishing bioequivalence of Diclofenac Sodium Topical Gel, 1%, was posted in March 2011. <sup>3</sup>
<b>BE Study Recommendations</b>	For demonstrating bioequivalence of this product, both pharmacokinetic and clinical endpoint bioequivalence studies are recommended.

<sup>3</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244644.pdf>

<b>Clinical Endpoint Study</b>	Subjects are to be randomized to receive an approximately 4 gram dose of the generic Diclofenac Sodium topical gel the reference listed drug (RLD), or placebo applied to the arthritic knee four times daily for 4 weeks. The primary endpoint is to be evaluated at the end of treatment (study Week 4).
<b>Primary Endpoint (s)</b>	The recommended primary endpoint of the study is the mean change from baseline to week 4 in the WOMAC pain score (pain score = 0 to 20), which is determined by the patient’s responses to five questions (S1–S5) using a 5-point Likert scale (i.e., ‘none’=0; ‘mild’=1, ‘moderate’=2; ‘severe’=3; ‘extreme’=4). The questions pertain to the amount of pain the patient is currently experiencing in the target knee [i.e., ‘How much pain do you have’ when ‘Walking on a flat surface’ (S1), ‘Going up or down stairs’ (S2), ‘At night while in bed’ (S3), ‘Sitting or lying’ (S4), ‘Standing upright’ (S5)].
<b>Secondary Endpoint</b>	None

**Reviewer’s Comment:** Per Division of Bioequivalence II Review dated 3/31/15, the test product was shown to be bioequivalent to the RLD based on a fasting bioequivalence study (ARL/12/443).

**2.1.2.1 Bio-INDs, Protocols, or Control Documents submitted by the Applicant**

Submission	Submission date	Description	Comment
11-0157	2/23/2011	Inquiring study requirement	Clinical endpoint BE study is requested

**2.1.2.2 Bio-INDs, Protocols, or Control Documents submitted by other generic applicants for the same product**

Control documents were submitted by other generic applicants (N=18)

Ctrl No	Title	Description	Status/Date	Doc Date	From	Comments
13-1037	Question for Diclofenac Sodium Topical Gel, 1%					(b) (4)
13-0668	Question for Diclofenac Sodium Topical Gel, 1%					
13-0599	Diclofenac Sodium Topical Gel, 1 %					
12-1110	Diclofenac Sodium Topical Gel 1%					
11-0665	Excipients in Diclofenac topical gel					
11-0709	Inactive in					

	Diclofenac topical gel
11-0393	Diclofenac topical gel formulation
10-0469	Diclofenac sodium topical gel
09-0464	Diclofenac topical gel
09-0255	Diclofenac sodium topical gel
09-0065	Diclofenac topical gel
09-0324	Formulation diclofenac gel
09-0644	Diclofenac topical gel formulation
09-0389	Diclofenac topical gel formulation
08-0687	Diclofenac topical gel
08-1031	Diclofenac gel
08-0338	Diclofenac Gel
08-0569	Acceptable Inactive Ingredients in Diclofenac Topical Gel

Source: compiled by this reviewer from OGD Tracking Systems search conducted on 6/8/2015

**Reviewer's Comment:**

In the control #12-1110, (b) (4) had questions about enrollment of 100% Indian demographic and racial profile in a potential clinical endpoint BE study, OGD's response to this control document is still pending.

**Protocols Submitted to Office of Generic Drugs for Diclofenac Gel, 1% (n=6)**

Ctl No	Title	Status/Date	Doc Date	From	Comments
07-032	Diclofenac Sodium				(b) (4)
08-099	Diclofenac Sodium				
09-005	Diclofenac Sodium				
09-009	Diclofenac Sodium				
130021	Diclofenac Sodium 1%				
150022	Diclofenac Sodium 1%				

Source: compiled by this reviewer from OGD Tracking Systems search conducted on 6/25/2015

**Reviewer Comments:**

*For inquiries about a study guidance on diclofenac gel 1%, FDA informed applicants that a draft guidance for diclofenac gel 1% is available on the FDA website.*

**2.1.2.3 Other ANDA submissions for same product**

**Table 1 ANDAs Submitted to Office of Generic Drugs for Diclofenac Gel, 1% (n=2)**

ANDA number	Applicant	Submission date	Comments on current status
(b) (4)			

**Reviewer's Comment:**

(b) (4)

**2.1.3 Other Relevant Information**

In the RLD labeling, the adverse reactions were 7% in RLD treated group and 2% in placebo for the short-term study period 8 to 12 weeks (16 g per day). The NDA 022122 review in the controlled efficacy trials states “there were 835 patients who reported a non-serious AE: 451 (49.5%) in the DSG (diclofenac sodium gel) group and 384 (43.8%) in the placebo group”.

**2.2 Description of Clinical Data and Sources**

<b>Protocol Number</b>	AM-DCG-001
<b>Study Title</b>	A Multi-Center, Double-Blind, Vehicle-Controlled, Parallel-Group Study Comparing a Generic Diclofenac Sodium Topical Gel, 1% to Voltaren <sup>®</sup> Gel (Diclofenac Sodium Topical Gel), 1% in the Treatment of Subjects with Osteoarthritis of the Knee
<b>CRO</b>	<ol style="list-style-type: none"> <li>1. Sristek Clinical Research Solutions Ltd. was responsible for conducting the study, statistically analyzing the data and writing the study report. The applicant did not provide the address for CRO, Sristek Clinical Research Solutions Ltd. Here is the address information from Google search: Head Office, DLF Cyber City, Block-3, 8th Floor, Gachibowli, Hyderabad – 500 019, Andhra Pradesh, India</li> <li>2. The Bilcare Global Clinical Supplies was responsible for storage of retention samples of study. The address of Bilcare Global Clinical Supplies is: 1028, Shirol, Rajgurunagar, Pune 410505, India</li> </ol>
<b>Study Period</b>	Study Initiation Date: April 9, 2014 (first subject visit) Study Completion Date: December 12, 2014 (last subject visit)

**Study Centers, Principal Investigators and Enrollment**

Total of 19 study sites were all located in India. See the following link for detail information:  
 \\cdsesub1\evsprod\anda208077\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoarthritis-of-knee\5351-stud-rep-contr\am-dcg-001\study-report-body.pdf (page 18)

**Reviewer’s Comment:**

*All subjects in the study are Asian. The applicant’s demographic information at baseline is comparable among the three treatment groups. The baseline WOMAC scores (Test=12.46, RLD=12.52 and vehicle=12.38) are balanced among the three groups (the test, RLD and vehicle groups).*

**2.3 Clinical Review Methods**

**2.3.1 Overview of Materials Consulted in Review**

<b>Original Submission</b>	12/19/2014 (0000)
<b>Amendments for clinical endpoint bioequivalence study</b>	01/13/2015: Provided SAS.xpt files and a data definition file. 01/15/2015: Placebo information 01/29/2015 :None requiring clinical review 8/5/15: ECD response for data accuracy questions at 14 clinical sites
<b>FDA Statistical Review</b>	05/18/2015: FDA statistical review prior to OSIS inspection result

**2.3.2 Overview of Methods Used to Evaluate Data Quality and Integrity**

<b>Office of Scientific Investigations and Surveillance (OSIS) Request Date</b>	01/15/2015: routine inspection 7/17/2015: For Cause Inspection for site #28 7/28/2015: For Cause Inspection for sites #24 and #33
<b>Office of Scientific Investigations (OSIS) Report Date</b>	<b>The routine inspection has been completed but the final report is still pending. For cause inspection result is pending.</b>
<b>OSIS inspection findings</b>	Pending

<b>Blinding</b>	The testing products were identical in appearance and packaged identically so that treatment blind was maintained. Neither the subject nor the investigational staff (sponsor, investigator, and evaluators) knew which treatment a subject was received. (study protocol page 20)
<b>Randomization</b>	The randomization scheme was generated according to a computer-generated randomization scheme. The randomization scheme was generated and maintained by a third-party vendor to minimize bias.  Subjects were randomized in a 1:1:1 ratio to the test product, the reference product, and vehicle.

<b>Retention of Reserve Samples:</b>	See the study protocol pages 22-23 <sup>4</sup>
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***Reviewer's Comment:*** *The procedure was adequate for maintaining blinding of the study treatment according to the study protocol (pages 20-23). The OSIS inspection result is still pending to verify it.*

### 2.3.3 Were Trials Conducted in Accordance with Accepted Ethical Standards

<b>Ethical Standards</b>	In compliance with accepted ethical standards. <sup>5</sup>  study-report-body.pdf (pages 14-15)
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***Reviewer's Comment:*** *The applicant's study appears to be in compliance with accepted ethical standards.*

### 2.3.4 Evaluation of Financial Disclosure

<b>Financial Disclosure Form</b>	The applicant submitted form FDA3454 with investigators' names.
<b>Form 3454</b>	\\cdsesub1\evsprod\anda208077\0000\m1\us\134-financial-certification.pdf

***Reviewer's Comment:*** *All investigator's names were listed in FDA form 3453. They are acceptable.*

## 2.4 Review of a Clinical Endpoint Bioequivalence Study

### 2.4.1 Brief Statement of Bioequivalence Conclusion

From a DCR perspective, this application is recommended for approval **pending satisfactory the routine OSIS inspection and For Cause Inspection results.**

### 2.4.2 General Approach to Review of the Comparative Efficacy of the Drug

The applicant's study (protocol #AM-DCG-001) was reviewed to evaluate the bioequivalence of the test product and the reference product. The primary endpoint of the study is the mean change from baseline to week 4 in the WOMAC pain score (pain score = 0 to 20).

<sup>4</sup> <\\cdsesub1\evsprod\anda208077\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\osteoarthritis-of-knee\5351-stud-rep-contr\am-dcg-001\protocol.pdf>

<sup>5</sup> <\\cdsesub1\evsprod\anda208077\0002\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\osteoarthritis-of-knee\5351-stud-rep-contr\am-dcg-001\study-report-body.pdf>

### 2.4.3 Detailed Review of Bioequivalence Studies with Clinical Endpoints

#### 2.4.3.1 Protocol Review

<b>Applicant's protocol #:</b>	AM-DCG-001
<b>Title</b>	A Multi-Center, Double-Blind, Vehicle-Controlled, Parallel-Group Study Comparing a Generic Diclofenac Sodium Topical Gel, 1% to Voltaren® Gel (Diclofenac Sodium Topical Gel), 1% in the Treatment of Subjects with Osteoarthritis of the Knee
<b>Objectives</b>	<p>To establish the therapeutic equivalence and safety of a generic Diclofenac Sodium Topical Gel, 1% with Voltaren® Gel (diclofenac sodium topical gel), 1% in subjects with osteoarthritis of the knee</p> <p>To compare efficacy of both the test and reference products to the vehicle gel to determine superiority of active products to the vehicle</p>
<b>Original Protocol Date (s)</b>	April 8, 2013 Version 03
<b>IRB approval Date(s)</b>	<p>March 1, 2014</p> <ul style="list-style-type: none"> <li>• Protocol</li> <li>• The principle investigators</li> <li>• Informed Consent Form (ICF)</li> </ul> <p>Source: <a href="\\cdsesub1\evsprod\anda208077\0001\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\osteoarthritis-of-knee\5351-stud-rep-contr\am-dcg-001\iec-irb-list.pdf">\\cdsesub1\evsprod\anda208077\0001\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\osteoarthritis-of-knee\5351-stud-rep-contr\am-dcg-001\iec-irb-list.pdf</a> page 4-5</p>
<b>Protocol Amendment(s)</b>	None

***Reviewer's Comment:*** *The applicant submitted IRB approval letter for the study protocol, principle investigators, and ICF. There was no protocol revision (version 03) changes to the conduct of the study or the planned analysis.*

**2.4.3.1.1 Study Design**

**Overall Study Design and Plan**

**Table 2: Procedures and Observations**

Procedure	Screening	Randomization	Treatment Phase (Weeks)	
	1 Screening	2 Baseline/Randomization	3 On therapy	4 On therapy
Visit				
Day/Week	Day -7	Day 0	Week 2 (±4 days)	Week 4 (±4 days)
Written informed consent	X			
Medical History/ Demographics	X			
Assessment of osteoarthritis	X			
X-ray evaluated/ ordered	X			
Safety laboratory <sup>1</sup>	X			
Physical examination	X	X		X
Vital signs	X	X	X	X
Urine pregnancy test	X	X	X	X
Inclusion/exclusion criteria	X	X		
OA assessments <sup>2</sup>		X	X	X
Randomization		X		
Dispense study medication		X	X	
Collect study medication			X	
Dispense diary/ dosing card <sup>3</sup>		X	X	
Collect and check diary			X	X
Dispense rescue medication		X	X	
Collect rescue medication			X	X
Concomitant medication		X	X	X
Adverse event reporting		X	X	X

1. Safety laboratory tests - Liver function test for transaminase (AST and ALT) and HBsAg was performed by the central laboratory.
2. OA assessments: WOMAC pain score (pain score = 0 to 20), which was determined by the subject's responses to five questions (S1–S5) using a 5-point Likert scale (i.e., 'none'=0; 'mild'=1, 'moderate'=2; 'severe'=3; 'extreme'=4). The questions pertain to the amount of pain the subject was experiencing in the target knee [i.e., 'How much pain do you have' when 'Walking on a flat surface' (S1), 'Going up or down stairs' (S2), 'At night while in bed' (S3), 'Sitting or lying' (S4), 'Standing upright' (S5)].
3. Dosing Card to be used to standardize amount of study medication applied.

**Reviewer's Comment:** *The rescue medication paracetamol/acetaminophen (up to four grams per day) was allowed during the study but it was prohibited in the washout period. Since the use of rescue analgesic treatments may adversely affect the ability of the study to distinguish between the benefit from the diclofenac and the benefit of the rescue therapy, specific guideline or criterion is recommended for the use of rescue medication other than "as needed". The study design and procedures were consistent with the draft guidance of this product.*

Assessments	Description
Signs and symptoms evaluated	The amount of pain the subject is currently experiencing in the target knee. Subjects with a history of OA pain in the contralateral knee requiring medication within 1 year prior to screening were excluded.
Scale for evaluation of signs and symptoms	The WOMAC pain score (pain score = 0 to 20), which was determined by the subject's responses to five questions (S1–S5) using a 5-point Likert scale (i.e., 'none'=0; 'mild'=1, 'moderate'=2; 'severe'=3; 'extreme'=4).

**Treatments:**

**Table 3: Treatment Arms**

Product	Test	Reference	Placebo/Vehicle
Treatment ID (if applicable)	A	B	C
Product Name	Diclofenac Sodium Topical Gel, 1%	Voltaren® Gel (Diclofenac Sodium Topical Gel), 1%	Placebo (Vehicle)
Manufacturer	Anneal Pharmaceuticals	Novartis Pharma Productions GmbH, Wehr, Germany & marketed by Endo Pharmaceuticals Inc.,	Anneal Pharmaceuticals
Batch/Lot No.	PW-ST-13015A	W2601 and W3679	PW-ST-13040A
Manufacture Date	May 24, 2013	N/A	November 13, 2013
Expiration Date	N/A	February 2015 and May 2016	N/A
Strength	1%	1%	N/A
Dosage Form	gel	gel	gel
Dose administered	4 grams	4 grams	4 grams

<b>Dosing regimen (e.g., BID, QD)</b>	qid	qid	qid
<b>Dosing time (e.g, am, pm)</b>	every 6 hours	every 6 hours	every 6 hours
<b>Dosing duration (e.g., 2 weeks)</b>	4-week treatment		
<b>Route of administration</b>	Topical	Topical	Topical
<b>Assignment ratio to test, reference, or vehicle/placebo</b>	1:1:1		

**Reviewer’s Comment:** *The treatment application was instructed as recommended by the approved labeling of the RLD. The subjects were treated for 4-week treatment period. Each subject was evaluated at visit 4 (4 weeks after completion of treatment).*

**Study Population:**

<b>Inclusion Criteria</b>	<ol style="list-style-type: none"> <li>1. Evidence of a signed and dated informed consent document(s) indicating that the subject has been informed of all pertinent aspects of the study.</li> <li>2. Healthy, ambulatory male or non-pregnant female subjects aged <math>\geq 35</math> years with a clinical diagnosis of osteoarthritis (OA) of the knee including: <ul style="list-style-type: none"> <li>• Presence of at least three (3) of the American College of Rheumatology (ACR) criteria (age <math>\geq 50</math>; stiffness lasting <math>&lt; 30</math> minutes; bony tenderness; crepitus; bony enlargement; no palpable warmth)</li> <li>• Symptoms for at least 6 months prior to screening, AND</li> <li>• Knee (not referred) pain for 15 days of the preceding month (periarticular knee pain due to OA and not due to other conditions such as bursitis, tendonitis, etc.), AND</li> <li>• The pain in the target knee required the use of non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol/acetaminophen (topical or oral treatments).</li> </ul> </li> <li>3. Had an X-ray of the target knee, taken not more than 1 year before baseline, showing evidence of OA with Kellgren-Lawrence grade 1-3 disease.</li> <li>4. After discontinuing all pain medications for at least 7 days, has at least moderate pain on movement (POM) for target knee, defined as a baseline score of <math>\geq 50</math> mm on a 0-100 mm Visual Analog Scale (VAS) immediately prior to randomization, AND a baseline Western Ontario McMaster Osteoarthritis (WOMAC) pain subscale of at least 9 immediately prior to randomization.</li> <li>5. If female and of child-bearing potential, agree to abstain from sexual intercourse or use a reliable method of contraception during the study (e.g., condom + spermicide, Intra Uterine Device (IUD), oral, transdermal, injected or implanted hormonal contraceptives).</li> <li>6. Able to tolerate rescue medication with paracetamol/acetaminophen.</li> </ol>
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	7. Willing and able to comply with the study requirements.
<b>Exclusion Criteria</b>	<ol style="list-style-type: none"> <li>1. Pregnant or lactating or planning to become pregnant during the study period.</li> <li>2. X-ray showing evidence of OA with Kellgren-Lawrence grade 4 disease.</li> <li>3. History of OA pain in the contralateral knee requiring medication (Over the Counter (OTC) or prescription) within 1 year prior to screening.</li> <li>4. After discontinuing all pain medications for at least 7 days, has a baseline score of <math>\geq 20</math> mm on a 0-100 mm Visual Analog Scale (VAS) for the contralateral knee immediately prior to randomization.</li> <li>5. History of secondary OA, rheumatoid arthritis, chronic inflammatory disease (e.g., colitis) or fibromyalgia.</li> <li>6. History of asthma, hypertension, myocardial infarction, thrombotic events, stroke, congestive heart failure, impaired renal function or liver disease.</li> <li>7. History of gastrointestinal bleeding or peptic ulcer disease.</li> <li>8. Use of warfarin or other anticoagulant therapy within 30 days of study randomization.</li> <li>9. Elevated transaminase at screening (AST or ALT more than 2 times the upper limit of normal at screening visit).</li> <li>10. Use of Angiotensin Converting Enzyme (ACE) inhibitors, cyclosporine, diuretics, lithium or methotrexate, within 30 days of study randomization.</li> <li>11. Concomitant use of corticosteroids (any formulation) or use within 30 days of study randomization.</li> <li>12. Concomitant acetylsalicylic acid therapy other than a stable low dose used for cardiac prophylaxis (maximum 162 mg daily) taken for at least 3 months prior to enrollment and maintained throughout the duration of the study.</li> <li>13. Known allergy to aspirin or nonsteroidal anti-inflammatory drug.</li> <li>14. Any other acute or chronic illness that in the opinion of the investigator could compromise the integrity of study data or place the subject at risk by participating in the study.</li> <li>15. Receipt of any drug as part of a research study within 30 days prior to screening.</li> <li>16. Previous participation in this study.</li> <li>17. Any use between screening and baseline of a treatment or medication that may potentially confound study assessment (e.g. use of topical analgesics or anti-inflammatory drugs).</li> <li>18. Recent history of major knee injury or surgery.</li> <li>19. Known history of positive Human Immunodeficiency Virus (HIV).</li> </ol>

**Reviewer's Comment:** *Applicant's inclusion and exclusion criteria are consistent with the recommendation posted in the draft guidance for this product. This reviewer concurs with these inclusion/exclusion criteria.*

<b>Criteria for removal from the study</b>	<ol style="list-style-type: none"> <li>1. Subject withdraws consent.</li> <li>2. Subject's study medication was unblinded.</li> <li>3. The investigator decided it was in the subject's best interest to</li> </ol>
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	<p>be withdrawn.</p> <ol style="list-style-type: none"> <li>4. Serious adverse reaction to the drug, unless it was not in the best interest of the subject's condition to withdraw, in the opinion of the treating physician.</li> <li>5. Intercurrent illness that may, in the investigator's opinion, significantly affect assessment of the clinical status.</li> <li>6. A concomitant therapy was reported or required that was likely to confound the assessment of the subject's OA.</li> <li>7. There was a significant protocol violation.</li> </ol> <p>Any subject who experienced a severe AE and considered to be related to study drug was discontinued from the study.</p>
<b>Prior and concomitant therapy</b>	<ul style="list-style-type: none"> <li>• Any other topical products applied to the knee(s).</li> <li>• ACE-inhibitors, anticoagulants, cyclosporine, diuretics, lithium, methotrexate, oral NSAIDs, aspirin [except cardiac prophylaxis (maximum 162 mg daily) taken for at least 3 months prior to enrollment and maintained throughout the duration of study].</li> <li>• Corticosteroid (any formulation) or immunosuppressive drugs.</li> <li>• Pain medication other than paracetamol/acetaminophen.</li> </ul>
<b>Treatment compliance</b>	Subjects were considered compliant with the assigned study treatment if they used at least 75% and no more than 125% of study treatment doses.

**Reviewer's Comment:** *This reviewer concurs with these criteria for removing subjects from the study. The limitation of prior and concomitant medication was acceptable.*

#### 2.4.3.1.2 Endpoints/Variables

<b>Primary Endpoint (s)</b>	The primary endpoint of the study was the mean change from baseline to week 4 in the WOMAC pain score (pain score = 0 to 20), which is determined by the subject's responses to five questions (S1–S5) using a 5-point Likert scale (i.e., 'none'=0; 'mild'=1, 'moderate'=2; 'severe'=3; 'extreme'=4). The questions pertain to the amount of pain the subject was currently experiencing in the target knee [i.e., 'How much pain do you have' when 'Walking on a flat surface' (S1), 'Going up or down stairs' (S2), 'At night while in bed' (S3), 'Sitting or lying' (S4), 'Standing upright' (S5)].
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**Reviewer's Comment:** *The applicant's primary endpoint is consistent with the draft guidance recommended for this product.*

<b>Efficacy Measures</b>	The analysis performed for the PP population was considered primary and that in the MITT population supportive. The analysis performed for the PP population was the 90% confidence interval for the test/reference ratio of mean change from baseline to week 4. Analyses were conducted in the MITT population to demonstrate superiority of both the test and reference products over the vehicle by
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	comparing mean change from baseline in WOMAC pain score to week 4.
<b>Safety Measures</b>	Safety was assessed by monitoring adverse events (AEs) and local skin reactions.

**2.4.3.1.3 Statistical analysis plan (per applicant)**

<b>Analysis Subject Populations</b>	Safety, MITT, PP
<b>Safety Population</b>	The safety population included all randomized subjects who received at least one dose of study treatment.
<b>Modified Intent-to-Treat (MITT) Population</b>	The MITT population included all randomized subjects who met all inclusion/exclusion criteria, received at least one dose of study treatment and returned for at least one post baseline evaluation visit.
<b>Per-Protocol (PP) Population</b>	The PP population included all randomized subjects who met all inclusion/exclusion criteria, were compliant with the assigned study treatment (used at least 75% and no more than 125% of study treatment doses), returned to the study site for the primary endpoint visit within the specified window (+/- 4 days) or discontinued from the study as treatment failure, and did not have any protocol violations.
<b>Population consideration</b>	Efficacy analyses were performed on the MITT and PP populations.  Safety analyses were performed on the safety population.
<b>Population consideration and statistical analysis</b>	See FDA statistical review dated May 28, 2015 for details.

**Reviewer’s Comment:**

*The definitions of the applicant’s MITT and PP population are consistent with the draft guidance recommended for this product. However, there is difference between the FDA MITT population definition and the applicant’s MITT population definition. The FDA MITT population is defined as all subjects who were randomized and received at least one dose of assigned study treatment.*

**2.4.3.2 Study Results**

**Subject Disposition**

Of a total of 1176 subjects randomized to the study treatment, 1175 subjects were included in the applicant’s safety population, 1166 subjects in MITT population and 1147 subjects in PP population, respectively. For the FDA subject disposition, see the below table for details.

**Table 4 Subject Disposition**  
**Subject Enrollment and Final Study Disposition in the Applicant’s and FDA’s Population**

	Applicant				FDA			
	Test	Reference	Vehicle	Total	Test	Reference	Vehicle	Total
<b>Randomized</b>	392	393	391	1176	392	393	391	1176
<b>Total Safety population</b>	391	393	391	1175	391	393	391	1175
Total exclusion from Safety population (No confirmed dose)	1	0	0	1	1	0	0	1
<b>Total MITT population</b>	389	391	386	1166	391	393	391	1175
Total exclusion from MITT population based on the safety population	2	2	5	9	1	0	0	0
Reason for exclusion from MITT								
Violation of inclusion/exclusion criteria	1	2	4	7	0	0	0	0
Withdrawn consent	0	0	1	1	0	0	0	0
Withdrawn requested by Investigator	1	0	0	1	0	0	0	0
<b>Total PP population</b>	383	388	376	1147	384	388	376	1148
Total exclusion from PP population based on MITT population	6	3	10	19	7 <sup>#</sup>	5	15	27
Reason for exclusion from PP								
Violation of inclusion/exclusion criteria	0	0	0	0	1	2	4	7
Outside window period	0	1	3	4	0	1	3	4
Non-compliance	2	0	2	4	1	0	2	3
Withdrawn Consent	2	1	3	6	2	1	4	7
Withdrawn requested by Investigator	1	0	0	1	2	0	0	2
Used Concomitant Therapy During Study Period	0	1	1	2	0	1	1	2
Lost to Follow Up	1	0	1	2	1	0	1	2

#: (b) (6) in the Diclofenac group was included in the FPP population based on the OGD clinical reviewer’s comment.

**Demographics**

**Table 5: Demographic Characteristics for Safety Population (Per the Applicant):**

Parameter	Statistics	Diclofenac Gel (n=391)	Voltaren® Gel (n=393)	Vehicle (n=391)	Overall (n=1175)
<b>Age (years)</b>	<b>Mean (SD)</b>	52.97 (9.40)	52.43(9.42)	51.44 (9.23)	52.28 (9.37)
<b>Gender</b>					
Male	n (%)	136 (34.78)	149 (37.91)	137 (35.04)	422 (35.91)
Female	n (%)	255 (65.22)	244 (62.09)	254 (64.96)	753 (64.09)
<b>Ethnicity</b>					
Hispanic or Latino	n (%)	0	0	0	0
Not Hispanic or Latino	n (%)	371 (94.88)	373 (94.91)	371 (94.88)	1115 (94.89)
Not Willing to Provide	n (%)	20 (5.12)	20 (5.09)	20 (5.12)	60 (5.11)
<b>Race</b>					
White	n (%)	0	0	0	0
Black or African American	n (%)	0	0	0	0
American Indian or Alaska Native	n (%)	0	0	0	0
Asian	n (%)	391 (100)	393 (100)	391 (100)	1175* (100)
Native Hawaiian or Other Pacific Islander	n (%)	0	0	0	0

Percentage (%) was calculated based on the number of subjects in Safety population corresponding to the treatment group.

\*One subject from Diclofenac Sodium Topical Gel, 1% group was randomized and provided the assigned study medication. This subject withdrew consent and was unable to be contacted to confirm if subject applied at least one dose of study medication, therefore this subject was not included in safety population.

Source: The study report (AM-DCG-001) Table 11.2-1, page 48

**Demographic characteristics for the FDA MITT population.**

	Total N=1175	Test N=391	Reference N=393	Vehicle N=391	p-value
<b>Gender</b>					
Female	753 (64.09%)	255 (65.22%)	244 (62.09%)	254 (64.96%)	0.5977 <sup>1</sup>
Male	422 (35.91%)	136 (34.78%)	149 (37.91%)	137 (35.04%)	
<b>Race</b>					
White	0	0	0	0	NA
Asian	1175 (100%)	391 (100%)	393 (100%)	391 (100%)	
Other	0	0	0	0	
<b>Age (years)</b>					
Mean (STD)	52.28 (9.37)	52.97 (9.40)	52.43 (9.42)	51.44 (9.23)	0.0674 <sup>2</sup>
Median	51	52	51	51	
Range	35-85	35-85	35-78	35-77	

Compiled by this reviewer.

<sup>1</sup>p-value for treatment comparison was obtained from CMH test for general association.

<sup>2</sup>p-value for treatment comparison was obtained from an analysis of variance (ANOVA) model with treatment group as the factor.

**Reviewer’s Comment:**

*All subjects in the study are Asian. The applicant’s demographic in gender and age at baseline is comparable among the three treatment groups in the FDA MITT population. The applicant did*

not provide the demographic information for PP population. In the FDA statistical review dated 5/28/15, no more than 10 subjects for each group (the test=6, RLD=3 and vehicle=10) were excluded from the MITT population. Therefore, a few subjects (3 to 10 subjects) excluded from the MITT population (391 to 393 subject in each group) would not likely cause unbalance in the PP population.

The study (AM-DCG-001) showed that a lower number of adverse events (less than 1%) was reported in the applicant’s data comparing to studies submitted for the approval of the RLD (7% in the RLD and 2% in placebo). It is unclear whether it is due to cultural/geographic factors (100% enrollment in India), different study design, or inadequate collection of adverse events. The results of clinical site inspections are pending.

**Baseline WOMAC score (per FDA statistical review dated 05/28/2015)**

	Total N=1175	Test N=391	Reference N=393	Vehicle N=391	p-value*
WOMAC score at Baseline					
Mean (SD)	12.46 (1.65)	12.46 (1.66)	12.53 (1.67)	12.38 (1.63)	0.4672
Median	12	12	12	12	
Range (Min- Max)	9 - 18	9 – 18	9 – 17	9 – 18	

Compiled by this reviewer.

\*p-value for treatment comparison was obtained from an analysis of variance (ANOVA) model with treatment group as the factor.

**Protocol Deviations/violations:**

**Table 6: Summary of Protocol Violations from Applicant (per the applicant’s data)**

Deviations/ Violations	Number (%) of Subjects			
	Diclofenac Gel n (%)	Voltaren® Gel n (%)	Vehicle n (%)	OVERALL n (%)
Any Deviation/Violation	3	4	10	17
Did Not Meet the Inclusion Criteria	1 (33.33)	2 (50.00)	4 (40.00)	7 (41.18)
Non Compliance	2 (66.67)	0	2 (20.00)	4 (23.53)
Out of Window Period	0	1 (25.00)	3 (30.00)	4 (23.53)
Used Concomitant Therapy During Study Period	0	1 (25.00)	1 (10.00)	2 (11.76)

Major protocol deviations/violations are those that exclude subjects from the per-protocol population.

Percentage (%) was calculated based on the number of protocol deviated/violated subjects corresponding to the treatment group.

Source: The study report AM-DCG-001 Table 10.2-1, page 46

**Reviewer’s Comments:**

Those protocol deviations were excluded from the applicant’s PP population. This is acceptable because they were considered protocol violations.

(b) (6) completed the study and was excluded from the applicant’s PP population for the reason of non-compliance by the applicant. However, the reason for excluding (b) (6) cannot be confirmed from the subject’s case report and the study report by this reviewer. Thus, (b) (6) was recommended to be included the FDA’s PP population by this clinical reviewer. See link below for details.

**Primary Endpoint analysis result (per applicant)**

The applicant’s primary endpoint of the study was the mean change from baseline to week 4 in the WOMAC pain score (pain score = 0 to 20).

**Table 5: Primary Endpoint Analysis (per applicant and FDA statistical review)**

	Sponsor*			FDA		
	Test	Reference	Vehicle	Test	Reference	Vehicle
<b>PP Population</b>						
N	383	388	376	384	388	376
LSMean (Std err) (WOMAC pain score)	-2.0050 (0.0978)	-1.7762 (0.0969)		-1.9926 (0.0981)	-1.7742 (0.0972)	
90% CI for Test and Reference (%)	(102.5, 124.56) <sup>1</sup>			(101.94, 124.00) <sup>1</sup>		
<b>MITT Population</b>						
N	389	391	386	391	393	391
LSMean (WOMAC pain score)	-2.2332	-2.0287	0.6387	-2.2299	-2.0256	0.6444
(Test or Reference) vs. Vehicle	<0.0001 <sup>2</sup>	0.0001 <sup>2</sup>		<0.0001 <sup>2</sup>	<0.0001 <sup>2</sup>	

\*Source: Table 11.4.1.1-1, CSR, page 50.<sup>F</sup>

<sup>1</sup>Confidence interval for test to reference was calculated using ANCOVA.

<sup>2</sup>P-value was calculated using ANCOVA (two sided α=0.05).

**Reviewer’s Comments:**

This reviewer has concerns about data integrity for 14 clinical sites (#5, #17, #19, #20, #22, #24, #26, #27, #28, #29, #30, #31 #32 and #33). Most subjects in the RLD group had a constant change from the baseline in WOMAC pain score equals to “-1” with lack of variability. In six study sites (#22, #24, #26, #28, #30, and #31), all subjects (n=72) in reference drug group had a constant change from the baseline of WOMAC pain score equals -1 with no variation among subjects in the reference listed drug (RLD, Voltaren®) treatment group. For an example, for (b) (6) (at site 28, treated with RLD, Voltaren®), WOMAC pain score at baseline is 12, and WOMAC pain score at week 4 is 11. The change from the baseline of WOMAC pain score for this subject is 11 minus 12 = -1.

*On July 22, 2015, an easily correctable deficiency (ECD) was sent to the applicant requesting an explanation of this lack of variability for the change from baseline in WOMAC pain score for most subjects in the reference listed drug (RLD) group. According to the applicant’s ECD response dated August 5, 2015, the applicant concluded that the lack of variability can only be ascribed to chance. The applicant stated that they reviewed the original source subject questionnaires, which were used by the subjects to record their individual pain scores at each visit and compared the subjects’ responses on the WOMAC 1-5 subscales to the Case Report Form. The applicant also reviewed the transcription of the raw data from the Case Report Form to the database which was used by the CRO to calculate the efficacy endpoints. Based on the applicant’s review of these data, no irregularities were found in the source data.*

*In order to confirm the data accuracy, a For Cause Inspection was requested for site #28 on July 17, 2015 and a For Cause Inspection addendum was requested for sites #24 and #33 on July 28, 2015. The results of the For Cause Inspections are pending.*

*In addition, the applicant found two errors during the data review in response to the FDA ECD. However, it had no impact on the conclusion of bioequivalence and superiority of vehicle to active treatments. The applicant noted as follows:*

- 1. (b) (6) WOMAC pain score was -2 instead of -1 for this subject.*
- 2. The applicant used the safety population to calculate the superiority of the active treatments versus the vehicle instead of mITT in the original submission. Thus, the applicant corrected these errors and provided a new statistical analysis results and updated them in the submission dated on August 5, 2015 as shown below.*

Original submission:

**Table 11.4.1.1-1: Summary of ANCOVA Analysis Results of Primary Efficacy Endpoint (Mean Change from Baseline to Week 4 in Total WOMAC pain score)**

Per Protocol Population				
Treatment Group	Number of Subjects (n)	LSMeans (WOMAC pain score)	Test-to-Reference Ratio	90% CI Evaluation
Diclofenac Gel	383	2.0050		102.5 - 124.56
Voltaren <sup>®</sup> Gel	388	1.7762	112.88	

Modified Intent-to-Treat Population					
Treatment	Number	LSMeans	Std Err	Difference of	p-value*

<b>Modified Intent-to-Treat Population</b>					
<b>Group</b>	<b>of Subjects (n)</b>	<b>(WOMAC pain score)</b>	<b>LSMeans</b>	<b>LSMeans (Active- Vehicle)</b>	
<b>Vehicle</b>	391	-0.6387	0.1172	--	--
<b>Diclofenac Gel</b>	391	2.2332	0.1160	2.8719	<.0001
<b>Voltaren<sup>®</sup> Gel</b>	393	2.0287	0.1157	2.6674	<.0001

Model: Change in Total WOMAC Score = Treatment Group+ Site + Baseline WOMAC Score

90% CI for T to R ratio was calculated using ANCOVA (two tailed, α= 0.1).

\*p-value was calculated using ANCOVA (two tailed, α= 0.05).

Note: LOCF method applied for Modified Intent-to-Treat population.

Corrected information submitted on August 5, 2015:

**Table 1a. Summary of ANCOVA Analysis Results of Primary Efficacy Endpoint (Mean Change from Baseline to Week 4 in Total WOMAC pain score)**

<b>Per Protocol Population</b>					
<b>Treatment Group</b>	<b>Number of Subjects (n)</b>	<b>LSMeans</b>	<b>Test-to-Reference Ratio</b>	<b>90% CI Evaluation</b>	
<b>Diclofenac Gel</b>	383	2.0052			
<b>Voltaren<sup>®</sup> Gel</b>	388	1.7791	112.71	102.38 - 124.36	
<b>Modified Intent-to-Treat Population</b>					
<b>Treatment Group</b>	<b>Number of Subjects (n)</b>	<b>LSMeans</b>	<b>Std Err LSMMeans</b>	<b>Difference of LSMMeans (Active- Vehicle)</b>	<b>p-value</b>
<b>Vehicle</b>	386	-0.6533	0.1184	--	--
<b>Diclofenac Gel</b>	389	2.2385	0.1166	2.8918	<.0001
<b>Voltaren<sup>®</sup> Gel</b>	391	2.0278	0.1162	2.6811	<.0001

Model: Change in Total WOMAC Score = Treatment Group + Site + Baseline WOMAC Score

90% CI for T to R ratio calculated using ANCOVA (two tailed, α= 0.1)

\*p-value calculated using ANCOVA (two tailed, α= 0.05)

Note: LOCF method was applied for Modified Intent-to-Treat population.

Original submission:

**Table 11.4.1.1-2: Summary of Change in Total WOMAC pain score- PP Population**

<b>Days/Visits</b>	<b>Statistics</b>	<b>Diclofenac Gel (n=383)</b>	<b>Voltaren® Gel (n=388)</b>	<b>Vehicle (n=376)</b>
<b>Visit 2/Baseline</b>	<b>Mean</b>	12.46	12.52	12.38
	<b>SD</b>	1.65	1.67	1.62
<b>Visit 4/Week 4/End of Treatment</b>	<b>Mean</b>	10.64	10.91	13.59
	<b>SD</b>	2.51	2.18	3.01
<b>Change from Baseline (Visit 2 minus Visit4)</b>	<b>Mean</b>	1.81	1.61	-1.21
	<b>SD</b>	1.93	1.59	2.93

Corrected information submitted on August 5, 2015:

**Table 2a Summary of Change in Total WOMAC pain score- PP Population**

<b>Days/Visits</b>	<b>Statistics</b>	<b>Diclofenac Gel (n=383)</b>	<b>Voltaren® Gel (n=388)</b>	<b>Vehicle (n=376)</b>
<b>Visit 2/Baseline</b>	<b>Mean</b>	12.46	12.52	12.38
	<b>SD</b>	1.65	1.67	1.62
<b>Visit 4/Week 4/End of Treatment</b>	<b>Mean</b>	10.64	10.90	13.59
	<b>SD</b>	2.51	2.18	3.01
<b>Change from Baseline (Visit 2 minus Visit4)</b>	<b>Mean</b>	1.81	1.61	-1.21
	<b>SD</b>	1.93	1.59	2.93

Original submission:

**Table 11.4.1.1-3: Summary of Change in Total WOMAC pain score- mITT Population**

Days/Visits	Statistics	Diclofenac Gel (n=391)	Voltaren® Gel (n=393)	Vehicle (n=391)
Visit 2/Baseline	Mean	12.46	12.53	12.38
	SD	1.66	1.67	1.63
Visit 4/Week 4/End of Treatment	Mean	10.67	10.92	13.48
	SD	2.50	2.19	3.05
Change from Baseline (Visit 2 minus Visit4)	Mean	1.79	1.60	-1.10
	SD	1.93	1.59	2.96

Corrected information submitted on August 5, 2015:

**Table 3a Summary of Change in Total WOMAC pain score- mITT Population**

Days/Visits	Statistics	Diclofenac Gel (n=389)	Voltaren® Gel (n=391)	Vehicle (n=386)
Visit 2/Baseline	Mean	12.46	12.53	12.39
	SD	1.67	1.67	1.63
Visit 4/Week 4/End of Treatment	Mean	10.66	10.93	13.51
	SD	2.50	2.19	3.06
Change from Baseline (Visit 2 minus Visit4)	Mean	1.80	1.60	-1.12
	SD	1.93	1.59	2.97

No additional FDA statistical analysis is necessary to confirm their new statistical analysis results for following two reasons:

1. One subject <sup>(b) (6)</sup>'s WOMAC score change from -1 to -2 in the reference group will not change the study outcome as noted by the applicant.
2. The FDA statistical analysis used the appropriate MITT population for testing sensitivity of the study.

## 2.5 Comparative Review of Safety

### 2.5.1 Brief Statement of Conclusions

Although the study showed no clinically significant difference between the test and reference products with regard to reported adverse events, there is a lower number of adverse events reported in the applicant's data compared to studies submitted for the approval of the RLD.

### 2.5.2 Description of Adverse Events (per applicant)

In the safety analyses, 1175 subjects were included. There were only 9 AEs reported in the study. Eight subjects reported at least one AE. No death or serious adverse events occurred during the study.

SOC/ Preferred Term	Diclofenac Gel (n=391) n (%)	Voltaren® Gel (n=393) n (%)	Vehicle (n=391) n (%)	OVERALL (N=1175) n (%)
<b>Number of Subjects with at least one (TEAEs)</b>	3 (0.77)	2 (0.51)	3 (0.77)	8 (0.68)
<b>Gastrointestinal disorders</b>	0	0	1 (0.26)	1 (0.09)
Gastroesophageal reflux disease	0	0	1 (0.26)	1 (0.09)
<b>General disorders and administration site condition</b>	1 (0.26)	1 (0.25)	1 (0.26)	3 (0.26)
Oedema	1 (0.26)	0	0	1 (0.09)
Pyrexia	0	1 (0.25)	1 (0.26)	2 (0.17)
<b>Infections and infestations</b>	0	0	1 (0.26)	1 (0.09)
Nasopharyngitis	0	0	1 (0.26)	1 (0.09)
<b>Nervous system disorders</b>	0	1 (0.25)	0	1 (0.09)
Headache	0	1 (0.25)	0	1 (0.09)
<b>Respiratory, thoracic and mediastinal disorders</b>	0	0	1 (0.26)	1 (0.09)
Cough	0	0	1 (0.26)	1 (0.09)
<b>Skin and subcutaneous tissue disorders</b>	2 (0.51)	0	0	2 (0.17)
Pruritus	1 (0.26)	0	0	1 (0.09)
Rash pruritic	1 (0.26)	0	0	1 (0.09)

Source: the study report table 12.2.1-1 page 54 \\cdsesub1\evsprod\anda208077\0000\m5\53-clin-stud-rep\535-rep-  
effic-safety-stud\osteoarthritis-of-knee\5351-stud-rep-contr\am-dcg-001\study-report-body.pdf

Adverse Events Listings is shown in details as shown below.

[\\cdsesub1\evsprod\anda208077\0000\m5\53-clin-stud-rep\535-rep-  
effic-safety-stud\osteoarthritis-of-knee\5351-stud-rep-contr\am-dcg-001\list-adverse-events.pdf](\\cdsesub1\evsprod\anda208077\0000\m5\53-clin-stud-rep\535-rep-<br/>effic-safety-stud\osteoarthritis-of-knee\5351-stud-rep-contr\am-dcg-001\list-adverse-events.pdf)

**Reviewer's Comment:**

*Of 1175 subjects evaluated, only nine adverse events were reported during the study. All 9 AEs were classified as mild to moderate in severity (3=test, 2=RLD and 4=vehicle). One application site related AE occurred in the test group (subject (b) (6)) and 2 application site related AEs occurred in the RLD group (b) (6)). One subject (b) (6) was discontinued from the study due to itching and rashes. The applicant noted that these signs and symptoms were resolved with sequelae (Source: Subject (b) (6) CRF and Adverse Events Listings dataset 16.2.7). Although the applicant did not provide detailed information for the sequelae, this adverse event was identified as "mild" in intensity. Therefore, it is highly unlikely to expect any serious sequelae due to use of the test product for this subject (b) (6).*

*The AE incidence observed in the study (AM-DCG-001) appears to be very low (less than 1% in total), 0.7% (3/391) in the test group, 0.5%(2/393) in the RLD group and 1% (4/391) in the vehicle group, compared to the studies submitted for the approval of the RLD. It is unclear whether it is due to a cultural/geographic factor (100% enrollment in India), differences in study design, or inadequate collection of adverse events.*

*In the RLD labeling, the adverse reactions were reported as 7% in RLD treated group and 2% in placebo for the short-term study period 8 to 12 weeks (16 g per day).<sup>6</sup> The NDA 022122 review in the controlled efficacy trials states "there were 835 patients who reported a non-serious AE: 451 (49.5%) in the DSG (diclofenac sodium gel) group and 384 (43.8%) in the placebo group"; "application site reactions were the most frequently reported dermal AE in both groups: 6.8% (62/912) of DSG-treated patients, and 2.2% (19/876) of placebo patients."<sup>7</sup> In the clinical endpoint BE study submitted to (b) (4)*

*In summary, the applicant's study showed no clinically significant difference between the test and reference products with regard to reported adverse events.*

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<sup>6</sup> <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=60045fc6-f0d9-4f67-ba91-c3b317596437>

<sup>7</sup> Source: NDA 022122 DARRTS REV-CLINICA-03(General Review) dated 10/02/2007 page 21-24

## 2.6 Relevant Findings From Other Consultant Reviews

### 2.6.1 Review of the OSIS Report

On January 15, 2015, DCR requested for routine inspection and provided all study sites to the Office of Scientific Inspection and Surveillance (OSIS). Of a total of 19 clinical sites, 3 sites were selected by OSIS for inspection. Although the routine inspection is complete, the final report is still pending at this time.

In addition, a For Cause Inspection was requested for site #28 for the potential data fraud on July 17, 2015 and two additional sites, #24 and #33, were included in the For Cause Inspection addendum on July 28, 2015.

**Reviewer Comments:**

*The OSIS inspection report is pending at this time.*

### 2.6.2 Review of the FDA Statistical Report (05/28/2015)

	Per Applicant	FDA
<b>Overall conclusion</b>	Demonstrates BE	Demonstrates BE
<b>Bioequivalence (e.g., test vs. reference)</b>	Pass 90% CI: (102.5, 124.56)	Pass <b>90% CI:</b> (1.0194, 1.2400)
<b>Efficacy (e.g., active treatment vs. vehicle)</b>	Pass Test vs. Vehicle: P<0.0001 Reference vs. Vehicle: P<0.0001	Pass Test vs. Vehicle: P<0.0001 Reference vs. Vehicle: P<0.0001
<b>Additional subject adjustments performed by the FDA statistician</b>	N/A	Subjects (b) (6) was included into the FDA's PP population since the reasons for excluding her from the applicant's PP population were not confirmed from the case report form and the study report.

See Statistical Review dated May 28, 2015 for details.

<http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880a42ad6>

**Reviewer's Comment:**

*According to the FDA statistical analysis, the test and reference products were found to be bioequivalent in the FDA PP population. In addition, both test and reference products were shown to be superior (p-value <0.0001) over the vehicle in the FDA MITT population.*

**2.7 Formulation**

**Table 7: The Test product Formulations**

Test				Reference*				IID Limit	Function
Ingredients	Quantity in %w/w	Quantity in %mg/g	Quantity in mg/day <sup>1</sup>	Ingredients	Quantity in %w/w	Quantity in %mg/g	Quantity in mg/day <sup>1</sup>		
Diclofenac Sodium USP	1.00	10.00	320.00	Diclofenac Sodium	1.00	10.0	320.00	---	Active
Isopropyl Alcohol USP	(b) (4)								
Carbomer Homopolymer Type C									
Strong Ammonia Solution NF									
Cocoyl Caprylocaprate									
Mineral Oil USP									
Polyoxyl 20 Cetostearyl Ether NF									
Propylene Glycol USP									
Test				Reference*				IID Limit	Function
Ingredients	Quantity in %w/w	Quantity in %mg/g	Quantity in mg/day <sup>1</sup>	Ingredients	Quantity in %w/w	Quantity in %mg/g	Quantity in mg/day <sup>1</sup>		
Purified Water USP	(b) (4)			Purified Water	(b) (4)				
<b>Total Weight</b>	<b>100%</b>	<b>1 g</b>	<b>32 g</b>	<b>Total Weight</b>	<b>100%</b>	<b>1 g</b>	<b>32 g</b>	(b) (4)	



## 2.8 Conclusion and Recommendation

### 2.8.1 Conclusion

The clinical data presented in this ANDA 208077 are adequate to demonstrate that Amneal Pharmaceuticals' Diclofenac Sodium Topical Gel 1%, is bioequivalent to the reference listed drug, Voltaren<sup>®</sup> (diclofenac sodium) Topical Gel, 1%. The data submitted to ANDA 208077, the 90% confidence interval for the test/reference ratio of mean change from baseline to week 4 in WOMAC pain score is [1.0194, 1.2400], within the bioequivalence limits of [0.80, 1.25]. Both test and reference products were shown to be superior (p-value < 0.0001) to the vehicle in the FDA MITT population. Therefore, from a DCR perspective, this application is recommended for approval, **pending satisfactory the routine OSIS inspection and For Cause Inspection results.**

### 2.8.2 Recommendations

DCR recommends that the clinical endpoint bioequivalence study (#AM-DCG-001) is adequate to support approval of the application, contingent on approval recommendations from the other disciplines on the review team. This conclusion is based on clinical data **prior to a routine OSIS inspection and the For Cause Inspection reports.**

CLINICAL BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

The Division of Clinical Review has completed its review pending the routine Office of Study Integrity and Surveillance (OSIS) inspection and For Cause Inspection findings and has no comments at this time.

APPEARS THIS WAY ON  
ORIGINAL

**Recommendation to FDA statistician from DCR (4/28/15)**

ANDA #	Study #	PP subject adjustment requested (yes/no)	Subject number	Reason for inclusion/exclusion	Comments
208077	AM-DCG-001	Yes	(b) (6)	Subject (b) (6) completed the study and was excluded from PP population for the reason of non-Compliance by the applicant. However, the reason for excluding subject (b) (6) cannot be confirmed from the subject's case report and the study report.	The subject (b) (6) should be included into FDA's PP population.

The applicant used rescue medications (e.g., acetaminophen) in addition to the study drug during the study. To ensure that there is no statistical difference in the use of rescue medications among treatment arms and the study outcome is not affected by its use, please provide additional statistical analyses as follows:

1. Subgroup analysis excluding all subjects who had rescue medications and compare the study outcome (e.g., 90% CI, superiority testing).
2. Descriptive statistics for acetaminophen use including occurrences, including dose range, number of subjects, by treatment arm during study treatment period.

#### 4. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

**Reviewer Comments:**

None

#### 5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other review discipline reviewer(s):

**Reviewer Comments:**

None

#### 6. SPECIAL CONSIDERATIONS

This drug product is not subjected to a REMS requirement.

##### 1.16.2 RISK EVALUATION AND MITIGATION STRATEGY

This drug product is not subjected to REMS Requirement.

Hence this module is Not Applicable.

#### 7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 12 and 13 provide a summary of recommendations for each material analyzed in this review.

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Draft	100 g	12/19/14	Revise
Blister	NA			
Carton	Draft	1 tube	12/19/14	Revise
Dosing Card	Draft	NA	12/19/14	Revise
Table 13 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Final	Rev. 07-2014-00	12/19/14	Revise
Medication Guide	Final	Rev. 07-2014-00	12/19/14	Revise
Patient Information	Final	Rev. 07-2014-00	12/19/14	Revise
SPL Data Elements	Final	Revised: 8/2014	12/19/14	Satisfactory

The applicant did not submit a stand-alone MG.

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 208077Orig1s000**

**CHEMISTRY REVIEWS**



# QUALITY ASSESSMENT



**Recommendation:**  
**ANDA: Approvable**

## ANDA #208077 Review #1

<b>Drug Name/Dosage Form</b>	Diclofenac Sodium Topical Gel
<b>Strength</b>	1% w/w
<b>Route of Administration</b>	Topical
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Amneal Pharmaceuticals
<b>US agent, if applicable</b>	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Amendment # 0008	04-DEC-2015	Quality Response to IR
Amendment # 0009	04-FEB-2016	Quality Response to IR

PREVIOUS SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	19-DEC-2014	CMC
Amendment # 0001	13-JAN-2015	Quality Response to IR Expedited Review Request
Amendment # 0002	15-JAN-2015	CMC
Amendment # 0007	28-SEP-2015	Quality Response to IR

### Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Josephine Jee	Branch II/ DLP
Drug Product	Josephine Jee	Branch II/ DLP
Process	Kelly Forney-Stevens/Peter Krommenhoek	Branch VIII/ DPA3
Microbiology	n/a	
Facility	Xiaohui Shen	Branch III/DIA
Biopharmaceutics	n/a	
Regulatory Business Process Manager	Filita Moore	Branch II/ OPRO
Application Technical Lead	Gil Jong Kang	Branch II/ DLP
Laboratory (OTR)	n/a	
ORA Lead	Katherine Jacobitz	
Environmental Assessment (EA)*	n/a	

\* Categorical exclusion per 21 CFR 25.31 (a)

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## Quality Review Data Sheet

**1. LEGAL BASIS FOR SUBMISSION:**

Reference listed drug: Voltaren® (Diclofenac Sodium Topical Gel) by Novartis.

Application Number: N022122 (Approved 17-OCT-2007)

Strength: 1%

Patent Certification: Paragraph I certification has been provided for the ANDA.

Exclusivity: No unexpired patents

**2. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	1	21-DEC-2015	Reviewed by F. Sequeira.
	Type III		1	09-JUL-2013 31-AUG-2009	Adequate F. Frankwich (Tube and ) C.Kim (Lacquer)	
	Type III		1	27-MAY-2014	Adequate S. McLamore	
	Type IV		N/A	N/A **		

<sup>1</sup> Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

\*\*Cocoyl Caprylocaprte was reviewed by L.S. Leshin, Ph.D., Pharmacolgy/Toxicology Reviewer, Div. of Analgesia, Anesthesia, and Rheumatology Products for NDA 22122. It was deemed acceptable to use in a similar formulation (This review was published and can be found in the internet).

**B. Other Documents: IND, RLD, or sister applications**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Voltaren® Gel (RLD)	NDA 022122	Diclofenac Sodium Topical Gel, 1%
Amneal	ANDA 203995 (Filed on 07-MAR-2012)	Diclofenac Sodium and Misoprostol Delayed Release



# QUALITY ASSESSMENT



		Tablets, 50 mg/ 0.2 mg and 75 mg/ 0.2 mg
Amneal	ANDA 206116 (Filed on 27-SEP-2013)	Diclofenac Sodium Topical Solution, 1.5% w/w

### 3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	complete	adequate	28-MAY-2015	M. Fan
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	complete	Adequate (prior to a routine OSIS inspection and the For Cause Inspection reports.)	13-AUG-2015	Z. Zhang
Bioequivalence	complete	adequate	31-MAR-2015	Y. Liu
Other	none			

## Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

ANDA is *approvable* from OPQ perspective.

-The firm provided satisfactory responses to all IR deficiencies pertaining to the drug substance, drug product and process.

-All drug substance and drug product-related facilities are acceptable.

1. Summary of Complete Response issues: None
2. Action letter language, related to critical issues such as expiration date: None
3. Benefit/Risk Considerations: N/A

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

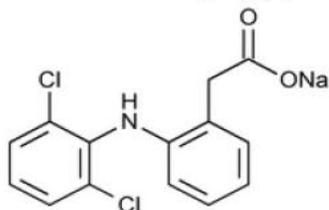
### II. Summary of Quality Assessments

#### A. Drug Substance [USAN Name] Quality Summary

1. Chemical Name or IUPAC Name/Structure:

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

-Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, monosodium salt



$C_{14}H_{10}Cl_2NNaO_2$

Mol. Wt. 318.13 g/mole

2.

3.

4.

5.

(b) (4)

6  
7

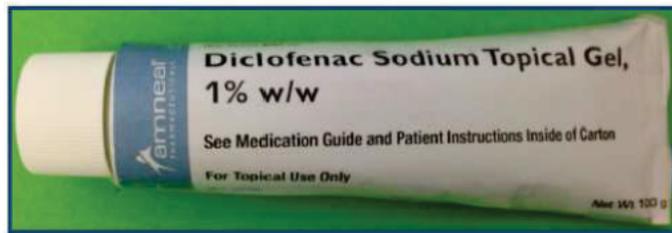


**B. Drug Product [Established Name] Quality Summary**

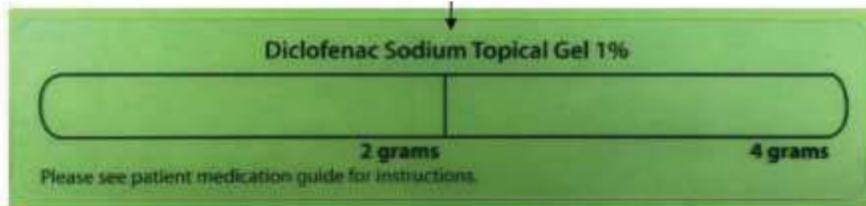
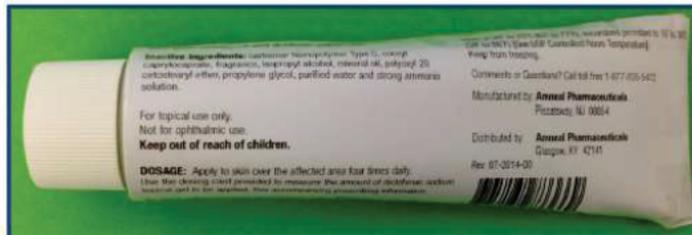
1. Strength: 1%

2. Description/Commercial Image:

***An opaque, white to off-white gel base free from any foreign particles***



Front View



Voltaren® Gel is available in tubes containing 100 g of the topical gel in each tube (NDC 63481-684-47). Each tube contains diclofenac sodium in a gel base (10 mg of diclofenac sodium per gram of gel or 1%).



Applying Voltaren Gel is simple and requires three steps using the dosing card as shown below:



3.



(b) (4)

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## QUALITY ASSESSMENT



- Biowaiver Requests: No
- PK studies: The firm's fasting BE study is acceptable by Bio reviewer (Y. Liu) on 31-MAR-2015.
- IVIVC: N/A (No in vitro studies are required.)

**E. Novel Approaches:** None

**F. Any Special Product Quality Labeling Recommendations:** None

**G. Life Cycle Knowledge Information (see Attachment A)**

### OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

**Application Technical Lead Signature:**

**Gil Kang/ 06/18/2015, 08/19/2015, 11/13/2015, 02/05/2016, 03/04/2016, 03/18/2016**

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



**IV. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

Reviewer Name/Date: Josephine Jee/ 01-28-2016

Secondary Reviewer Name/Date: GilJong Kang/ 02-05-2016, 03-04-2016,  
03-18-2016

Project Manager Name/Date: Filita Moore/2-08-2016/

**APPROVABLE**

**CHECKLIST FOR THE CHEMISTRY REVIEW ANDA 208077 - Diclofenac Sodium  
Topical Gel 1% w/w**

<b>Function</b>	<b>Performed By (Initial and Date)</b>	<b>Check appropriate box</b>
Is this package for new strength PAS?	PQRPM	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
DMF adequate?	PQRPM	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No *(see comments)
Any outstanding consults?	PQRPM	<input type="checkbox"/> Yes *(see comments) <input checked="" type="checkbox"/> No
<b>Final recommended dissolution method/specification acknowledged by Firm?</b>	DD, DDD or designee	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Are all facility inspections acceptable?	PQRPM	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Is microbiology recommendation adequate for sterile products?	PQRPM	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Chemistry Post Marketing Agreement (PMA)?	PQRPM	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
If PMA is yes, was OGD informed?	PQRPM	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
<b>If USP monograph exists, do the specifications conform to the current USP?</b>	DD, DDD or designee	<input type="checkbox"/> Yes <input type="checkbox"/> No *(see comments) <input checked="" type="checkbox"/> N/A**
Is the final review uploaded into the current IT platform?	PQRPM	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Comments:</b>		
**Drug product is not compendial		
Division Director	Signature	Date
DLBP		

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 208077Orig1s000**

**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**  
ADDENDUM TO REVIEW COMPLETED IN MAY 2015

**ANDA #:** 208077

**Drug Name:** Diclofenac Sodium Topical Gel, 1%

**Indication(s):** Treatment of Osteoarthritis of the Knee

**Reference Listed Drug:** Voltaren<sup>®</sup> Topical Gel (Novartis)

**Applicant:** Amneal Pharmaceuticals Ltd.

**Date(s):** Originally Submitted December 19, 2014  
Response to Information Request (Sequence 0001) on January 13, 2015

**Biometrics Division:** Division of Biometric VIII

**Statistical Reviewer:** Yu-te Wu, Ph.D. Team Leader

**Concurring Reviewer:** Stella Grosser, Ph.D., Division Director

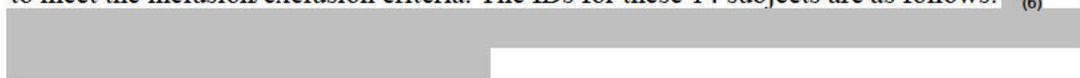
**Medical Division:** Division of Clinical Review, OGD

**Clinical Team:** Joe Zhang, M.D., Ph.D., Carol Kim, Pharm.D.

**Keywords:** Bioequivalence, superiority, WOMAC pain score

This memo is an addendum to the original statistical review completed on 5/18/2015 by the statistical reviewer, Dr. Milton Fan. Based on the “For Cause” Clinical Establishment Inspection Report (EIR) by Dr. Getie-Kehtie dated on January 27, 2016; and a follow-up email communication on Feb 16, 2016 (see appendix), changes are made to remove subjects from the FDA’s modified ITT population (FMITT) and FDA’s per-protocol (FPP) population for the following reasons:

- Data from the BJ Medical College and Hospitals (Site # 28) are not acceptable for further agency review, because it is not possible to confirm whether 101 of 103 study subjects enrolled in the study met the inclusion/exclusion criteria prior to randomization.
- 14 subjects from the Andhra Medical College (Site #24) were recommended to be excluded from the analysis due to insufficient verification of subjects’ age to confirm the eligibility and to meet the inclusion/exclusion criteria. The IDs for these 14 subjects are as follows: <sup>(b)</sup><sub>(6)</sub>



**Results:**

As a result of the inspection, FMITT population excluded additional 113 subjects from site #24 and #28, compared to FDA’s original MITT population. The FMITT population includes 1062 subjects, with 352, 357 and 353 subjects in the test, reference and vehicle groups, respectively. The FPP population consists of 1036 subjects, with 345, 352 and 339 subjects in the test, reference and vehicle groups, respectively. Table 1 shows the enrollment and final disposition of subjects. It also reflects the discrepancy between the sponsor’s and the FDA’s analysis populations.

**Table 1 Subject Enrollment and Final Study Disposition in the Sponsor’s and FDA’s Population**

	Applicant				FDA			
	Test	Reference	Vehicle	Total	Test	Reference	Vehicle	Total
<b>Randomized</b>	392	393	391	1176	392	393	391	1176
<b>Total Safety population</b>	391	393	391	1175	352	357	353	1062
Total exclusion from Safety population (No confirmed dose)	1	0	0	1	1	0	0	1
<i>Additional exclusion per OSIS finding</i>	0	0	0		39	36	38	113
<b>Total MITT population</b>	389	391	386	1166	352	357	353	1062
Total exclusion from MITT population based on the safety population	2	2	5	9	0	0	0	0
Reason for exclusion from MITT								
Violation of inclusion/exclusion criteria	1	2	4	7	0	0	0	0
Withdrawn consent	0	0	1	1	0	0	0	0
Withdrawn requested by Investigator	1	0	0	1	0	0	0	0
<b>Total PP population</b>	383	388	376	1147	345	352	339	1036

Total exclusion from PP population based on MITT population	6	3	10	19	7 <sup>#</sup>	5	14	26
Reason for exclusion from PP								
Violation of inclusion/exclusion criteria	0	0	0	0	1	2	3	6
Outside window period	0	1	3	4	0	1	3	4
Non-compliance	2	0	2	4	1	0	2	3
Withdrawn Consent	2	1	3	6	2	1	4	7
Withdrawn requested by Investigator	1	0	0	1	2	0	0	2
Used Concomitant Therapy During Study Period	0	1	1	2	0	1	1	2
Lost to Follow Up	1	0	1	2	1	0	1	2

#. Subject (b) (6) in the Diclofenac group was included in the FPP population based on the OGD clinical reviewer's comment.

Age, gender and race by treatment groups in the FMITT population are shown in Table 2. Treatment groups were balanced with respect to age and gender with p-value > 0.05. Mean age was 52.3 years old. Females comprised the majority (63%). All study subjects were Asians.

Table 2 Demographic Characteristics in the FMITT Population

	Total N=1062	Test N=352	Reference N=357	Vehicle N=353
<b>Gender</b>				
Female	669 (62.99%)	225 (63.92%)	217 (60.78%)	227 (64.31%)
Male	393 (37.01%)	127 (36.08%)	140 (39.22%)	126 (35.69%)
<b>Race</b>				
Asian	1062 (100%)	352 (100%)	357 (100%)	353 (100%)
Other	0	0	0	0
<b>Age (years)</b>				
Mean (STD)	52.31 (9.31)	53.11 (9.31)	52.37 (9.49)	51.46 (9.07)
Range	35-79	35-79	35-78	35-77

Table 3 displays the baseline WOMAC score by treatment group in the FMITT population. Three treatment groups had comparable WOMAC scores at baseline, with a mean of 12.54 (p-value > 0.05).

Table 3 WOMAC Score at Baseline in the FMITT Population

	Total N=1062	Test N=352	Reference N=357	Vehicle N=353
WOMAC score at Baseline				
Mean (SD)	12.54 (1.64)	12.56 (1.64)	12.58 (1.65)	12.48 (1.62)
Range (Min- Max)	9 - 18	9 - 18	9 - 17	9 - 18

Exploratory analysis, as suggested by the FDA clinical team, was conducted to compare the proportion of subjects who took rescue medications during the study in three treatment groups (Table 4). There were more subjects in the test group (46.02%) and vehicle group (49.58%) taking rescue medications during the study compared to those in the reference group (27.45%).

Table 4 Proportion of Subjects who took Rescue Medications During the Study in the FMITT Population

	<b>Total N=1062</b>	<b>Test N=352</b>	<b>Reference N=357</b>	<b>Vehicle N=353</b>
<b>Yes</b>	435 (40.96%)	162 (46.02%)	98 (27.45%)	175 (49.58%)
<b>No</b>	627(59.04%)	190 (53.98%)	259 (72.55%)	178 (50.42%)

Number of rescue medication tablets consumed by subjects who used rescue medication during the study by treatment group is given in Table 5. Subjects in the test and vehicle groups used more tablets of rescue medication compared to those in the reference group.

Table 5 Number of Tablets used by Subjects who took Rescue Medications During the Study

	<b>Total N=435</b>	<b>Test N=162</b>	<b>Reference N=98</b>	<b>Vehicle N=175</b>
<b>Mean per subject ± SD</b>	11.14 (13.15)	11.80 (14.63)	8.57 (10.49)	11.96 (12.91)
<b>Min-Max</b>	1 - 60	1 - 57	1 - 58	1 - 60

Below are the study results for the primary endpoint, mean change from baseline to week 4 in WOMAC pain score, based on FDA’s analysis populations – FMITT and FPP.

Equivalence testing

The test product was bioequivalent to the reference product for the mean change from baseline to week 4 in WOMAC pain score in the FPP population with the 90% CI on the ratio of two means being (97.7%, 120.4%). This is within the range of 80% to 125%, demonstrating equivalence.

The least squares mean of reference group (-1.84) in this re-analysis was slightly smaller than that (-1.77) in the original analysis by Dr. Fan. This numerical difference shifts the confidence interval but the overall conclusion remains the same.

Superiority testing

The test and reference products were both statistically significantly better than the vehicle control for the mean change from baseline to week 4 in WOMAC pain score in the FMITT population with p-value<0.05.

Table 6 Primary Endpoint Analysis Results in Both Sponsor's and FDA's PP Population

	Sponsor*			FDA		
	Test	Reference	Vehicle	Test	Reference	Vehicle
<b>PP Population</b>						
N	383	388	376	345	352	339
LSMean (WOMAC pain score)	-2.0050	-1.7762		-1.9977	-1.8430	
Point estimate of ratio and 90% CI for Test and Reference (%)	112.88(102.5, 124.56)			108.4 (97.7, 120.4)		
<b>MITT Population</b>						
N	389	391	386	352	357	352
LSMean (WOMAC pain score)	-2.2332	-2.0287	0.6387	-2.25	-2.109	0.524
(Test or Reference) vs. Vehicle	<0.0001	0.0001		<0.0001	<0.0001	

Per request from clinical reviewer, exploratory analysis was conducted for those subjects who did not use rescue medications during study period. Results from this subgroup analysis are given in Table 7. The bioequivalence between the test and the reference groups was not established in the PP population since the 90% CI of the test-to-reference ratio was (100.6%, 126.8%), which was not within [80, 125]. The test and reference groups were both superior over vehicle for the mean change from baseline to Week 4 in total WOMAC pain score in the FMITT population (p-value<0.05).

Table 7 Subgroup Analysis for Subjects Who Did Not Use Rescue Medication During the Study

Parameter	Test	Reference	Vehicle	Point estimate of Ratio and 90% C.I. for Bioequivalence of Test to Reference	p-values*	
					Test vs. vehicle	Reference vs. vehicle
<b>FDA's Per-Protocol Subjects</b>						
	n=186	n=257				
LSMean (std err) (WOMAC pain score)	-2.2764 (0.1461)	-2.0165 (0.1311)		112.89 (100.6, 126.8)	NA	NA
<b>FDA's Modified Intent-to-Treat Subjects</b>						
	n=190	n=259	n=178			
LSMean (WOMAC pain score)	-2.37 (0.1719)	-2.3185 (0.1531)	0.498 (0.1753)	NA	<0.0001	<0.0001

## Conclusion

This re-analysis was performed using FDA's mITT and PP populations based on the "For Cause" Clinical Establishment Inspection Report (EIR) by Dr. Getie-Kebtie. The results show numerical differences from the previous analyses by Dr. Fan. The overall conclusions remain the same as those of Dr. Fan's review.

APPEARS THIS WAY ON  
ORIGINAL

## APPENDIX

**From:** Fenty-Stewart, Nicola

**Sent:** Tuesday, February 16, 2016 8:33 AM

**To:** Thomas, Teena

**Subject:** RE: Comment on Clinical Endpoint Sites on ANDA-208077-ORIG-1 (ref# 5381343)

1. Here are the Subject IDs for the 14 subjects:

Subject No.	Randomization No.
(b) (6)	



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:** 208077

**Drug Name:** Diclofenac Sodium Topical Gel, 1%

**Indication(s):** Treatment of Subjects with Osteoarthritis of the Knee

**Reference Listed Drug:** Voltaren<sup>®</sup> (diclofenac sodium topical gel, 1%) (Novartis)

**Applicant:** Amneal Pharmaceuticals

**Date(s):** Original Submitted 12/19/2014  
Response to Information Request (Sequence 0001) 1/13/2015

**Biometrics Division:** DBVIII

**Statistical Reviewer:** Milton C. Fan, Ph.D.

**Concurring Reviewers:** Yu-te Wu, Ph.D.

**Medical Division:** Division of Clinical Review, Office of Generic Drugs

**Clinical Team:** Joe Zhang, Ph.D., Lesley-Anne Furlong, M.D.

**Project Manager** Teena Thomas

**Keywords:** Bioequivalence, ANCOVA, superiority, WOMAC pain score

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## 1 Executive Summary

The data from one clinical study in ANDA 208077 supports the conclusion that Amneal Pharmaceuticals Diclofenac Sodium Topical Gel, 1% (test product) is clinically equivalent to Novartis Pharms Voltaren<sup>®</sup> Diclofenac Sodium Topical Gel, 1% (reference product) in the treatment of Osteoarthritis (OA) of the knee based on the FDA's per-protocol population. Exploratory analyses were conducted in the subgroup of subjects who did not use rescue medication during the study. The results showed that the bioequivalence between test and reference products was not established in this subgroup.

The purpose of this review is to assess the safety and bioequivalence of the generics Diclofenac Sodium Topical Gel, 1% and the reference listed Voltaren<sup>®</sup> (Diclofenac Sodium Topical Gel, 1%), and to determine whether the efficacy of each of the 2 active treatments was superior to that of the vehicle control in subjects with OA of the knee. Study AM-DCG-001 is the only clinical study that the sponsor submitted to support this application. AM-DCG-001 was a multi-center, double-blind, randomized, vehicle-controlled and parallel-group study. Eleven hundred and seventy-six (1,176) eligible subjects with a clinical diagnosis of OA of the knee were randomized in a 1:1:1 ratio to receive one of three treatment groups (Test, Reference, or Vehicle) at Visit 2/Baseline (Day 0). The randomized subjects self-administered study drug four times daily for 4 weeks. Subjects then returned for two additional visits [Visit 3/On therapy (Week 2 ± 4 days) and Visit 4/End of Treatment (Week 4 ± 4 days) for safety and efficacy evaluations. The primary efficacy endpoint was the mean change from baseline to Week 4 in total WOMAC (Western Ontario McMaster Osteoarthritis Index) pain score. Use of rescue medication (paracetamol/acetaminophen) was permitted during the study. The bioequivalence of test versus reference was evaluated in the FDA's per-protocol (FPP) population, and the superiority of both active treatments versus Vehicle was evaluated in the FDA's mITT (FMITT) population.

There were no major data quality issues in this application. The test product was bioequivalent to the reference product for the mean change from baseline to week 4 in total WOMAC pain score in the FPP population with the 90% CI on the ratio of two means being (101.94, 124.00). This is within the range of 80% to 125%, demonstrating equivalence. The test and reference products were both statistically significantly better than the vehicle control in the FMITT population with p-value < 0.05.

## **2 Introduction**

### **2.1 Overview**

Osteoarthritis (OA), commonly known as wear-and-tear arthritis, is a condition in which the natural cushioning between joints -- cartilage -- wears away. When this happens, the bones of the joints rub more closely against one another with less of the shock-absorbing benefits of cartilage. The rubbing results in pain, swelling, stiffness, decreased ability to move and, sometimes, the formation of bone spurs.

In the New Drug Application (NDA) for the reference listed product, data from one clinical study was presented. In patients with OA of the knee, Voltaren group had statistically significant better average outcomes in the three primary efficacy endpoints [Western Ontario McMaster Osteoarthritis Index (WOMAC) pain index, WOMAC function index, and global rating of disease] than the Vehicle group.

Study AM-DCG-001 is the only clinical study that the sponsor submitted to support this application. Study AM-DCG-001 was a multi-center, double-blind, randomized, vehicle-controlled, parallel-group study to evaluate the safety and bioequivalence of the generic Diclofenac Sodium Topical gel, 1% and the reference listed Voltaren<sup>®</sup> (Diclofenac Sodium Topical Gel, 1%) and to compare both active treatments to a vehicle control for superiority in the treatment of Osteoarthritis (OA) of the knee.

### **Regulatory Background**

Amneal Pharmaceuticals has not submitted any INDs, Protocols, Controlled Correspondences, or additional ANDAs to the OGD for Diclofenac Sodium Topical Gel, 1%. No INDs have been submitted to the OGD for Diclofenac Sodium Topical Gel, 1%.

### **2.2 Data Sources**

The data were submitted electronically. The data files are located in DARRTS under ANDA-208077, Module 5.3.5.1, Study AM-DCG-001:

[\\cdsesub1\evsprod\anda208077\0000\m5\datasets\am-dcg-001\listings\](\\cdsesub1\evsprod\anda208077\0000\m5\datasets\am-dcg-001\listings)  
[\\cdsesub1\evsprod\anda208077\0001\m5\datasets\am-dcg-001\listings\](\\cdsesub1\evsprod\anda208077\0001\m5\datasets\am-dcg-001\listings)

## **3 Statistical Evaluation**

### **3.1 Study Objectives, Design and Endpoints**

#### **Objective**

The objective of this study is to evaluate the therapeutic equivalence and safety of the Test, Diclofenac Sodium Topical Gel, 1% (Amneal Pharmaceuticals), and the Reference, Voltaren<sup>®</sup> (diclofenac sodium topical) gel, 1% (Novartis Pharms), in subjects with OA of the knee; and also to assess the superiority of the two active treatments to the Vehicle control (Amneal Pharmaceuticals).

## **Study Design**

AM-DCG-001 was a multi-center, double-blind, randomized, vehicle-controlled, parallel-group study. This study was performed at 19 study sites located in India. Eligible subjects were enrolled and randomized in a 1:1:1 ratio to one of the three treatment groups. The three gels were generic Diclofenac Sodium Topical Gel, 1%, Voltaren<sup>®</sup> (Diclofenac sodium topical gel, 1%), and the Vehicle control.

Male and female subjects, at least 35 years of age, with a clinical diagnosis of OA of the knee were enrolled in this study. To be included in the study, subjects must have

- Presence of at least three (3) of the American College of Rheumatology (ACR) criteria (age  $\geq$  50; stiffness lasting  $<$  30 minutes; bony tenderness; crepitus; bony enlargement; no palpable warmth)
- Symptoms for at least 6 months prior to screening, AND
- Knee (not referred) pain for 15 days of the preceding month (periarticular knee pain due to OA and not due to other conditions such as bursitis, tendonitis, etc.), AND
- The pain in the target knee required the use of non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol/acetaminophen (topical or oral treatments).

There were a total of four study visits: Visit 1/Screening (Day -7), Visit 2/Baseline/Randomization (Day 0), Visit 3/On therapy (Week 2  $\pm$  4 days), and Visit 4/End of Treatment (Week 4  $\pm$  4 days).

## **Treatments**

A total of eleven hundred and seventy-six (1,176) subjects who met the entry criteria were enrolled in this study. They were randomized to receive the test product (Amneal Pharmaceuticals' generic Diclofenac Sodium Topical Gel, 1%), the reference product (Novartis Pharma's Voltaren<sup>®</sup> diclofenac sodium topical gel, 1%) and the vehicle (Amneal Pharmaceuticals) in a 1:1:1 ratio, respectively.

Subjects were instructed to apply 4 gm of study medication self-administered to the target knee 4 times daily for 4 weeks. With the exception of the washout period prior to baseline assessments, the use of paracetamol/acetaminophen (up to 4 grams per day) was permitted as rescue medication for symptomatic pain relief due to intolerable pain, if experienced by any subject any time throughout the treatment period. Subjects were required to use subject diaries in order to record the date and time of study treatment administration, any missed treatments, paracetamol/acetaminophen (rescue medication) use, concomitant medication use, and the occurrence of Adverse Events (AEs) or intolerability to study medication. Follow up evaluations were at 2 weeks and 4 weeks after starting the study.

<b>Article</b>	<b>Description</b>
<b>Test</b>	Diclofenac Sodium Topical Gel, 1% (Amneal Pharmaceuticals) Batch # PW-ST-13015A, manufactured 05/24/2013
<b>Reference</b>	Voltaren <sup>®</sup> (diclofenac sodium topical) gel, 1% ( Novartis Pharma Produktions GmbH, Wehr, Germany) Batch # W2601, expired on Feb 2015 Bath #3679, expired on May 2016
<b>Vehicle</b>	Vehicle Topical Gel, 1% (Amneal Pharmaceuticals) Batch #PW-ST-13040A, manufactured on 11/13/2013

## **Primary Efficacy Endpoint**

The primary efficacy endpoint was the mean change from baseline to Week 4 in the WOMAC pain score. The change from baseline score for each subject was calculated as the pain score at Week 4 minus the pain score at baseline (Visit 2). The WOMAC pain score (pain score = 0 to 20) was determined by the subject's responses to five questions (S1–S5) using a 5-point Likert scale (i.e., 'none'=0; 'mild'=1, 'moderate'=2; 'severe'=3; 'extreme'=4). The questions pertain to the amount of pain the subject was experiencing in the target knee [i.e., 'How much pain do you have' when 'Walking on a flat surface' (S1), 'Going up or down stairs' (S2), 'At night while in bed' (S3), 'Sitting or lying' (S4), 'Standing upright' (S5)].

## **Analysis Population**

The sponsor's per-protocol (SPP) population included all randomized subjects who met all inclusion/exclusion criteria, were compliant with the assigned study treatment (used at least 75% and no more than 125% of study treatment doses), returned to the study site for the primary endpoint visit within the specified window (+/- 4 days) or discontinued from the study as a treatment failure, and did not have any protocol violations. The PP population was used for the bioequivalence evaluation of test vs. reference.

The sponsor's modified ITT (SmITT) population included all randomized subjects who met all inclusion/exclusion criteria, receive study treatment, and returned for at least one post-baseline visit. The SmITT population was used to compare both test and reference products to vehicle, as a test of study sensitivity.

Missing efficacy data were imputed via the Last Observation Carried Forward (LOCF) method for the SmITT analysis and for those PP subjects who discontinued due to treatment failure.

All subjects who were randomized and used the study drug on at least one occasion were included in the safety analysis.

### *Comments:*

*Sponsor's definition of PP population followed the recommendation of FDA's guidance on Diclofenac Sodium Topical Gel 1%, therefore, it was adequate. The Division of Clinical Review in the Office of Generic Drugs has considered a new definition of mITT (FMITT) population which consists of all subjects randomized and applied or used at least one dose of assigned drug product to be more appropriate for the superiority testing. Statistical reviewer followed the new definition to perform the superiority testing of active treatments versus vehicle.*

*The FDA's per-protocol (FPP) population was the same as the SPP population except for one subject <sup>(b) (6)</sup> in the diclofenac group. The sponsor excluded this subject for the reason of non-compliance. However, the reason to exclude this subject cannot be confirmed by the case report from and clinical study report. Therefore, this subject should be included in the FPP population based on the recommendation of clinical reviewer.*

## 3.2 Statistical Methodologies

### Equivalence Analysis

Test for equivalence between test and reference for the primary endpoint (mean change of WOMAC pain score at Week 4 from baseline) is conducted using the FPP population.

The compound hypothesis to be tested is:

$$H_0: \mu_T / \mu_R \leq \theta_1 \text{ or } \mu_T / \mu_R \geq \theta_2$$

Versus

$$H_A: \theta_1 < \mu_T / \mu_R < \theta_2$$

Here,  $\mu_T$  and  $\mu_R$  denote the mean values of the outcome for test and reference groups, respectively

In order to test the clinical equivalence for test and reference groups in the primary endpoint (mean change of WOMAC pain score from baseline to week 4), the 90% confidence interval (corresponding to two one-sided tests each at level  $\alpha=0.05$ ) (Schuman 1987) is constructed for the ratio of  $\mu_T/\mu_R$  using Fieller's method (Fieller 1940). The needed statistics for Fieller's method (mean and variance-covariance of the respective primary endpoint for each treatment group) are derived from the least square (LS) mean estimates from Analysis of Covariance (ANCOVA) model. The ANCOVA had change in WOMAC score as a dependent variable, treatment group and site as independent tables, and baseline WOMAC score as a covariate. Equivalence is established (that is, the null hypothesis  $H_0$  is rejected) if the 90% confidence interval for the ratio of  $\mu_T/\mu_R$  is contained within the interval  $[\theta_1, \theta_2]$ , where  $\theta_1 = 0.80$  and  $\theta_2 = 1.25$  as specified in the guidance.

### Superiority Analysis

Superiority of test and reference over vehicle ( $p<0.05$ ) was tested using the same ANCOVA model with 2-sided tests (test vs. vehicle; reference vs. vehicle) in the FMITT population. For each evaluation, superiority was concluded if the active treatment response is greater than that for the vehicle, and the p-value for the difference between the two treatments is  $<0.05$ .

## 3.3 Subject Disposition, Demographics and Baseline Characteristics

Eleven hundred and seventy-six (1,176) subjects were randomized to three treatment groups [Test (n=392), Reference (n=393), or Vehicle (n=391)]. Eleven hundred and sixty-six (1,166) subjects were eligible for the sponsor's mITT population; with 389, 391 and 386 subjects in the test, reference and vehicle groups, respectively. Eleven hundred and forty-seven (1,147) subjects were eligible for the sponsor's per-protocol population. Of 1,147 subjects, 383 subjects were in the test group, 388 subjects were in the reference group, and 376 subjects were in the vehicle group. One subject (test group) was randomized, but was withdrawn without any application of medication. This subject was excluded from the sponsor's safety population.

FDA's modified ITT population (FMITT) excluded one subject who did not take any dose of study drug from the randomized population, with 391, 393 and 391 subjects in the test, reference and vehicle groups, respectively. Nine subjects, who were excluded from sponsor's mITT population, were included in the

FMITT population. Among them, two subjects were in the test group, two subjects were in the reference group and five subjects were in the vehicle group.

FDA's reviewers agreed with the sponsor for the definition of the SPP population, and the inclusion of most subjects in the SPP population, except for subject [REDACTED]<sup>(b) (6)</sup> in the test group. The sponsor excluded this subject for the reason of non-compliance. However, the reason to exclude this subject cannot be confirmed by the case report form and clinical study report. Therefore, this subject should be included in the FPP population based on the recommendation of the clinical reviewer.

The FPP population consists of 1148 subjects, with 384, 388 and 376 subjects in the test, reference and vehicle groups, respectively. Table 1 shows the enrollment and final disposition of subjects. It also reflects the discrepancy between the sponsor's and the FDA's analysis populations.

Table 1 Subject Enrollment and Final Study Disposition in the Sponsor's and FDA's Population

	Applicant				FDA			
	Test	Reference	Vehicle	Total	Test	Reference	Vehicle	Total
<b>Randomized</b>	392	393	391	1176	392	393	391	1176
<b>Total Safety population</b>	391	393	391	1175	391	393	391	1175
Total exclusion from Safety population (No confirmed dose)	1	0	0	1	1	0	0	1
<b>Total MITT population</b>	389	391	386	1166	391	393	391	1175
Total exclusion from MITT population based on the safety population	2	2	5	9	1	0	0	0
Reason for exclusion from MITT								
Violation of inclusion/exclusion criteria	1	2	4	7	0	0	0	0
Withdrawn consent	0	0	1	1	0	0	0	0
Withdrawn requested by Investigator	1	0	0	1	0	0	0	0
<b>Total PP population</b>	383	388	376	1147	384	388	376	1148
Total exclusion from PP population based on MITT population	6	3	10	19	7 <sup>#</sup>	5	15	27
Reason for exclusion from PP								
Violation of inclusion/exclusion criteria	0	0	0	0	1	2	4	7
Outside window period	0	1	3	4	0	1	3	4
Non-compliance	2	0	2	4	1	0	2	3
Withdrawn Consent	2	1	3	6	2	1	4	7
Withdrawn requested by Investigator	1	0	0	1	2	0	0	2
Used Concomitant Therapy During Study Period	0	1	1	2	0	1	1	2
Lost to Follow Up	1	0	1	2	1	0	1	2

#. Subject (b) (6) in the Diclofenac group was included in the FPP population based on the OGD clinical reviewer's comment.

The demographic characteristics at baseline by treatment group in the FMITT population are presented in Table 2. Gender was analyzed using a Chi-square test. Age was analyzed using a general linear model. Treatment groups were balanced with respect to gender, race and age with p-value >

0.05. Mean age was 52.3 years old. Females comprised the majority (64%). All study subjects were Asian. Demographic characteristics in the FPP population were similar to those in the FMITT population.

Table 2 Demographic Characteristics in the FMITT Population

	Total N=1175	Test N=391	Reference N=393	Vehicle N=391	p-value
<b>Gender</b>					
Female	753 (64.09%)	255 (65.22%)	244 (62.09%)	254 (64.96%)	0.5977 <sup>1</sup>
Male	422 (35.91%)	136 (34.78%)	149 (37.91%)	137 (35.04%)	
<b>Race</b>					
White	0	0	0	0	NA
Asian	1175 (100%)	391 (100%)	393 (100%)	391 (100%)	
Other	0	0	0	0	
<b>Age (years)</b>					
Mean (STD)	52.28 (9.37)	52.97 (9.40)	52.43 (9.42)	51.44 (9.23)	0.0674 <sup>2</sup>
Median	51	52	51	51	
Range	35-85	35-85	35-78	35-77	

Compiled by this reviewer.

<sup>1</sup>p-value for treatment comparison was obtained from CMH test for general association.

<sup>2</sup>p-value for treatment comparison was obtained from an analysis of variance (ANOVA) model with treatment group as the factor.

Table 3 displays the baseline WOMAC score by treatment group in the FMITT population. Three treatment groups had comparable WOMAC scores at baseline, with a mean of 12.46. There were no statistically significant differences among three treatment groups (p-value >0.05).

Table 3 WOMAC Score at Baseline in the FMITT Population

	Total N=1175	Test N=391	Reference N=393	Vehicle N=391	p-value*
WOMAC score at Baseline					
Mean (SD)	12.46 (1.65)	12.46 (1.66)	12.53 (1.67)	12.38 (1.63)	0.4672
Median	12	12	12	12	
Range (Min- Max)	9 - 18	9 - 18	9 - 17	9 - 18	

Compiled by this reviewer.

\*p-value for treatment comparison was obtained from an analysis of variance (ANOVA) model with treatment group as the factor.

Duration of study therapy and compliance rate by treatment groups are shown in Table 4. The mean duration and compliance rates were comparable among three treatment groups (p-value > 0.05).

Table 4 Exposure to Study Drug and Treatment Compliance in the FMITT Population

	<b>Total N=1175</b>	<b>Test N=391</b>	<b>Reference N=393</b>	<b>Vehicle N=391</b>	<b>p-value*</b>
<b>Duration (days)</b>					
<b>Mean ± SD</b>	28.35 (1.74)	28.30 (2.15)	28.42 (1.05)	28.54 (1.85)	0.6620
<b>Median</b>	28.00	28.00	28.00	28.00	
<b>Min-Max</b>	5 – 39	5 – 39	21 – 33	5 – 35	
<b>Missing</b>	0	0	0	0	
<b>Compliance Rate</b>					
<b>Mean ± SD</b>	.096 (0.05)	0.96 (0.05)	0.96 (0.04)	0.96 (0.05)	0.6503
<b>Median</b>	0.97	0.97	0.97	0.97	
<b>&lt;75%</b>	6(0.5%)	3(0.77%)	1(0.25%)	2(0.51%)	
<b>75-125%</b>	1165(99.15%)	386(98.72%)	392(99.75%)	387(98.98%)	
<b>Missing</b>	4	2	0	2	

Compiled by this reviewer.

\*p-values for treatment comparisons were obtained from an analysis of variance (ANOVA) model with treatment group as the factor.

According to the study protocol and FDA’s guidance, the use of paracetamol/acetaminophen (up to 4 grams per day) was permitted as rescue medication for symptomatic pain relief due to intolerable pain. Exploratory analysis, as suggested by the FDA clinical team, was conducted to compare the proportion of subjects who took rescue medications during the study in three treatment groups (Table 5). It was observed that there were more subjects in the test group (47.3%) and vehicle group (45.8%) taking rescue medications during the study as compared to that in the reference group (25.7%).

Table 5 Proportion of Subjects who took Rescue Medications during the Study in the FMITT Population

	<b>Total N=1175</b>	<b>Test N=391</b>	<b>Reference N=393</b>	<b>Vehicle N=391</b>	<b>p-value*</b>
	465 (39.6%)	185 (47.3%)	101 (25.7%)	179 (45.8%)	<0.0001
<b>Missing</b>	9	5	0	4	

Compiled by this reviewer.

\*p-value for treatment comparison was obtained from Chi-square test.

Number of rescue medication tablets consumed by subjects who used rescue medication during the study by treatment group is given in Table 6. Subjects in the reference group used less tablets compared to those in the other two treatment groups (test and vehicle).

Table 6 Number of Tablets used by Subjects who took Rescue Medications during the Study

	<b>Total N=465</b>	<b>Test N=185</b>	<b>Reference N=101</b>	<b>Vehicle N=179</b>
<b>Mean ± SD</b>	11.00	11.12 (14.03)	8.38 (10.40)	12.36 (13.06)
<b>Median</b>	6	6	5	6
<b>Min-Max</b>	1 - 60	1 – 57	1 – 58.	1 - 60

Compiled by this reviewer.

## **Missing Data and Imputation**

Among the 1176 subjects who were randomized in the study, 21 subjects (1.8%) discontinued from the study including 2 withdrawals by investigator, 8 withdrawals by patient, 7 with protocol violation, 4 with adverse events, 1 with a concomitant therapy reported or required that likely to confound the assessment of the subject's OA, and 1 with other reasons (some subjects had multiple reasons for discontinuation. Therefore, the sum was greater than 21). Among the 21 discontinued subjects, 20 subjects were included in the FMITT population, but not included in the FPP population.

The Last Observation Carried Forward (LOCF) method was used to impute the missing data in the FMITT population. If a subject discontinued from the study, data from the last available post-baseline visit was carried forward and used as the measurement at the final visit for this subject. In the FMITT population, 20 (1.7%) of the 1175 subjects did not have final measurements (Table 7). The LOCF method was used to impute the missing final measurements for these subjects.

Table 7 Number of Subjects Who Had Missing Data by Treatment Group

	<b>Total</b>	<b>TEST</b>	<b>Reference</b>	<b>Vehicle</b>
<b>Randomized</b>				
<b>N</b>	1176	392	393	391
<b>Missing Data, N (%)</b>	21 (1.8%)	10 (2.6%)	4 (1.0%)	7 (1.8%)
<b>FITT</b>				
<b>N</b>	1175	391	393	391
<b>Missing Data using LOCF, N (%)</b>	20 (1.7%)	10 (2.6%)	4 (1.0%)	6 (1.5%)
<b>FPP</b>				
<b>N</b>	1148	384	388	376
<b>Missing Data using LOCF, N (%)</b>	0	0	0	0

Compiled by this reviewer.

## **3.4 Results and Conclusions**

### **3.4.1 Sponsor's Results**

The primary assessment of bioequivalence was evaluated using the per protocol (PP) population. For this analysis, the estimates of least square means and the 90% CI were obtained using Analysis of Covariance (ANCOVA) with change in total WOMAC score as a dependent variable and treatment group and site as independent variables and baseline WOMAC score as a covariate. If the estimated 90% CI for change from baseline to week 4 in total WOMAC score between the test and reference groups falls within [0.80, 1.25] then bioequivalence would have been considered demonstrated.

The sponsor used the MITT population to evaluate the superiority of both the test and reference products to Vehicle. Subjects discontinued early were included in the MITT population using LOCF. The sponsor used the same ANCOVA model with 2 sided tests (test vs. vehicle; reference vs. vehicle). For each evaluation, if the active treatment response was statistically significantly greater ( $p < 0.05$ , two-sided) to that in the vehicle group, then the primary endpoint in the study shall be considered validated.

The sponsor concluded that the test and the reference groups were clinically equivalent in their PP population since the 90% CI of the test-to-reference ratio (112.88%) was (102.5%, 124.56%) which was within [80, 125]. Also the test and reference groups were both superior over vehicle for the mean change from baseline to Week 4 in total WOMAC pain score in their MITT population (p-value<0.05 in both cases).

Table 8 Primary Efficacy Analyses: Mean Change from Baseline to Week 4 in Total WOMAC Score, per Sponsor\*

Parameter	Test	Reference	Vehicle	90% C.I. for Bioequivalence of Test to Reference	p-values**	
					Test vs. vehicle	Reference vs. vehicle
<b>Per-Protocol Subjects</b>						
	n=383	n=388	n=376			
LSMean (WOMAC pain score)	-2.0050	-1.7762		(102.5, 124.56)	NA	NA
Test-to-Reference Ratio	112.88					
<b>Modified Intent-to-Treat Subjects</b>						
	n=389	n=391	n=386			
LSMean (WOMAC pain score)	-2.2332	-2.0287	0.6387	NA	<0.0001	<0.0001
Std Err LSMeans	0.1160	0.1157	0.1172			
Difference of LSMeans (Active-Vehicle)	-2.8719	-2.6674	-			

\*Source: Table 11.4.1.1-1, CSR page 50.

\*\*p-value was calculated using ANCOVA (two sided  $\alpha=0.05$ ).

Note: LOCF method applied for Modified ITT population.

### 3.4.2 Reviewer's Results

The findings from the reviewer's analyses were consistent with those from the sponsor's analyses. The discrepancies in numbers reflect the difference between sponsor's and FDA's analysis populations.

#### Equivalence testing

The test product was bioequivalent to the reference product for the mean change from baseline to week 4 in WOMAC pain score in the FPP population with the 90% CI on the ratio of two means being (101.94%, 124%). This is within the range of 80% to 125%, demonstrating equivalence. The point estimate of the test-to-reference ratio was 112.31%. The modification of FPP population did not affect the conclusion of equivalence testing between test and reference products.

#### Superiority testing

The test and reference products were both statistically significantly better than the vehicle control for the mean change from baseline to week 4 in WOMAC pain score in the FMITT population with p-value<0.05.

Table 9 Primary Endpoint Analysis Results in Both Sponsor's and FDA's PP Population

	Sponsor*			FDA		
	Test	Reference	Vehicle	Test	Reference	Vehicle
<b>PP Population</b>						
N	383	388	376	384	388	376
LSMean (Std err) (WOMAC pain score)	-2.0050 (0.0978)	-1.7762 (0.0969)		-1.9926 (0.0981)	-1.7742 (0.0972)	
90% CI for Test and Reference (%)	(102.5, 124.56) <sup>1</sup>			(101.94, 124.00) <sup>1</sup>		
<b>MITT Population</b>						
N	389	391	386	391	393	391
LSMean (WOMAC pain score)	-2.2332	-2.0287	0.6387	-2.2299	-2.0256	0.6444
(Test or Reference) vs. Vehicle	<0.0001 <sup>2</sup>	0.0001 <sup>2</sup>		<0.0001 <sup>2</sup>	<0.0001 <sup>2</sup>	

\*Source: Table 11.4.1.1-1, CSR page 50.<sup>F</sup>

<sup>1</sup>Confidence interval for test to reference was calculated using ANCOVA.

<sup>2</sup>P-value was calculated using ANCOVA (two sided  $\alpha=0.05$ ).

Per request from clinical reviewer, exploratory analysis was conducted for those subjects who did not use rescue medications during study period. Results from this subgroup analysis are given in Table 10.

For those subjects who did not use rescue medication during study period, the bioequivalence between the test and the reference groups was not established in the FPP population since the 90% CI of the test-to-reference ratio (116.31%) was (104.4%, 129.68%), which was not within [80, 125]. The point estimate of test-to-reference ratio was 116.31% that was greater than the test-to-reference ratio in the overall FPP population. The treatment effect was actually greater, i.e., bigger test-to-reference ratio and LS means (in numeric value), in this subgroup. The upper bound of 90% CI being greater than 125 could also be due to the wider confidence interval in the subgroup, i.e., smaller number of subjects (N) leading to greater standard error which was observed in Tables 9 and 10. Baseline characteristics were compared between subjects who took rescue medication and those who did not take rescue medication. The results showed that these two groups were balanced in terms of age, gender and WOMAC score at baseline. Therefore, the difference in results between overall pp population and subgroup pp population could possibly not be explained by the baseline characteristics examined.

The test and reference groups were both superior over vehicle for the mean change from baseline to Week 4 in total WOMAC pain score in the MITT population (p-value<0.05 in both cases).

Table 10 Subgroup Analysis for Subjects Who Did Not Use Rescue Medication during the Study

Parameter	Test	Reference	Vehicle	90% C.I. for Bioequivalence of Test to Reference	p-values*	
					Test vs. vehicle	Reference vs. vehicle
<b>FDA's Per-Protocol Subjects</b>						
	n=202	n=290	n=206			
LSMean (std err) (WOMAC pain score)	-2.2467 (0.1337)	-1.9316 (0.1190)		(104.4, 129.68)	NA	NA
Test-to-Reference Ratio	116.31					
<b>FDA's Modified Intent-to-Treat Subjects</b>						
	n=206	n=292	n=211			
LSMean (WOMAC pain score)	-2.4020	-2.2352	0.6469	NA	<0.0001	<0.0001
Std Err	0.1578	0.1386	0.1565			
Difference of LSMeans (Active-Vehicle)	-3.0489	-2.8821	-			

Complied by this reviewer.

## 4 Conclusions

### 4.1 Comments on the Sponsor's Analyses

Sponsor and FDA use the same definition for the clinical outcome. There are minor differences between the sponsor's and FDA's results due to the differences between the sponsor's and FDA's modified intent-to-treat and per-protocol populations.

### 4.2 Conclusions

**Equivalence:** The test and reference products were found to be clinically equivalent for the mean change from baseline to Week 4 in total WOMAC pain score with 90% C.I on the ratio of two means being (101.94%, 124.00%) in the FPP population. This is within the range of 80% and 125%, demonstrating equivalence.

**Superiority:** The test and reference products were statistically significantly better than the Vehicle in the FMITT population with p-value < 0.05.

## 5 References

Schuirman, DJ. (1987) A Comparison of the Two One-sided Test Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability, *Journal of Pharmacokinetics and Biopharmaceutics*, 15(6): 657-680.

Fieller, EC. (1940) The Biological Standardisation of Insulin, *Journal of the Royal Statistical Society (Supplement)*, 1:1-54.

Draft Guidance on Diclofenac Sodium, March 2011.

## Appendix I Outline of Statistical analysis method for WOMAC data, using SAS PROC GLM

Let  $Y$  = mean WOMAC change from baseline (the endpoint of interest)  
Baseline = mean WOMAC at baseline (the covariate)

Let  $\mu_T(b)$  be the mean of  $Y$  for the Test product when Baseline =  $b$

Let  $\mu_R(b)$  be the mean of  $Y$  for the Reference product when Baseline =  $b$

$\mu_T(b)$  and  $\mu_R(b)$  are both *weighted* means, depending on which weights are chosen (explicitly or implicitly) for the clinical sites.

Assume that the code used for the Test treatment comes before the code used for the Reference treatment in SAS sort order (for example, if the Test product is coded as "1" and the Reference product is coded as "2", then this would be so. Similarly if Test were coded as "A" and Reference were coded as "B". On the other hand, if Test were coded as "T" and Reference were coded as "R", Reference would come before Test in SAS sort order, and the coefficients for the treatment levels in what follows would have to be reversed.)

The initial statements of a SAS PROC GLM analysis would be

```
Proc glm class site trt  
model Y = site trt Baseline;
```

These statements would be followed by ESTIMATE statements, as follows:

To test the null hypothesis  $H_0: \mu_T(b)/\mu_R(b) < c$ , against the alternative  $H_1: \mu_T(b)/\mu_R(b) \geq c$ , we would use the statement

```
estimate 'ratio= c, baseline= b' intercept (1-c) trt 1 -c Baseline (1-c)b;
```

In the resulting analysis, we would reject  $H_0$  if the (two-sided) p-value given by SAS is  $\leq 0.1000$  and if the value of the point estimate is positive (note that if the p-value is  $\leq 0.1000$  but the point estimate is *negative*, we would have rejected  $H_0$  "in the wrong direction".)

Similarly, to test  $H_0: \mu_T(b)/\mu_R(b) > c$ , against the alternative  $H_1: \mu_T(b)/\mu_R(b) \leq c$ , we would use the same ESTIMATE statement, and we would reject  $H_0$  if the p-value is  $\leq 0.1000$  and if the point estimate is *negative*.

Note that in these analyses, we have not explicitly specified coefficients for the levels of site. By default, SAS PROC GLM implicitly puts *equal weight* on each site in this case. If a sponsor feels that site weights other than equal weights should be used, they should make their case in their submission. With unequal weights, the weights would have to be given explicitly in the ESTIMATE statement, with appropriate multipliers.

To find the minimum value of Baseline (this assumes that the estimated slope is positive) for which the products pass the usual equivalence test, first use  $c = 0.80$ , so that the ESTIMATE statement would be

```
estimate 'ratio= 0.80, baseline= b' intercept 0.20 trt 1 -0.80 Baseline 0.20b;
```

Through trial and error ("by hand" or with some sort of computer search algorithm), find the value of  $b$  for which the resulting p-value is exactly 0.1000 (and for which the point estimate is positive.) Call it  $b_L$ .  $b_L$  is the minimum value of baseline for which the products pass "on the low end". Now use  $c = 1.25$ , so that the ESTIMATE statement is

```
estimate 'ratio= 1.25, baseline= b' intercept -0.25 trt 1 -1.25 Baseline -0.25b;
```

Through trial and error ("by hand" or with some sort of computer search algorithm), find the value of  $b$  for which the resulting p-value is exactly 0.1000 (and for which the point estimate is negative.) Call it  $b_U$ .  $b_U$  is the minimum value of baseline for which the products pass "on the high end". The *larger* of  $b_L$  and  $b_U$  is the minimum value of baseline for which you pass both one-sided tests, and so pass the equivalence test.

For a given value of Baseline, for example Baseline = sample mean baseline from the study or Baseline = sample median baseline from the study, call it Baseline =  $b^*$ , you can use the estimate statement

```
estimate 'ratio= c, baseline= b*' intercept (1-c) trt 1 -c Baseline (1-c)b*;
```

to obtain a confidence interval at Baseline =  $b^*$  by finding ("by hand" or through computer search) the two values of  $c$  (call them  $C_L$  and  $C_U$ ) that make the p-value exactly equal to 0.1000 (verifying that values of  $c$  between  $C_L$  and  $C_U$  produce a p-value  $> 0.1000$  and values of  $c$  either below  $C_L$  or above  $C_U$  produce a p-value  $< 0.1000$ .)

Donald J. Schuirmann  
Huaixiang Li, Ph.D.  
Office of Biostatistics/CDER/FDA  
December 21, 2007

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 208077Orig1s000**

**BIOEQUIVALENCE REVIEWS**

**DIVISION OF BIOEQUIVALENCE  
ACCEPTABLE OSIS INSPECTION REPORT REVIEW**

<b>ANDA No.</b>	208077
<b>Drug Product Name</b>	Diclofenac Sodium Topical Gel
<b>Strength(s)</b>	1% w/w
<b>Applicant Name</b>	Amneal Pharmaceuticals
<b>Original Submission Date(s)</b>	12/19/2014
<b>Date of Report</b>	01/07/2015 (clinical site) (OSIS declined to inspect) 02/02/2015 (analytical site) (OSIS declined to inspect) (b) (4) (analytical site) (EIR report)
<b>Reviewer</b>	Yajun Liu, Ph.D.
<b>Study Number (s)</b>	ARL/12/443
<b>Study Type (s)</b>	Fasting
<b>Strength (s)</b>	1% w/w
<b>Clinical Site</b>	Accutest Research Lab (I) Pvt. Ltd. (Unit-II)
<b>Clinical Site Address</b>	Opposite The Grand Bhagwati Hotel, Sarkhej-Gandhinagar Highway, Bodakdev, Ahmedabad -380059, INDIA
<b>Analytical Site</b>	(b) (4)
<b>Analytical Site Address</b>	(b) (4)
<b>OUTCOME DECISION</b>	<b>ADEQUATE</b>

### EXECUTIVE SUMMARY

OSIS declined to inspect the clinical site, Accutest Research Lab (I) Pvt. Ltd. (Unit-II) (Opposite The Grand Bhagwati Hotel, Sarkhej-Gandhinagar Highway, Bodakdev, Ahmedabad -380059, India) citing the rationale that the site was inspected within the last four years and the inspectional outcome was classified as No Action Indicated (NAI)<sup>1</sup>.

OSIS declined to inspect the analytical site, (b) (4) (b) (4) citing the rationale that “although the last inspection at the firm was classified as a (b) (4), based on the inspection outcome and the recommendation to the review division to accept study data from the studies reviewed, an analytical inspection is not needed at this time”<sup>2</sup>. The last routine inspection at this analytical site was conducted covering studies submitted to ANDA (b) (4) 204844, (b) (4) from (b) (4) (b) (4) and completed with an outcome of (b) (4). One objectionable finding related to studies in ANDA (b) (4) was identified. The reviewer of the parent ANDA (b) (4) reviewed the inspection report and concluded the finding is isolated<sup>3</sup>. Based on reviewing the inspection report<sup>4</sup>, the reviewer of current ANDA is in

<sup>1</sup> GDRP, ANDA-208077-ORIG-1, Site: ACCUTEST RESEARCH LAB (I) PVT. LTD. (UNIT-II), [Decline to Inspect NAIMemo A208077 Accutest.pdf](#), completion date 07-Jan-2015

<sup>2</sup> GDRP, ANDA-208077-ORIG-1, Site: (b) (4) (b) (4) [DeclineMemo A208077 \(b\) \(4\).pdf](#), completion date 02-Feb-2015

opinion that the findings at the analytical site at [REDACTED] (b) (4) should not have any impact on the outcome of the study of the current application.

Given the acceptable inspection of the clinical and analytical site, the bioequivalence section of the application is adequate.

**DEFICIENCY COMMENTS:**

None

**COMMENTS:**

No OSIS inspection is pending or necessary for the analytical or clinical site.

**RECOMMENDATIONS:**

From a bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence. The bioequivalence section of the application is acceptable.

## BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 208077

APPLICANT: Amneal Pharmaceuticals

DRUG PRODUCT: Diclofenac Sodium Topical Gel, 1% w/w

The Division of Bioequivalence II (DBII) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns 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.  
Director, Division of Bioequivalence II  
Office of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

### DIVISION OF BIOEQUIVALENCE REVIEW

<b>ANDA No.</b>	208077		
<b>Drug Product Name</b>	Diclofenac Sodium Topical Gel		
<b>Strength(s)</b>	1% w/w		
<b>Applicant Name</b>	Anneal Pharmaceuticals		
<b>Applicant Address</b>	85 Adams Avenue, Hauppauge, New York, 11788		
<b>US Agent Name and the mailing address</b>	Alpesh Patel, Vice President - Global Regulatory Affairs 85 Adams Avenue, Hauppauge, New York, 11788		
<b>US agent's Telephone Number</b>	(631) 656 5007		
<b>US Agent's Fax Number</b>	(631) 527 3523		
<b>Original Submission Date(s)</b>	12/19/2014		
<b>Submission Date(s) of Amendment(s) Under Review</b>	N/A		
<b>Reviewer</b>	Yajun Liu, Ph.D.		
<b>Study Number (s)</b>	ARL/12/443	120049	
<b>Study Type (s)</b>	Fasting	Failed Fasting	
<b>Strength (s)</b>	1% w/w	1% w/w	
<b>Clinical Site</b>	Accutest Research Lab (I) Pvt. Ltd. (Unit-II)	PharmaNet	
<b>Clinical Site Address</b>	Opposite The Grand Bhagwati Hotel, Sarkhej-Gandhinagar Highway, Bodakdev, Ahmedabad -380059, INDIA	2500, rue Einstein Québec (Québec), Canada G1P 0A2	
<b>Analytical Site</b>	(b) (4)		
<b>Analytical Site Address</b>			
<b>OSIS Status</b>	TBD by OSIS		
<b>OVERALL REVIEW RESULT</b>	ADEQUATE		
<b>REVISED/NEW DRAFT GUIDANCE INCLUDED</b>	NO		
<b>BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #</b>	<b>STUDY/TEST TYPE</b>	<b>STRENGTH</b>	<b>REVIEW RESULT</b>
<b>1</b>	Fasting	1%	ADEQUATE

## 1 EXECUTIVE SUMMARY

This application contains the results of fasting bioequivalence (BE) study comparing a test product Amneal Pharmaceuticals' Diclofenac Sodium Topical Gel, 1% to the corresponding reference product Novartis' VOLTAREN® (diclofenac sodium) Topical Gel, 1%. The fasting BE study was designed as a single-dose, three way reference replicated crossover study in healthy male and female subjects. The firm's fasting BE study is acceptable. The results are summarized in the tables below.

Diclofenac Sodium Topical Gel 1% w/w						
Fasting Bioequivalence Study (Study No: ARL/12/443)						
No of subjects=40 (Male n=32; Female n=8)						
Parameter (units)	T/R Ratio	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT(pg*h/mL)	0.98	0.424754	0.6517315	-0.241797	Scaled/PE	PASS
LAUCI (pg*h/mL)	0.96	0.5422809	0.7363973	-0.305624	Scaled/PE	PASS
LCMAX (pg/mL)	0.92	0.5330421	0.7300973	-0.291434	Scaled/PE	PASS

The firm conducted a three way reference replicated crossover fasting BE study and submitted 16 summary tables (Appendix 4.6.1). This failed fasting study was conducted with 46 healthy male and female subjects and failed on the point estimates (test/reference ratio) and criteria bounds for AUC<sub>t</sub>, AUC<sub>inf</sub> and C<sub>max</sub>. The firm examined the formulation of failed fasting study (Batch# PW-ST-12001A) and found that Batch # PW-ST-12001A (b) (4)



similar *in vitro* diffusion profiles were achieved between test (Bio-lot# PW-ST-13015A) and RLD products (Bio-lot#W2601). This formulation was used in the bio-lot.

The firm's clinical site and analytical site inspection status is to be reviewed separately by Office of Study Integrity and Surveillance (OSIS).

The BE study with clinical endpoint will be reviewed separately by Division of Clinical Review.

The application is **acceptable** with no deficiencies.

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### 3 SUBMISSION SUMMARY

#### 3.1 Drug Product Information<sup>1</sup>

<b>Test Product</b>	Diclofenac Sodium Topical Gel, 1%
<b>Reference Product</b>	VOLTAREN® (diclofenac sodium) Topical Gel, 1%
<b>RLD Manufacturer</b>	Novartis
<b>NDA No.</b>	N022122
<b>RLD Approval Date</b>	Oct 17, 2007
<b>Indication<sup>2</sup></b>	VOLTAREN® GEL is a non-steroidal anti-inflammatory drug indicated for the relief of the pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands. VOLTAREN® GEL was not evaluated for use on joints of the spine, hip, or shoulder.

#### 3.2 PK/PD Information<sup>2,3</sup>

<b>Bioavailability</b>	After application of 4 grams of the 1% gel to the knee four times daily (total daily dose of 160 mg of diclofenac sodium) for 7 days, the mean C <sub>max</sub> was 15 +/- 7.3 ng/ml, the time to the maximum concentration was 14 hours (range, 0-24 hours), and the AUC over 24 hours was 233 +/- 128 ng x h/ml. This equates to a C <sub>max</sub> of 0.6% and an AUC of 5.8% of the values obtained after administration of oral diclofenac sodium 50 mg three times daily. Systemic exposure after application of 4 grams of the 1% gel to each knee and 2 grams to each hand four times daily (total daily dose of 480 mg of diclofenac sodium) for 7 days equated to a C <sub>max</sub> of 2.2% and an AUC of 19.7% of the values obtained after administration of oral diclofenac sodium 50 mg three times daily.
<b>Food Effect</b>	N/A
<b>T<sub>max</sub></b>	The time to the maximum concentration was 14 hours (range, 0—24 hours)
<b>Metabolism</b>	Metabolism via hepatic cytochrome P450 2C9 and 3A4 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. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CYP2C8 may also play a role in metabolism. <i>In vitro</i> , the biotransformation of diclofenac to 4'-hydroxy-3'-(glutathion-S-yl) diclofenac is CYP2C9-dependent, and metabolism to 5-hydroxy-4-(glutathion-S-yl) diclofenac and 5-hydroxy-6-(glutathion-S-yl) diclofenac mainly involves CYP3A4. Although both CYP2C9 and CYP3A4 catalyze the bioactivation, CYP2C9 is capable of producing the benzoquinone imine intermediate at lower drug concentrations. For

<sup>1</sup> Electronic Orange Book, [http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl\\_No=022122&TABLE1=OB\\_Rx](http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=022122&TABLE1=OB_Rx)

<sup>2</sup> RLD Label approved on 11/25/2014, Drugs@FDA, [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/022122s007lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022122s007lbl.pdf)

<sup>3</sup> Clinical Pharmacology, <http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=183&sec=monphar&t=0>

	<p>example, 4'-hydroxy-3'-(glutathion-S-yl) diclofenac was the dominant metabolite over a substrate concentration range of 10—50 micromolar. The metabolites 5-hydroxy-4-(glutathion-S-yl) diclofenac and 5-hydroxy-6-(glutathion-S-yl) diclofenac became equally important products at diclofenac concentrations of at least 100 micromolar. The 4'-hydroxy- diclofenac metabolite, which is formed via CYP3A4, has very weak pharmacologic activity</p>
<b>Excretion</b>	<p>The metabolites after administration are subsequently excreted through urinary and biliary pathways. About 65% of a dose is excreted in the urine and about 35% in the bile. Less than 1% is excreted in the urine unchanged, with the remainder as metabolites or conjugates of the drug. Conjugates of unchanged diclofenac account for 5—10% of the dose excreted in the urine and &lt; 5% excreted in the bile. Little or no unchanged unconjugated drug is excreted.</p>
<b>Half-life</b>	<p>The elimination half-life of diclofenac from diclofenac epolamine medicated topical patch is approximately 12 hours. (Half-life not reported on RLD label for Voltaren® Gel.)</p>
<b>Dosage and Administration</b>	<p>Total dose should not exceed 32 g per day, over all affected joints. VOLTAREN® GEL should be measured onto the enclosed dosing card to the appropriate 2 g or 4 g designation.</p> <ul style="list-style-type: none"> <li>• Lower extremities: Apply the gel (4 g) to the affected area 4 times daily. Do not apply more than 16 g daily to any one affected joint of the lower extremities.</li> <li>• Upper extremities: Apply the gel (2 g) to the affected area 4 times daily. Do not apply more than 8 g daily to any one affected joint of the upper extremities.</li> </ul>
<b>Maximum Daily Dose</b>	32 g
<b>Drug Specific Issues (if any)</b>	<p><b>BOXED WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISK</b></p> <p><b>Cardiovascular Risk</b></p> <ul style="list-style-type: none"> <li>• Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.</li> <li>• Voltaren® Gel is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.</li> </ul> <p><b>Gastrointestinal Risk</b></p> <ul style="list-style-type: none"> <li>• Non-steroidal anti-inflammatory drugs (NSAIDs), including VOLTAREN® GEL, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. Elderly patients are at greater risk for serious gastrointestinal events.</li> </ul>

### 3.3 OGD Recommendations for Drug Product

<b>Number of studies recommended:</b>	2
---------------------------------------	---

<b>1.</b>	<b>Type of study:</b>	Fasting
	<b>Design:</b>	Single-dose, two-way crossover in vivo
	<b>Strength:</b>	1%
	<b>Subjects:</b>	Healthy males and non-pregnant females, general population
	<b>Additional Comments:</b>	

<b>2.</b>	<b>Type of study:</b>	Bioequivalence (BE) Study with Clinical Endpoint
	<b>Design:</b>	Randomized, double blind, parallel, placebo-controlled in vivo
	<b>Strength:</b>	1%
	<b>Subjects:</b>	Healthy males and females with osteoarthritis of the knee.
	<b>Additional Comments:</b>	Specific recommendations are provided in <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244644.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244644.pdf</a>

<b>Analytes to measure (in plasma/serum/blood):</b>	Diclofenac in plasma (Study 1)
<b>Bioequivalence based on:</b>	(90% CI) Diclofenac (Study 1); Clinical endpoint (Study 2)
<b>Waiver request of in-vivo testing:</b>	Not applicable
<b>Source of most recent recommendations:</b>	Draft Guidance on Diclofenac Sodium Topical Gel, Recommended on Mar 2011 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244644.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244644.pdf</a>  Control #12-0177 \\cdsnas\OGDS6\CONTROLS\2012-docs\12-0177.pdf
<b>Summary of OGD or DB History</b>	Per Orange Book, there is no approved generic version of VOLTAREN® Gel as of Mar 3, 2015.  There are two <b>pending</b> ANDAs: ANDA 208077 (Amneal) (current ANDA) ANDA (b) (4)  There is one ANDA that was given <b>complete response</b> : ANDA (b) (4)  For details, see Appendix 4.3

### 3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	No	--
Waiver requests	No	--
BCS Waivers	No	--
Clinical Endpoints	Yes	1
Failed Studies	No	--
Amendments	No	--

### 3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	<b>Module 5.3.1.4</b>
Analyte	Diclofenac
Internal standard (IS)	Diclofenac-d <sub>4</sub>
Method description	This method involves the extraction of Diclofenac and the internal standard Diclofenac-d <sub>4</sub> from human EDTA K <sub>2</sub> plasma using an automated liquid-liquid extraction procedure and LC-MS/MS determination according to method SOP (b)(4). Samples are kept frozen at -20°C prior to analysis and 0.100 mL of human EDTA K <sub>2</sub> plasma was used for analysis.
Limit of quantitation (pg/mL)	50.00  Original validation report
Average recovery of drug (%)	75.66, 76.77 and 79.28%  Original validation report
Average recovery of IS (%)	71.19%  Original validation report
Standard curve concentrations (pg/mL)	50.00, 100.00, 400.00, 2000.00, 4000.00, 8000.00, 16000.00, 20000.00*  <u>Original validation report</u>  (Partial validation report)
QC concentrations (pg/mL)	LLQC: 50.00, QC1: 150.00, QC2: 10000.00, QC3: 15000.00, ULQC: 20000.00*  <u>Original validation report</u>  (Partial validation report)
QC Intraday precision range (%)	0.88 to 3.62%  <u>Original validation report</u>  (Partial validation report)
QC Intraday accuracy range (%)	-2.98 to 1.24%  <u>Original validation report</u>  (Partial validation report)

Information Requested	Data
QC Interday precision range (%)	2.81 to 16.69% Original validation report
QC Interday accuracy range (%)	-5.15 to 1.73% Original validation report
Bench-top stability (hrs)	22 hours and 50 minutes at room temperature Original validation report
Stock stability (days)	Analyte: 105 days at -20°C IS: 265 days at -20°C Original validation report
Processed stability (hrs)	71 hours and 08 minutes at room temperature Original validation report
Freeze-thaw stability (cycles)	4 cycles at -20°C and at -80°C Original validation report
Long-term storage stability (days)	133 days at -20°C and at -80°C Original validation report
Dilution integrity	DQC diluted 1/20:                      DQC diluted 1/50: %CV : 3.39%                              %CV : 2.92% %Bias: -3.56%                            %Bias: -3.55% Original validation report <b>Partial validation report</b>
Selectivity	No interfering peaks noted in blank plasma samples for analyte and its internal standard Original validation report

\* See reviewer's comments below.

**Reviewer's note:** Some information in the above summary table provided by the firm is either incorrect (underlined) or missing. The reviewer corrected or added the information (in red) per firm's method validation report.

SOPs submitted	(b) (4)
Was the % recovery consistent across QC concentrations?	Yes
Is the same anticoagulant used in the pre-method validation study used in	Yes, K <sub>2</sub> EDTA

the sample assay?	
If not, was cross validation study conducted?	N/A
Was the dilution factor adequate for the current study sample analysis?	Yes
Was the same dilution medium (plasma/solvent) used during validation and sample analysis?	Yes
Does the duration of the each of the stability parameters support the sample preparation and assay dates	Yes
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	No See comments below

**Comments on the Pre-Study Method Validation:**

1. The method was originally validated using calibration standards over concentration range of 50-50000 pg/mL and QC levels of LLQC: 50.00, QC1: 150.00, QC2: 25000.00, QC3: 37500.00 pg/mL. The bioanalytical assays for fasting BE study were carried out using standards of a truncated calibration range of 50-20000 pg/mL and new set of QCs at levels of LLQC: 50.00, QC1: 150.00, QC2: 10000; QC3: 15000, ULQC: 20000 pg/mL.

The validation of new calibration standards was provided in the partial validation report along with the intraday accuracy and precision data of new QCs. However, the inter-day accuracy and precision data of new QCs were not reported. Since the within study inter-day accuracy and precision data for QCs are acceptable, the firm will not be asked to provide such information.

Note: the data for inter-day precision and accuracy of QCs in the above summary table was from original QCs at levels of LLQC: 50.00, QC1: 150.00, QC2: 25000.00, QC3: 37500.00 pg/mL.

2. Plasma containing K<sub>2</sub>EDTA was used for preparation of calibration standards and QC samples. K<sub>2</sub>EDTA was also used as the anticoagulant in the *in vivo* BE studies.

3. The firm provided long-term storage stability (LTSS) data of **133 days** at -20°C and -80°C for diclofenac. The LTSS data provided is sufficient to cover the maximum storage periods (**73 days**) at -20 °C of study samples in the fasting BE studies.

The pre-study validation report is incomplete.

### 3.6 In Vivo Studies

**Table 1. Summary of all in vivo Bioequivalence Studies**

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters (+/-SD)						Study Report Location
					C <sub>max</sub> (pg/mL)	T <sub>max</sub> (hr)	AUC <sub>0-t</sub> (pg*hr/mL)	AUC <sub>∞</sub> (pg*hr/mL)	T <sub>½</sub> (hr)	K <sub>el</sub> (hr <sup>-1</sup> )	
ARL/12/443	A Randomized, Open Label, Balanced, Two-Treatment, Three-Period, Three-Sequence, Single Topical Application, Reference Replicated, Crossover, Bioequivalence Study of Diclofenac Sodium Topical Gel, 1% of Amneal Pharmaceuticals, USA with Voltaren® Gel (diclofenac sodium topical gel) 1 % of Novartis Pharmaceuticals Corporation., USA., in Normal, Healthy, Adult, Human Subjects under Fasting Condition.	A Randomized, Open Label, Balanced, Two-Treatment, Three-Period, Three-Sequence, Single Topical Application, Reference Replicate, Crossover Study design.	Test Product (T) Single topical application [8 g topical gel (4 g on the left knee and 4 g on the right knee)],  Diclofenac Sodium Topical Gel 1% w/w  Topical [Batch No.: PW-ST-13015A]	38 Normal, Healthy, Adult, male and female human Subjects  32.34 ± 06.72	5305.038 ± 3967.900 (74.795)	28.000 (6.000-60.570)	250956.912 ± 151086.969 (60.204)	254928.179 ± 151879.731 (59.577)	32.078 ± 18.077 (56.353)	0.029 ± 0.015 (51.520)	Module 5.3.1.2
			Reference Product (R)  Single topical application [8 g topical gel (4 g on the left knee and 4 g on the right knee)],  Voltaren® Gel (diclofenac sodium topical gel) 1 %  Topical [Lot No.: W2601]	39 Normal, Healthy, Adult, male and female human Subjects 32.31 ± 06.63	5381.351 ± 5396.506 (100.282)	28.000 (5.000-144.000)	252580.651 ± 324832.257 (128.605)	257180.352 ± 324322.260 (126.107)	30.639 ± 17.371 (56.696)	0.028 ± 0.012 (42.896)	

\* Median (Range)

**Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer**

Diclofenac Sodium Topical Gel 1% w/w Fasting Bioequivalence Study (Study No: ARL/12/443) No of subjects=40								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.98	85.90	110.86	0.424754	0.6517315	-0.241797	Scaled/PE	PASS
LAUCI	0.96	82.31	109.83	0.5422809	0.7363973	-0.305624	Scaled/PE	PASS
LCMAX	0.92	78.71	105.69	0.5330421	0.7300973	-0.291434	Scaled/PE	PASS

**Table 3. Reanalysis of Study Samples**

Study No. 130222AIKS								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Unacceptable internal standard response	0	1	0.00	0.03	0	1	0.00	0.03
Loss of sample during processing	1	0	0.03	0.00	1	0	0.03	0.00
Sample concentration above upper limit of quantitation	0	8	0.00	0.21	0	8	0.00	0.21
Sample reanalyzed to obtain confirming value	7	28	0.19	0.75	1	2	0.03	0.05
<b>Total</b>	<b>8</b>	<b>37</b>	<b>0.21</b>	<b>0.99</b>	<b>2</b>	<b>11</b>	<b>0.05</b>	<b>0.30</b>

**Table 4. SOPs Dealing with Bioanalytical Repeats of Study Samples**

SOP No.	Effective Date of SOP	SOP Title
	(b) (4)	Sample Reassays and Reporting of Final Concentrations

Reanalysis SOPs submitted?	Yes
Do you agree that the reassay criteria: <b>analytical and pharmacokinetic</b>	No
If not, list the criteria that you don't agree and provide additional comment below	Pharmacokinetic, see comments below
Are the data in the summary table consistent with the data in the full analytical report?	Yes
If not, provide comment below	N/A

Did reviewer reanalyze study results?	No
Was the study outcome changed based on reviewer reanalysis?	N/A
Did the firm provide a comprehensive table of repeat samples in the format recommended by the DB?	Yes
Did the firm provide numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log)?	Yes, for the 20% chromatograms

**Comments from the Reviewer:**

A total of 45 reanalysis (1.21%) corresponding to 37 reanalyzed study samples were performed out of the 3721 study samples for diclofenac as per the SOP for repeat analysis ( (b) (4) ). Among them, Thirty-five reanalysis corresponding to 28 samples were carried out to “obtain confirming values”, which the reviewer considers as pharmacokinetic repeats. All these reanalysis pertain to pre-dose samples that presented higher concentration than limit of quantitation. The original concentrations of 25 samples were confirmed. Three reanalyzed values that were below limit of quantitation were used by the firm for statistical analysis (see table summarized by the reviewer below). The original pre-dose value of subject (b) (6) in period 3 was more than 5 percent of its respective Cmax. However, subject (b) (6) was excluded from statistical analysis by the firm due to pre-dose concentration higher than 5% of Cmax in period 1. Since using the original pre-dose values for subject (b) (6) is not likely to affect the statistical analysis outcome, the reanalysis using original values were not performed by the reviewer.

The use of reanalyzed plasma concentration data did not change the study outcome.

Subject	Period	Time	Original Concentration (pg/mL)	Reassayed Concentration (pg/mL)	Reported Concentration (pg/mL)	Cmax (pg/mL)	Predose (original conc)/Cmax
(b) (6)	3	T01/0h	133.77	<50.00, <50.00	<50.00	2249.41	5.9%
	3	T01/0h	56.43	<50.00, <50.00	<50.00	2150.05	2.6%
	3	T01/0h	84.92	<50.00, 57.51, <50.00	<50.00	2422.86	3.5%

### 3.7 Formulation

Location in appendix	Section 4.2, Page 35
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biostudy/exhibit batch scored	N/A
Is the formulation acceptable?	<b>FORMULATION ACCEPTABLE</b>
If not acceptable, why?	

### 3.8 In Vitro Dissolution

Not applicable.

### 3.9 Deficiency Comments

None.

### 3.10 Recommendations

The Division of Bioequivalence II (DB II) **accepts** the fasting BE study (ARL/12/443) conducted by the Amneal Pharmaceuticals on its Diclofenac Sodium Topical Gel 1% , lot# PW-ST-13015A, comparing it to Novatis' VOLTAREN® (diclofenac sodium) Topical Gel, 1%, lot # W2601.

### 3.11 Comments for Other OGD Disciplines

Discipline	Comment
All	Clinical end-point study will be reviewed by Division of Clinical Review.

## 4 APPENDIX

### 4.1 Individual Study Reviews

#### 4.1.1 Single-dose Fasting Bioequivalence Study

##### 4.1.1.1 Study Design

**Table 5 Study Information**

<b>Study Number</b>	ARL/12/443			
<b>Study Title</b>	A Randomized, Open Label, Balanced, Two-Treatment, Three-Period, Three-Sequence, Single Topical Application, Reference Replicated, Crossover, Bioequivalence Study of Diclofenac Sodium Topical Gel, 1% of Amneal Pharmaceuticals, USA with Voltaren® Gel (diclofenac sodium topical gel) 1 % of Novartis Pharmaceuticals Corporation., USA., in Normal, Healthy, Adult, Human Subjects under Fasting Condition.			
<b>Study Type</b>	<input checked="" type="checkbox"/> In Vivo BE	<input type="checkbox"/> In Vitro BE	<input type="checkbox"/> Permeability	<input type="checkbox"/> Other
<b>Submission Location:</b>				
<b>Study Report</b>	5.3.1.2			
<b>Validation Report</b>	5.3.1.4			
<b>Bioanalytical Report</b>	5.3.1.4			
<b>Clinical Site (Name, Address, Phone #, Fax #)</b>	Accutest Research Lab (I) Pvt. Ltd. (Unit-II) Opposite The Grand Bhagwati Hotel, Sarkhej-Gandhinagar Highway, Bodakdev, Ahmedabad -380059, INDIA, Tel. No.: +91 79-4023 1600; Fax. No.: +91 79-4002 9317			
<b>Principal Clinical Investigator (Name, Email)</b>	Dr. Rupesh Vala, M.B.B.S. rupesh.vala@accutestindia.com			
<b>Dosing Dates</b>	Period I : 22 July 2013 Period II : 08 August 2013 Period III : 25 August 2013			
<b>Analytical Site (Name, Address, Phone #, Fax #)</b>	(b) (4)			
<b>Analysis Dates</b>	15-SEP-2013 to 03-OCT-2013			
<b>Principal Analytical Investigator (Name, Email)</b>	(b) (4)			
<b>Sample Storage :</b>				
<b>(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)</b>	73 days (22-JUL-2013 to 03-OCT-2013)			

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<b>(b) Temperature Range (e.g., -20° C to -80° C)</b>	-20°C
<b>Long-Term Storage Stability Coverage (no. days @ temp °C)</b>	133 days at -20°C
<b>LTSS Data Location</b>	Module 5.3.1.4 130222-bioanalyt-methval.pdf, <b>page 51</b> and <b>page 52</b>

**Table 6. Product information**

<b>Product</b>	<b>Test</b>		<b>Reference</b>	
<b>Treatment ID</b>	<b>T</b>		<b>R</b>	
<b>Product Name/</b>	Diclofenac Sodium Topical Gel 1% w/w		Voltaren® Gel (diclofenac sodium topical gel) 1 %	
<b>Manufacturer</b>	Manufactured by: Amneal Pharmaceuticals, USA		Manufactured by: Novartis Pharma produktions GmbH Wehr, Germany  Manufactured for: Novartis Consumer Health, Inc Parsippany, NJ 07054  Marketed by: Endo Pharmaceuticals Inc. Chadds Ford, PA 19317	
<b>Batch No./Lot. No.</b>	PW-ST-13015A		W2601	
<b>Manufacture Date</b>	05/24/2013		N/A	
<b>Expiration Date</b>	N/A		02/15	
<b>Strength</b>	1% w/w		1% w/w	
<b>Dosage Form</b>	Gel		Gel	
<b>Bio-batch Size</b>	(b) (4)		N/A	
<b>Production Batch Size</b>	(b) (4)		N/A	
<b>Potency</b>	101.9%		99.8%	
<b>Content Uniformity (mean, %CV)</b>  <i>Uniformity in Containers</i>	Top:	101.3%	Top:	100.4%
	Middle:	100.8%	Middle:	99.8%
	Bottom:	101.4%	Bottom:	99.9%
	Mean:	101.2%	Mean:	100.0%
	%RSD	0.3%	%RSD	0.3%
<b>Dose Administered</b>	Single topical application [8 g topical gel (4 g on the left knee and 4 g on the right knee)]		Single topical application [8 g topical gel (4 g on the left knee and 4 g on the right knee)]	
<b>Route of Administration</b>	Topical		Topical	
<b>pH*</b>	(b) (4)		(b) (4)	
<b>Viscosity*</b>	(b) (4)		(b) (4)	

\*The reviewer included the comparison data of pH and viscosity for test and reference drugs.

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<b>Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?</b>	Yes See comments below
--	---------------------------

**Reviewer’s Comments:**

Per the RLD label<sup>2</sup>, “external heat and/or occlusive dressings should not be applied to treated joints” and “wearing of clothing or gloves should be avoided for at least 10 minutes after applying VOLTAREN® GEL.”

In the firm’s fasting study report, it indicated “the application sites were allowed to dry sufficiently (a minimum of 60 minutes post-application). After the gel has completely dried, subjects were asked to cover the application sites with long-loose fitting clothing” and “heating pads were not used or bandages were not applied”. Therefore, the administration of drug in the fasting study is consistent with the instruction of RLD labeling.

**Table 7. Study Design, Single-Dose Fasting Bioequivalence Study**

<b>Number of Subjects</b>	<b>Enrolled: 60</b> <b>Dosed: 60 in period I, 56 in period II, 52 in period III</b> <b>Completed: 52</b> <b>Samples Analyzed: 53</b> (52 subjects who completed all three periods and one subject (b) (6) who only completed two periods of reference product) <b>Data Analyzed: 38 for test and 39 for reference</b> (subject (b) (6) were excluded from statistical analysis)
<b>No. of Sequences</b>	3
<b>No. of Periods</b>	3
<b>No. of Treatments</b>	2
<b>No. of Groups</b>	1
<b>Washout Period</b>	17 days
<b>Randomization Scheme (Sequence of T and R)</b>	<b>TRR:</b> (b) (6) <b>RTR:</b> (b) (6) <b>RRT:</b> (b) (6)
<b>Blood Sampling Times</b>	Predose, 01.00, 02.00, 03.00, 04.00, 05.00, 06.00, 08.00, 10.00, 12.00, 16.00, 20.00, 24.00, 28.00, 32.00, 36.00, 48.00, 60.00, 72.00, 96.00, 120.00, 144.00, 192.00 and 240.00 hours
<b>Blood Volume Collected/Sample</b>	6 mL
<b>Anticoagulant Used</b>	K2EDTA

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<b>Blood Sample Processing &amp; Storage (include storage temperature)</b>	Centrifugations of the samples were done within 01.00 hour of sample collection. All the blood samples were centrifuged under refrigeration with the machine set at 3000 RPM, 10 minutes and $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ . the plasma was transferred to appropriate size polypropylene screw top (previously labeled with study code and sample code) biological sample storage tubes in duplicate (one aliquot as control samples and one aliquot for analysis, the aliquot for analysis should contain at least 1.0 mL of plasma) and plasma samples were placed in a deep freezer maintained at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ within 180 minutes from the start of centrifugation.
<b>IRB Approval (Y/N, Date)</b>	Yes, 12 July 2013
<b>Informed Consent (Y/N, Date)</b>	Yes, 01/07/13
<b>Length of Fasting</b>	at least 10.00 hours
<b>Length of Confinement</b>	at least 16.00 hours prior to dosing until 48.00 hours post application
<b>Safety Monitoring</b>	<p>Blood pressure and pulse rate measurement were done at pre-treatment application and at 02.00, 04.00, 10.00, 16.00 and 24.00 hours post-treatment application <math>\pm 45</math> minutes (except for pre-treatment application) of scheduled time in each study period.</p> <p>Physical examination and vital examination (Blood pressure, pulse rate, oral temperature and respiratory rate) were done at the time of check-in and check-out of each study period.</p> <p>Skin irritation measurement was done at 00.50, 04.00, 12.00 and 24.00 hours post treatment application <math>\pm 45</math> minutes of scheduled time in each study period.</p> <p>Wellbeing assessment was done at pre-treatment application and at 02.00, 04.00, 10.00, 16.00, 24.00, 48.00, 60.00, 72.00, 96.00, 120.00, 144.00, 192.00 and 240.00 hours posttreatment application in each study period.</p> <p>Physical examination including vital examination, well-being assessment, haemogram, biochemistry and urinalysis were done at the end of study or on discontinuation of subjects from the study.</p>

**Comments on Study Design:**

The Study Design is acceptable.

**4.1.1.2 Clinical Results**

**Table 8A. Demographics Profile of Subjects Completing the Bioequivalence Study**

Study No. ARL/12/443			
		Treatment Groups	
		Test Product T N=37	Reference Product R N =37
Age (years)	Mean ± SD	32.35 ± 06.81	32.35 ± 06.81
	Range	18 - 42	18 - 42
Age Groups	< 18	Nil	Nil
	18 – 40	32 (86.48 %)	32 (86.48 %)
	41 – 64	05 (13.51 %)	05 (13.51 %)
	65 – 75	Nil	Nil
	> 75	Nil	Nil
Sex	Male	30 (81.08 %)	30 (81.08 %)
	Female	07 (18.92 %)	07 (18.92 %)
Race		37 (100.00%)	37 (100.00%)
	Asian	Nil	Nil
	Black	Nil	Nil
	Caucasian	Nil	Nil
	Hispanic Other	Nil	Nil
BMI (Kg/m <sup>2</sup> )	Mean ± SD	22.28 ± 01.86	22.28 ± 01.86
	Range	18.96 - 24.86	18.96 - 24.86
Other Factors		-	-

**Table 9. Dropout Information, Fasting Bioequivalence Study**

Study No. ARL/12/443				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b) (6)	Subject was dropped out from the study at 07:11 on 25 August 2013 due to personal reason. Treatment given was Reference Product R in Period-II.	III	NA	NA
	Subject was withdrawn from the study at 18:00 on 07 August 2013 due to protocol non-compliance. Treatment given was Test Product T in Period-I.	II	NA	NA
	Subject was dropped out from the study at 21:00 on 24 August 2013 due to Personal reason. Treatment given was Reference Product R in Period-II.	III	NA	NA
	Subject was dropped out from the study at 20:59 on 07 August 2013 due to Personal reason. Treatment given was Reference Product R in Period-I.	II	NA	NA
	Subject was dropped out from the study at 21:10 on 24 August 2013 due to Personal reason. Treatment given was Test Product T in Period-II.	III	NA	NA
	Subject was dropped out from the study at 21:25 on 07 August 2013 due to Personal reason. Treatment given was Reference Product R in Period-I.	II	NA	NA
	Subject was dropped out from the study at 22:00 on 07 August 2013 due to Personal reason. Treatment given was Reference Product R in Period-I.	II	NA	NA
	Subject was dropped out from the study at 21:29 on 24 August 2013 due to Personal reason. Treatment given was Reference Product R in Period-II.	III	NA	NA

**Table 10. Study Adverse Events, Fasting Bioequivalence Study**

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study No. ARL/12/443	
	Test N=56	Reference N=112
Total	00 (00.00 %)	00 (00.00 %)

**Note from firm:** *The reported clinically significant abnormal laboratory value was considered as adverse event. Two clinically significant abnormal laboratory values were found in post study assessment. As the subjects had received both the treatments, it was difficult to attribute these adverse events to either of the treatments Test product or Reference product.*

**Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.**

Yes, the adverse event profile is comparable for the test and reference product.

**Are there any safety concerns based on the adverse event profile?**

No.

**Table 11. Protocol Deviations, Fasting Bioequivalence Study**

Study No. ARL/12/443		
Type	Subject #s (Test)	Subject #s (Ref.)
Pre-dose Housing Deviation	(b) (6)	
Treatment Application Deviation		
Dose Application Deviation		
Blood Sample Time Point Deviation		
Pre-dose Sample Collection Deviation		
Missing Sample Deviation		
Sample Processing Deviation		

Subject Withdrawal/Dropout Deviation	(b) (6)
Post study Safety Evaluation Deviation	(b) (6)

**Did dropouts/adverse events/protocol deviations affect the study outcome?**

No.

**Comments on Dropouts/Adverse Events/Protocol Deviations:**

**Dropouts:**

1. Sixty healthy, adult human subjects were dosed in the study. Fifty two subjects completed all three periods of the study as per protocol. One subject (b) (6) was withdrawn from study prior to period II dosing due to protocol non-compliance. Three subjects (b) (6) were dropped out from study due to person reason prior to period II dosing. Four subjects (b) (6) were dropped out from study due to personal reason prior to period III dosing.

**Adverse Events:**

1. Two adverse events (AEs) were reported during post study laboratory assessment due to clinically significant abnormal laboratory values. Subject (b) (6) (Low Hemoglobin - 8.4 g/dL) and (b) (6) (Low Hemoglobin - 8.6 g/dL), had clinically significant abnormal laboratory value. However, the AEs were considered to be not related to the study medication and were mild to moderate in severity

2. No serious or significant adverse events were observed during the study.

**Protocol Deviations:**

1. Dose application deviation was due to dispensing gel from one tube to eight subjects in the fasting study instead of following “each tube will only be given to one volunteer” as per the protocol. This was judged to have no significant impact on final study outcome.

2. The deviation in sampling time points was considered during pharmacokinetic and statistical analyses and actual time points were taken for pharmacokinetic parameter calculations.

3. Missing blood samples due to subject not reporting for ambulatory sample visit was represented as “MSV” or “MS” in the plasma concentration tables and considered during pharmacokinetic and statistical analysis.

4. The other protocol deviations listed by the firm did not affect the outcome of the study results.

**4.1.1.3 Bioanalytical Results**

**Table 12. Sample Analysis Calibration and Quality Control – Within the Fasting Bioequivalence Study**

Bioequivalence Study No. 130222AIKS Diclofenac								
Parameter	Standard Curve Samples							
Concentration (pg/mL)	50.00	100.00	400.00	2000.00	4000.00	8000.00	16000.00	20000.00
Interday Precision (%CV)	6.47	5.86	3.16	1.95	2.24	1.98	1.96	2.05
Interday Accuracy (% Bias)	1.64	-3.04	-0.31	-0.27	1.51	0.86	0.59	-0.77
Linearity	0.9945 to 0.9993							
Linearity Range (pg./mL)	50.00 to 20000.00							
Sensitivity/LOQ (pg/mL)	50.00							

Bioequivalence Study No. 130222AIKS Diclofenac				
Parameter	Quality Control Samples			
Concentration (pg/mL)	150.00	10000.00	15000.00	1000.00
Interday Precision (%CV)	5.41	2.57	2.21	2.63
Interday Accuracy (%)	95.71	98.09	97.71	96.20

<b>Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?</b>	Yes
<b>Do you agree with the firm's accepted and rejected runs?</b>	Yes

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Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes, 12 subjects ( (b) (6) (b) (6)
Were chromatograms serially or randomly selected?	Serially selected
Were the chromatograms submitted by the firm acceptable?	Yes

**Table 13. SOPs Dealing with Bioanalytical Repeats of Study Samples**

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Sample Reassays and Reporting of Final Concentrations

**Table 14. Additional Comments on Repeat Assays**

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	Yes, see comments in section 3.6
If no, reason for disagreement	

**Were Calibration and Quality Control for the Sample Analysis acceptable?**

Yes

**Summary/Conclusions, Study Assays:**

The study assay is **adequate**.

#### 4.1.1.4 Pharmacokinetic Results

**Table 15. Arithmetic Mean Pharmacokinetic Parameters<sup>4</sup>**

Mean plasma concentrations are presented in Table and Figure 1

Fasting Bioequivalence Study (Study No: ARL/12/443) (N=38 for Test, N=39 for reference)										
Parameter	Unit	Test 1		Reference 1		Reference 2		Ratio (T/R1)	Ratio (T/R2)	Ratio (R1/R2)
		Mean	CV %	Mean	CV%	Mean	CV %			
AUCT	pg hr/mL	250956.9	60.20	293897.0	150.50	211264.3	57.30	0.85	1.19	1.39
AUCI	pg hr/mL	254928.2	59.58	297564.6	148.55	216796.1	55.34	0.86	1.18	1.37
C <sub>MAX</sub>	pg/mL	5305.038	74.79	6037.467	113.99	4725.235	69.44	0.88	1.12	1.28
T <sub>MAX</sub>	hr	28.000	.	28.000	.	28.000	.	1.00	1.00	1.00
KE	hr <sup>-1</sup>	0.029	51.47	0.029	44.25	0.027	41.11	0.98	1.05	1.07
THALF	hr	32.079	56.35	30.255	56.89	31.024	57.20	1.06	1.03	0.98

Fasting Bioequivalence Study (Study No: ARL/12/443)			
Parameter (units)	Test	Reference (Avg R1 and R2)	T/R
	Mean	Mean	
AUCT (pg hr/mL)	250956.9	252580.7	0.9935
AUCI (pg hr/mL)	254928.2	257180.4	0.9912
C <sub>max</sub> (pg/ml)	5305.038	5381.351	0.9858
T <sub>max</sub> (hr)	28.000	28	1
KE (hr <sup>-1</sup> )	0.029	0.028	1.0357
THALF (hr)	32.079	30.6395	1.0470

\* T<sub>max</sub> values are presented as median, range

<sup>4</sup> Since the current 3-way Highly Variable Drug SAS program does not provide summary of arithmetic mean data, the reviewer used the regular 3-way crossover SAS program (Macro: CONTINU.SAS) to obtain the results

**Table 16. Geometric Means and 90% Confidence Intervals - Firm Calculated**  
**Including outlier subject** (b) (6)

**Table 06(C): Criteria for selection of bioequivalence approach:**

Parameters	#S <sub>WR</sub> for the Reference Product	Bioequivalence Approach used
AUC <sub>0-inf</sub>	0.384	Scaled average bioequivalence
AUC <sub>0-t</sub>	0.394	Scaled average bioequivalence
C <sub>max</sub>	0.405	Scaled average bioequivalence

# If S<sub>WR</sub> ≥ 0.294 then Bioequivalence Approach = Scaled average bioequivalence

# If S<sub>WR</sub> < 0.294 then Bioequivalence Approach = Average bioequivalence

Statistical analysis for the test product to reference product for ln-transformed parameters based on Scaled average bioequivalence approach are summarized below: (N=38)

Parameters	Criteria 1: 95% Upper Confidence Bound for ln-transformed data *	Criteria 2:		Conclusion as per acceptance of Criteria 1 & 2
		T/R Ratio	Acceptance Limits on T/R Ratio	
AUC <sub>0-inf</sub>	-0.0740	1.0712	0.80 -1.25	Bioequivalent
AUC <sub>0-t</sub>	-0.0786	1.0784	0.80 -1.25	Bioequivalent
C <sub>max</sub>	-0.0923	1.0344	0.80 -1.25	Bioequivalent

\*The 95% Upper confidence bound should be less than or equal to zero to meet the acceptance as per the Individual Bioequivalence Criterion

**Excluding outlier subject** (b) (6)

Diclofenac Sodium Topical Gel 1% w/w, (No of subjects completed= 37) Dose (Single topical application [8 g topical gel (4 g on the left knee and 4 g on the right knee)]) Fasting Bioequivalence Study (Study Code: ARL/12/443), Scaled								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	S <sub>2wr</sub>	s <sub>WR</sub>	Criteria Bound	Method Used	Outcome
LAUC <sub>0-t</sub>	1.0947	101.6868	119.8427	0.125	0.354	-0.0558	Scaled average bioequivalence (SABE)	Bioequivalent
LAUC <sub>0-inf</sub>	1.0870	101.1022	118.8125	0.118	0.344	-0.0520		
LC <sub>MAX</sub>	1.0509	96.0854-	115.1863	0.145	0.381	-0.0781		

**Table 17. Geometric Means and 90% Confidence Intervals - Reviewer Calculated**

**a. Including outlier subject** (b) (6)

Diclofenac Sodium Topical Gel 1% w/w Fasting Bioequivalence Study (Study No: ARL/12/443) No of subjects=38								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	1.08	99.80	117.56	0.1568591	0.3960544	-0.078614	Scaled/PE	PASS
LAUCI	1.07	99.27	116.54	0.1462328	0.382404	-0.074054	Scaled/PE	PASS
LCMAX	1.03	94.32	113.20	0.1685025	0.4104906	-0.092398	Scaled/PE	PASS

**b. Including outlier subject** (b) (6) **& Including subject** (b) (6)

Diclofenac Sodium Topical Gel 1% w/w Fasting Bioequivalence Study (Study No: ARL/12/443) No of subjects=40								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.98	85.90	110.86	0.424754	0.6517315	-0.241797	Scaled/PE	PASS
LAUCI	0.96	82.31	109.83	0.5422809	0.7363973	-0.305624	Scaled/PE	PASS
LCMAX	0.92	78.71	105.69	0.5330421	0.7300973	-0.291434	Scaled/PE	PASS

### Reviewer's Comments on Statistical Analysis:

1. A total of 52 subjects completed all three periods of fasting study and one subject (subject (b) (6)) completed only two period of reference product of the study. The firm considered the data of 39 subjects for pharmacokinetic analysis after excluding 14 subjects. Subject (b) (6) was considered for the calculation of within subject variability of reference product and the data of 38 subjects was considered for establishing bioequivalence.

2. The firm performed outlier analysis per protocol and identified subject (b) (6) as an outlier. Per the firm's statement "*abnormal high concentration observed in post dose 144.00 in period -III of subject (b) (6) may be due to noncompliance of subject with the study requirements because he had not informed to medical officer during ambulatory visit that he had taken tablet for common cold*". The statistical analysis was performed both including and excluding the outlier subject. The reviewer conducted statistical analysis including the outlier (subject (b) (6)) the results were in agreement with the firm's calculation.

The within-subject standard deviation  $s_{WR}$  of the reference product for  $AUC_{0-t}$ ,  $AUC_{inf}$ , and  $C_{max}$  in the fasting study were larger than 0.294. Therefore, reference-scaled average BE approach was applied to these parameters. The 95% upper confidence bounds for  $(\bar{Y}_T - \bar{Y}_R)^2 - \theta s_{WR}^2$  for  $AUC_{0-t}$ ,  $AUC_{inf}$ , and  $C_{max}$  are negative, and the point estimates (test/reference geometric mean ratio) for  $AUC_{0-t}$ ,  $AUC_{inf}$ , and  $C_{max}$  falls within [0.80, 1.25].

3. There are 22 subjects having measurable drug concentration at pre-dose. Twelve subjects (subject (b) (6)) had pre-dose concentration greater than 5% of its respective  $C_{max}$  and therefore were excluded from statistical analysis by the firm. The reviewer concurs with the firm's decision of excluding these subjects (see the summarized table below) from statistical analysis. However, two additional subjects (subject (b) (6)) were also excluded due to "abnormal plasma concentration" as the firm claimed. Investigations were done to identify the underlying reasons. According to the firm's report, for subject (b) (6), "*abnormal high concentration observed in post dose 240.00 in period -III of subject (b) (6) may be due to noncompliance of subject with the study requirements because he had not given proper history to medical officer during medical examination that he had taken tablet for headache*". For subject (b) (6), "*abnormal high concentration observed in post dose 72.00 in period -III of subject no. 60 may be due to noncompliance of subject with the study requirements because he had not given proper history to medical officer during medical examination that he had taken tablet for bodyache*".

The reviewer conducted the statistical analysis including subject (b) (6) (see results in Table 17b), and the study outcome did not change.

4. The median  $T_{max}$  between test product (28.000 hours (6.000- 60.570)) and reference product (28.000 hours (5.000- 144.000)) is comparable.

The fasting BE study is **acceptable**.

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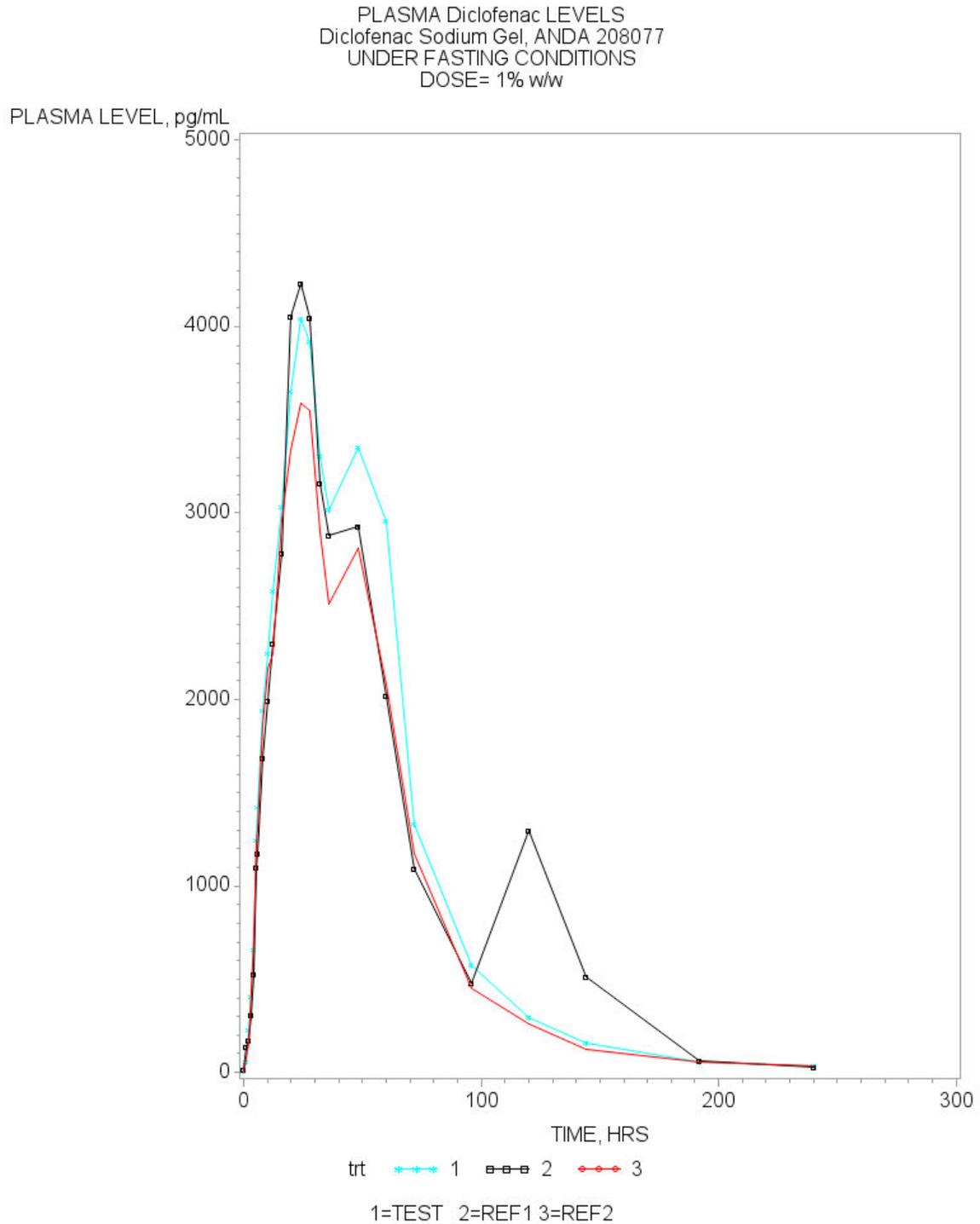
ANDA 208077  
Single-Dose Fasting Bioequivalence Study Review

<b>Measurable drug concentrations at 0 hr</b>				
Subject #, Period, Treatment	drug concentration at 0 hr (pg/mL)	Cmax (pg/mL)	Drug concentration at 0 hr/Cmax (%)	Included or Excluded from Statistical Analysis
(b) (6) Period III, Test	56.21	8083.7	0.65%	Included
(b) (6) Period III, Reference	458.53	3448.61	13.30%	Excluded
(b) (6) Period III, Reference	519.87	2035.13	25.54%	Excluded
(b) (6) Period III, Reference	57.1	5454.85	1.05%	Included
(b) (6) Period II, Reference	62.8	53786.05	0.12%	Included
(b) (6) Period III, Reference	1229.85	5428.71	22.65%	Excluded
(b) (6) Period III, Reference	3480.24	7544.16	46.13%	Excluded
(b) (6) Period III, Test	100.62	5138.22	1.96%	Included
(b) (6) Period I, Reference	106.43	1663.39	6.40%	Excluded
(b) (6) Period II, Reference	632.46	2169.35	29.15%	Excluded
(b) (6) Period III, Reference	726.93	3387.74	21.46%	Excluded
(b) (6) Period III, Reference	620.92	4204.91	14.77%	Excluded
(b) (6) Period III, Test	84.82	1805.54	4.70%	Included
(b) (6) Period III, Test	846.38	4506.9	18.78%	Excluded
(b) (6) Period II, Reference	62.17	4801.45	1.29%	Included
(b) (6) Period II, Reference	660.9	7476.39	8.84%	Excluded
(b) (6) Period II, Reference	206.15	3195.69	6.45%	Excluded
(b) (6) Period III, Test	86.74	13907.22	0.62%	Included
Period II, Reference	53.36	1703.55	3.13%	Included
(b) (6) Period III, Reference	259.62	2974.42	8.73%	Excluded
(b) (6) Period III, Reference	77.32	3277.44	2.36%	Included
(b) (6) Period III, Reference	92.23	5996.21	1.54%	Included
(b) (6) Period III, Reference	402.98	6438.44	6.26%	Excluded
(b) (6) Period III, Reference	96.79	4378.9	2.21%	Included
(b) (6) Period III, Reference	124.98	3207.43	3.90%	Included

**Table 19. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study**

Time (hr)	Test (n=38)		Reference 1 (n=39)		Reference 2 (n=39)		RatioTR 1	RatioTR 2	RatioR1 R2
	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R1)	(T/R2)	(R1/R2)
0.00	8.55	303.11	11.63	272.19	1.46	624.50	0.74	5.84	7.94
1.00	53.86	138.63	140.34	276.39	73.36	357.64	0.38	0.73	1.91
2.00	227.16	124.26	172.01	144.07	155.41	148.78	1.32	1.46	1.11
3.00	404.51	119.03	306.33	125.84	436.18	153.71	1.32	0.93	0.70
4.00	654.67	80.83	528.00	118.05	724.74	110.04	1.24	0.90	0.73
5.00	1241.61	79.81	1096.31	103.23	1235.68	91.29	1.13	1.00	0.89
6.00	1419.22	81.55	1174.62	97.84	1303.95	90.31	1.21	1.09	0.90
8.00	1940.91	96.76	1684.23	97.28	1863.52	92.69	1.15	1.04	0.90
10.00	2242.50	75.93	1995.16	93.36	2162.58	81.43	1.12	1.04	0.92
12.00	2583.00	73.05	2302.73	90.45	2248.14	78.33	1.12	1.15	1.02
16.00	3033.37	80.45	2787.33	68.36	2961.15	85.62	1.09	1.02	0.94
20.00	3651.58	81.67	4052.61	102.36	3339.26	92.33	0.90	1.09	1.21
24.00	4042.40	83.16	4234.65	95.67	3589.58	77.37	0.95	1.13	1.18
28.00	3918.93	67.74	4049.57	88.00	3549.46	79.78	0.97	1.10	1.14
32.00	3306.08	64.04	3157.91	68.85	2898.46	65.48	1.05	1.14	1.09
36.00	3018.02	60.72	2877.09	69.41	2513.41	62.44	1.05	1.20	1.14
48.00	3351.49	69.18	2927.01	61.58	2814.72	70.27	1.15	1.19	1.04
60.00	2955.65	94.36	2022.74	48.37	2081.72	58.29	1.46	1.42	0.97
72.00	1334.85	62.33	1095.61	57.29	1171.86	53.63	1.22	1.14	0.93
96.00	574.53	76.24	475.92	117.30	450.14	59.41	1.21	1.28	1.06
120.00	295.18	77.97	1296.51	495.55	261.41	105.01	0.23	1.13	4.96
144.00	160.85	93.86	512.19	443.73	124.32	81.49	0.31	1.29	4.12
192.00	58.31	127.96	59.91	120.88	58.52	108.43	0.97	1.00	1.02
240.00	36.83	122.83	28.08	171.93	31.62	244.49	1.31	1.16	0.89

**Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study**



**Reviewer's Note:**

The “peak” observed in the elimination phase of plasma concentration profile of ref1 was resulted from the presence of an abnormally high concentration (39284.85 pg/mL) at the time point of 120hr (from subject (b) (6) period 2, which is also the Cmax for this subject at period 2)

## 4.2 Formulation Data

Ingredients	Quantity in %w/w	Quantity mg/g	Quantity mg/day <sup>1</sup>			
Diclofenac Sodium EP/USP	1.00	10.00	320.00			
Isopropyl Alcohol USP	(b) (4)	(b) (4)	(b) (4)			
Carbomer Homopolymer Type C USP/NF (b) (4)						
Strong Ammonia Solution NF (b) (4)						
Cocoyl Caprylocaprate (b) (4)						
Mineral Oil USP (b) (4)						
(b) (4) Fragrance						
Polyoxyl 20 Cetostearyl Ether NF (b) (4)						
Propylene Glycol USP (b) (4)						
Purified Water USP						
<b>Total Weight</b>				<b>100%</b>	<b>1 g</b>	<b>32 g</b>
<sup>1</sup> Calculated based on the maximum daily dose of 32g of gel. OS : Quantity Sufficient (b) (4)						

**Comparison of Test vs. Reference Formulation**

Ingredients	Amneal's Diclofenac Sodium Topical Gel (Test) %w/w	Novatis's VOLTAREN® Gel (Reference) <sup>5</sup> % w/w
Diclofenac Sodium EP/USP	1.00	1.00
Isopropyl Alcohol USP	(b) (4)	
Carbomer Homopolymer Type C USP/NF (b) (4)		
Strong Ammonia Solution NF		
Cocoyl Caprylocaprate Ph.Eur (b) (4)		
Mineral Oil USP (b) (4)		
Polyoxyl 20 Cetostearyl Ether/PH (b) (4)		
Propylene Glycol USP		
(b) (4) Fragrance		
(b) (4)		

<sup>5</sup> NDA 022122 DAARTS REV-QUALITY-03(General Review); Final Date: 02/02/2007

**Reviewer's Comments on Drug Formulation:**

1. As indicated from the table above, the amounts of all inactive ingredients except (b)(4) are (b)(4) than that of present in RLD formulation.

2. The test formulation contains ingredient “(b)(4) Fragrance” at (b)(4), which is not present in the RLD formulation. This excipient is not listed in the IIG database. The firm did not provide the composition of this excipient either. In the firm's submission, the firm provided a letter from the fragrance manufacturer, (b)(4) confirming that all the individual components present in the (b)(4) Fragrance composition are meeting the criteria of within (b)(4) of the total drug product weight.

3. All the inactive ingredients are within the limits of the IIG.

The test formulation is **acceptable**.

### 4.3 Detailed Regulatory History (If Applicable)

#### ANDAs from DARRTS:

Application Type/Number	Submitter	Current Status	Status Date
ANDA-208077	AMNEAL PHARMACEUTICALS	Pending	12/19/2014

(b) (4)

#### Controls:

<a href="#">08-0338</a>	Diclofenac Gel			
<a href="#">08-0569</a>	Acceptable Inactive Ingredients in Diclofenac Topical Gel			
<a href="#">08-0687</a>	Diclofenac topical gel			
<a href="#">08-1031</a>	Diclofenac gel			
<a href="#">09-0065</a>	Diclofenac topical gel			
<a href="#">09-0255</a>	Diclofenac sodium topical gel			
<a href="#">09-0324</a>	Formulation diclofenac gel			
<a href="#">09-0389</a>	Diclofenac topical gel formulation			
<a href="#">09-0464</a>	Diclofenac topical gel			
<a href="#">09-0644</a>	Diclofenac topical gel formulation			
<a href="#">10-0469</a>	Diclofenac sodium topical gel			
<a href="#">11-0157</a>	Diclofenac	Request for bioequivalence	Closed	Amneal

(b) (4)

	topical gel	guidance.	3/3/2011	
<a href="#">11-0393</a>	Diclofenac topical gel formulation	(b) (4)		
<a href="#">11-0632</a>	Use of inactive in Diclofenac gel			
<a href="#">11-0665</a>	Excipients in Diclofenac topical gel			
<a href="#">11-0709</a>	Inactive in Diclofenac topical gel			
<a href="#">12-0177</a>	Diclofenac topical gel			
<a href="#">12-0952</a>	Diclofenac Sodium Topical Gel 1%			
<a href="#">12-1110</a>	Diclofenac Sodium Topical Gel 1%			
<a href="#">13-0599</a>	Diclofenac Sodium Topical Gel, 1%			
<a href="#">13-0668</a>	Question for Diclofenac Sodium Topical Gel, 1%			

**Protocols:**

<a href="#">09-005</a>	Diclofenac Sodium	Topical Gel, 1%	(b) (4)	Clinical endpoint study.
<a href="#">09-009</a>	Diclofenac Sodium	Topical Gel, 1%		Clinical endpoint study. (originally assigned as control #09-0065)
<a href="#">130021</a>	Diclofenac Sodium 1%	Gel		Clinical endpoint study in patients with osteoarthritis of the knee

#### **4.4 Consult Reviews**

None.

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## 4.5 SAS Output

### 4.5.1 Fasting Study Data

FASTING CONCENTRATION DATASET

Obs	sub	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
1	(b) (6)	2	1	R2	0.00	0.00	0.00	0.00	55.54	110.39	152.25	494.69	828.69	1607.22	1998.79	4676.24	5026.87	4450.56
2		2	2	T	0.00	56.01		117.21	163.16	243.42	462.82	791.37	1149.32	2229.73	3775.17	6035.65	5867.47	6535.72
3		2	3	R1	0.00	74.47		121.61	147.70	262.53	332.14	713.61	997.31	1653.52	2585.16	5035.09	4318.00	5360.34
4		3	1	R1	0.00	0.00	0.00	0.00	0.00	1948.13	1171.48	1186.48	2036.00	2510.24	5446.51	4892.72	4647.28	3993.55
5		3	2	R2	0.00	57.90	128.71	162.59	334.86	2028.13	1975.38	1789.15	1861.94	2104.27	8221.10	5385.24	6598.59	6026.47
6		3	3	T	52.61	260.27	163.44	246.84	910.09	808.36	854.71	3137.50	4508.23	4034.47	4925.51	5584.37	7701.56	8083.70
7		3	1	R1	0.00	0.00	50.76	221.20	591.89	2116.03	2125.62	2943.24	3022.86	3462.83	3845.44	3618.44	3725.47	2985.85
8		3	2	R2	0.00	0.00	0.00	393.50	778.71	1756.11	1514.30	2376.08	2407.01	1662.57	1310.09	1884.20	1577.00	1626.80
9		3	3	T	0.00	0.00	434.71	193.61	387.51	1692.26	1423.09	1857.77	2298.78	2295.78	1961.13	3184.51	2528.14	3275.12
10		1	1	T	0.00	79.22	753.50	1250.12	1369.10	2146.51	2562.89	3703.73	4430.28	4109.80	4625.61	4987.88	5511.59	4567.04
11		1	2	R1	0.00	0.00	429.02	206.94	348.17	1382.83	1694.45	2686.14	3184.54	3209.46	2751.87	3050.88	3599.00	3802.27
12		1	3	R2	57.10	136.79	240.25	429.13	654.43	831.54	1092.93	2768.04	5454.85	3062.46	2737.71	2966.11	3514.60	3971.22
13		2	1	R1	0.00	0.00	61.60	160.05	196.83	273.12	350.72	568.53	1148.08	1428.20	4824.25	6863.03	7127.06	5309.84
14		2	2	T	0.00	0.00	68.77	103.35	179.88	267.96	702.25	723.48	860.90	2392.36	2976.98	3075.76	3872.18	3445.15
15		2	3	R2	0.00	305.88	214.47	330.09	459.22	385.52	488.32	766.03	716.55	956.36	4655.89	7208.63	9009.50	14380.61
16		3	1	R1	0.00	0.00	0.00	61.75	73.07	147.93	265.93	780.06	839.92	1599.81	3296.33	4399.05	3422.75	2687.33
17		3	2	R2	0.00	56.88	167.45	174.71	96.42	110.51	268.51	519.27	548.25	731.20	1017.59	1445.38	1625.93	1590.32
18		3	3	T	0.00	166.14	176.68	130.00	248.98	358.82	454.00	883.06	999.60	1045.90	1798.05	2230.01	2198.11	2559.68
19		3	1	R1	0.00	0.00	81.33	96.50	163.39	286.89	449.91	975.00	1382.26	2339.90	3219.77	2980.65	4187.35	3434.75
20		3	2	R2	0.00	0.00	320.74	1652.35	2939.24	3385.65	3840.00	3848.53	3680.27	4528.00	4669.16	5584.63	5500.71	5200.35
21		3	3	T	0.00	50.99	173.81	403.46	1315.25	2756.18	2327.86	3143.39	3751.24	3897.47	4504.59	4381.58	4521.37	4723.31
22		2	1	R1	0.00	0.00	0.00	0.00	289.39	903.67	1130.27	1649.28	3373.44	2359.30	1853.09	1349.85	1274.22	1368.37

Obs	sub	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
23	(b) (6)	2	2	T	0.00	0.00	73.19	90.36	174.21	2584.91	3780.53	1721.28	1647.86	1719.50	1671.18	1328.08	1427.67	1573.38
24		2	3	R2	0.00	93.96	128.03	204.04	260.75	1775.47	3227.93	1527.26	1340.79	1517.19	1497.74	1535.06	1169.34	1284.55
25		3	1	R1	0.00	0.00	288.38	1043.55	1868.11	5427.98	4972.43	7500.32	8904.17	7519.54	5851.72	10787.01	11642.19	11120.63
26		3	2	R2	0.00	0.00	228.11	1052.73	2157.12	3658.07	3896.60	4092.35	4267.34	4106.70	4127.99	5762.59	6473.10	8062.87
27		3	3	T	0.00	54.85	297.30	986.86	1794.68	2577.42	2990.14	3681.61	4068.12	4470.84	4431.50	5413.78	6432.93	9238.47
28		3	1	R1	0.00	0.00	84.77	288.73	478.48	695.31	739.34	952.56	1253.73	1859.62	2279.87	4468.61	3484.42	2637.56
29		3	2	R2	0.00	0.00	0.00	60.19	162.31	113.18	133.20	186.99	368.29	895.74	3297.28	2816.44	7566.24	4803.07
30		3	3	T	100.62	115.13		153.90	257.97	679.03	626.93	1297.16	1087.15	1897.20	1876.21	5136.34	4332.34	3106.88
31		1	1	T	0.00	0.00	185.20	61.28	177.96	315.93	289.19	392.53	609.23	489.20	651.31	988.27	873.31	788.71
32		1	2	R1	0.00	0.00	0.00	0.00	0.00	389.22	151.45	281.81	297.58	768.99	296.40	296.57	320.28	263.77
33		1	3	R2	0.00	0.00	78.10		334.23	155.78	165.93	219.37	259.76	290.28	405.61	474.87	601.97	605.56
34		3	1	R1	0.00	0.00	0.00	135.52	106.12	474.96	350.67	1225.79	1378.64	1400.05	958.06	834.42	1439.71	1840.75
35		3	2	R2	0.00	0.00	0.00	748.40	1087.47	750.18	565.69	1425.40	1249.11	1193.40	1005.40	1546.12	1438.36	2374.77
36		3	3	T	84.82	53.32	92.25	231.98	466.79	739.21	601.88	1004.82	776.08	836.46	775.85	1363.99	1805.54	1655.10
37		1	1	T	0.00	0.00	0.00	68.14	245.65	928.04	845.53	1204.38	2357.88	2389.97	2903.02	4402.31	4699.17	4007.21
38		1	2	R1	62.17	55.41		114.56	178.58	349.14	241.11	482.25	836.68	1532.17	1985.63	2726.62	3194.15	4793.90
39		1	3	R2	0.00	0.00	53.77	66.13	153.72	394.79	512.06	845.05	969.42	1538.34	1901.60	2581.33	4066.44	4898.25
40		3	1	R1	0.00	0.00	0.00	0.00	0.00	128.39	114.09	88.75	159.98	200.78	388.42	453.81	770.84	824.85
41		3	2	R2	0.00	0.00	0.00	0.00	0.00	78.11	84.07	178.45	305.68	415.36	388.01	600.94	699.95	820.85
42		3	3	T	0.00	0.00	0.00	139.83	262.00	335.54	1351.02	400.32	270.22	407.49	586.65	785.67	890.34	1173.94
43		3	1	R1	0.00	2384.08	338.44	732.75	1391.18	2983.49	3832.41	6346.08	7651.01	12078.96	9621.70	13704.55	19830.41	14442.28
44	3	2	R2	0.00	73.45	193.34	385.07	828.09	936.28	1554.22	2372.03	4076.85	4152.24	6680.65	6314.56	7113.08	9830.13	
45	3	3	T	86.74	254.78	461.16	1019.84	1851.13	2601.95	4056.02	10121.38	7203.09	7477.65	12068.78	11167.23	13907.22	11030.86	
46	2	1	R1	0.00	0.00	0.00	136.65	579.14	2147.76	2389.83	2523.00	2960.11	3274.74	2878.70	3079.91	2767.83	2813.39	
47	2	2	T	0.00	0.00	56.01	88.21	178.63	292.68	603.31	852.26	1251.39	1606.66	1642.14	1761.27	2156.67	2091.27	
48	2	3	R2	77.32		193.10	164.42	1970.17	821.68	790.77	1484.09	1836.36	2832.87	2740.61	2674.67	3277.44	3085.76	
49	1	1	T	0.00	0.00	379.48	727.86	1659.10	4440.75	5065.60	6664.99	6604.63	8949.83	10143.38	16367.07	17495.00	9359.25	
50	1	2	R1	0.00	149.93	1172.80	1767.04	2484.51	3063.33	3362.90	4380.48	5964.27	4635.92	6522.53	19636.83	14483.96	9158.72	
51	1	3	R2	0.00	218.46	1113.42	2460.22	3196.29	3553.95	4034.90	7718.25	6481.22	7820.05	4804.10	13460.72	11377.47	8319.91	

Obs	sub	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
52	(b) (6)	3	1	R1	0.00	192.80	163.54	469.90	515.00	976.56	709.10	1452.26	1823.98	2201.66	2264.67	2365.88	2444.48	2577.86
53		3	2	R2	0.00	0.00	62.85	175.39	241.21	723.50	617.97	1071.20	997.34	1078.84	1025.35	999.90	1219.01	1377.12
54		3	3	T	0.00	0.00	0.00	128.02	821.53	1123.00	797.78	822.25	1148.95	1359.79	1434.79	2002.66	2527.66	2658.80
55		2	1	R1	0.00	0.00	124.23	694.57	1205.86	3080.07	2100.44	2476.47	2949.80	2938.18	2465.39	2135.60	1897.58	2033.27
56		2	2	T	0.00	125.94	550.97	1245.75	1828.55	2363.09	2582.39	1781.20	1908.44	1708.75	2695.87	1377.23	1585.42	1728.55
57		2	3	R2	0.00	352.87	871.33	1287.43	2179.59	2051.22	2008.57	1962.10	2185.87	2105.07	1693.19	1360.15	1874.46	2335.18
58		1	1	T	0.00	118.87	126.37	2520.27	845.81	2277.92	2593.06	3502.77	4308.02	5958.29	6012.49	5288.24	5907.87	5295.27
59		1	2	R1	0.00	58.68	239.37	318.32	653.74	956.11	1198.57	1354.18	1536.20	2487.67	2742.07	3190.08	4782.48	4339.18
60		1	3	R2	0.00	202.15	477.64	3105.06	2570.29	2775.68	3778.30	5129.26	3632.40	4530.07	3459.61	4551.66	5039.19	4857.11
61		2	1	R1	0.00	0.00	149.60	275.44	503.88	1447.06	1349.39	1797.05	2720.48	2875.63	3282.32	4841.01	5002.18	6126.07
62		2	2	T	0.00	0.00	85.58	144.23	243.02	435.47	556.51	745.35	1490.44	2138.63	2429.93	3120.61	3668.65	4717.95
63		2	3	R2	92.23	70.35	109.72	211.86	254.32	690.01	562.58	1608.17	2844.06	2797.24	2414.39	5636.39	5996.21	3884.92
64		3	1	R1	0.00	97.52	107.36	183.19	363.01	589.60	626.55	925.94	1091.01	1154.15	2982.82	2994.37	3877.18	2793.52
65		3	2	R2	0.00	1631.55	576.65	560.98	1073.76	715.24	848.81	979.17	1229.62	1251.05	1301.84	1504.89	1729.61	1766.26
66		3	3	T	0.00	188.75	513.56	221.17	350.08	365.36	580.93	729.86	857.20	843.58	1496.50	1994.48	2082.60	2150.05
67		2	1	R1	0.00	0.00	78.16	228.08	648.06	3206.59	2641.74	5361.93	6738.88	6116.83	6180.53	5402.43	6190.79	3671.74
68		2	2	T	0.00	0.00	126.56	234.94	720.71	1132.20	937.65	1375.70	1587.18	1699.14	2433.84	1972.18	2134.67	1862.51
69		2	3	R2	0.00	85.51	200.61	440.22	535.48	808.10	880.09	1361.99	2025.21	1517.28	2766.58	3418.18	3581.25	3369.45
70		3	1	R1	0.00	268.68	108.04	670.00	641.68	3003.57	2659.28	4599.21	3203.45	2744.57	2897.57	2987.05	2433.10	2262.73
71		3	2	R2	0.00	146.60	482.85	501.74	963.83	2144.26	2944.10	3489.56	2588.86	2497.53	1871.12	1695.91	1748.84	1568.23
72	3	3	T	0.00	121.01	231.16	376.34	802.14	1420.15	1320.08	1770.85	1422.24	2009.49	1642.65	1995.60	3034.08	2728.57	
73	3	1	R1	0.00	0.00	0.00	67.34	166.12	482.34	639.88	901.13	1423.40	2354.44	2049.27	2955.53	3505.83	3742.60	
74	3	2	R2	0.00	0.00	79.21	124.61	249.34	386.58	567.27	958.57	1608.81	3131.10	2091.72	2005.70	2238.08	2231.84	
75	3	3	T	0.00	0.00	90.83	606.32	918.40	1429.71	1795.33	2262.78	2573.86	3251.85	3437.45	4416.67	4460.92	10141.01	
76	1	1	T	0.00	88.70	55.49	262.25	596.44	2321.89	1749.23	2683.47	3129.26	3135.44	3791.81	4281.58	4899.80	4738.87	
77	1	2	R1	0.00	0.00	91.29	98.85	306.36	240.68	387.39	982.11	920.01	1204.52	1378.97	1589.17	2118.53	2614.21	
78	1	3	R2	0.00	0.00	97.05	111.51	476.09	794.77	405.47	713.93	690.27	1117.06	2241.13	2492.66	2849.00	3637.46	
79	2	1	R1	0.00	65.74	62.36	69.60	378.63	1656.92	1809.01	2653.59	2221.62	2656.07	4689.85	8812.20	7352.03	5105.02	
80	2	2	T	0.00	51.19	105.93	168.85	595.30	1182.96	2166.43	2039.49	3287.81	2719.73	2554.70	4627.86	5168.15	3355.15	

Obs	sub	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
81	(b) (6)	2	3	R2	96.79	200.89	177.09	908.87	505.50	3041.76	2886.83	3980.05	2411.51	2121.00	3028.71	4110.93	4378.90	3188.40
82		3	1	R1	0.00	249.64	92.22	146.01	434.83	943.43	864.36	1547.29	2864.72	2964.39	3289.08	3130.72	2874.72	3019.34
83		3	2	R2	0.00	0.00	81.24	261.15	1162.62	993.16	1105.94	1538.19	3281.52	2002.30	1874.00	1737.24	1542.84	1657.18
84		3	3	T	0.00	0.00	113.79	457.21	884.72	1250.75	1509.25	2310.14	3763.10	3006.48	2240.71	3593.52	3256.85	3533.97
85		1	1	T	0.00	120.79	304.61	722.39	1115.54	2367.46	2215.75	2737.90	3945.19	3876.16	6182.01	6564.71	7809.53	6566.87
86		1	2	R1	0.00	0.00	85.43	150.96	331.11	1043.57	1117.12	1432.79	2781.71	3250.11	4952.13	15301.41	12497.17	13070.99
87		1	3	R2	0.00	81.76	276.96	421.71	797.56	1791.51	2336.02	4895.03	5624.37	6155.16	12519.34	13144.89	10622.87	14182.35
88		1	1	T	0.00	0.00	290.86	544.66	830.76	1416.16	1421.07	2345.84	3376.67	4720.94	4751.37	4836.33	4137.87	4772.53
89		1	2	R1	0.00	220.46	471.86	671.35	1105.21	1180.76	1538.82	2409.60	2319.56	2583.84	4776.16	5165.90	4848.94	5931.38
90		1	3	R2	0.00	65.84	67.43	141.38	347.55	721.70	1569.86	1457.90	1300.74	1778.14	1829.57	2130.55	2422.86	2347.89
91		3	1	R1	0.00	0.00	0.00	152.56	724.50	1187.62	1173.34	1915.27	2726.32	2890.66	4195.09	4048.14	3992.03	4707.11
92		3	2	R2	0.00	63.55	627.62	969.26	1602.41	3072.56	1860.58	2045.24	1929.85	1872.65	1611.62	1511.28	2337.50	2021.08
93		3	3	T	0.00	0.00	334.08	574.49	1121.44	1179.40	1443.81	2291.79	2665.51	3116.09	3538.28	3059.72	3940.44	3602.63
94		3	1	R1	0.00	0.00	0.00	63.70	94.31	178.26	303.21	323.90	456.16	956.60	937.31	1286.58	933.00	1521.01
95		3	2	R2	0.00	60.47				261.69	292.18	329.17	329.12	370.79	1251.13	1403.08	1630.43	1662.21
96		2	1	R1	0.00	0.00	0.00	195.68	180.16	546.61	337.55	633.55	817.09	887.64	1262.40	1131.27	1321.69	1710.48
97		2	2	T	0.00	0.00	106.08	155.90	338.96	334.55	502.80	742.61	1108.60	1431.08	1849.93	2500.93	2240.48	2275.30
98		2	3	R2	124.98	147.97	190.54	187.24	326.85	861.56	818.65	1304.34	1265.78	1430.33	1883.30	3032.91	3207.43	2511.49
99		1	1	T	0.00	0.00	0.00	73.87	119.14	129.71	232.38	387.04	601.11	2155.76	1537.65	1550.27	1453.28	1445.89
100		1	2	R1	0.00	242.91		178.23	359.22	182.60	889.84	343.43	346.12	379.61	745.13	454.22	642.55	692.38
101		1	3	R2	0.00	0.00	76.21	153.84	223.86	488.20	783.63	1072.24	771.59	713.27	1803.31	861.36	1205.70	779.87
102		3	1	R1	0.00	0.00	0.00	55.02	85.44	671.72	286.88	744.49	549.14	620.05	820.77	1289.79	1358.73	1389.40
103		3	2	R2	0.00	0.00	0.00	0.00	343.91	183.62	511.79	414.75	1115.00	627.67	972.54	1281.37	1100.45	1847.66
104		3	3	T	0.00	0.00	52.65	259.14	331.24	503.30	497.53	722.97	801.85	812.36	834.64	1340.65	1290.13	1942.35
105		1	1	T	0.00	140.87		230.91	344.86	758.83	596.55	944.09	1043.12	1231.74	1815.77	1998.43	2526.92	2160.99
106		1	2	R1	0.00	80.92		82.23	175.78	361.61	980.19	694.57	746.85	755.60	1144.29	1390.35	2440.71	2243.74
107		1	3	R2	0.00	0.00	0.00	79.94	201.76	285.65	311.04	611.30	935.93	1259.44	1839.21	2104.13	3175.76	2377.28
108		2	1	R1	0.00	0.00	0.00	94.59	82.94	210.80	377.57	368.65	647.05	785.05	873.60	904.73	1046.69	1341.23
109		2	2	T	0.00	0.00	1471.40	293.87	192.13	510.79	310.62	543.09	650.61	793.82	913.88	1578.88	2188.19	2378.81

Obs	sub	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
110	(b) (6)	2	3	R2	0.00	0.00	0.00	54.27	149.41	227.99	240.81	478.41	844.27	955.30	1109.12	1438.75	1837.53	2132.28
111		1	1	T	0.00	0.00	0.00	0.00	60.00	95.22	279.46	209.55	470.73	665.88	894.14	1015.82	1255.24	1484.55
112		1	2	R1	0.00	0.00	130.88	60.72	71.33	116.64	313.49	205.73	443.55	473.21	716.47	767.74	965.00	872.12
113		1	3	R2	0.00	0.00	0.00	92.47	164.09	1295.67	384.87	564.67	973.20	1132.92	7988.47	1547.53	2522.70	2170.97
114		3	1	R1	0.00	0.00	0.00	0.00	91.70	321.39	413.49	838.01	1199.57	1780.83	1975.26	1834.07	2039.16	2636.46
115		3	2	R2	0.00	0.00	0.00	0.00	278.39	222.47	259.52	541.51	996.78	730.10	929.61	1239.58	1448.57	1884.04
116		3	3	T	0.00	0.00	75.34	137.79	174.47	814.14	844.15	1224.95	1201.28	1268.64	1462.72	1449.74	1821.95	2163.75

Obs	c15	c16	c17	c18	c19	c20	c21	c22	c23	c24	trt
1	3894.63	3911.20	3956.16	6514.00	2188.24	475.50	154.47	89.34		65.44	3
2	10234.37	8948.85	3844.63	5555.76	2690.39	771.99	309.90	83.77	0.00	0.00	1
3	3203.37	8356.34	3260.34	4378.79	1581.78	686.78	1176.28	130.11	62.44	0.00	2
4	3608.66	2522.28	5011.81	1397.60	937.61	296.84	221.70	162.16	0.00	0.00	2
5	9514.46	6769.39	8585.77	2317.50	1784.48	1086.48	983.01	341.84	95.94	0.00	3
6	6667.30	5488.67	7694.24	3129.16	2963.69	982.11	947.58	438.64	197.96	68.82	1
7	2525.24	2127.56	1803.11			103.42	62.20	0.00	0.00	0.00	2
8	1291.36	1065.03	972.67			0.00	0.00	0.00	0.00	0.00	3
9	2822.03	2122.04	1748.23		451.96	231.67	89.11		0.00	0.00	1
10	4534.29	4071.23	4846.02	4545.03	1478.02	435.62	241.79	237.73	95.31	60.31	1
11	3147.71	2923.66	2413.29	2490.46	1537.67	1367.58	410.82	224.18	191.57	68.64	2
12	3096.39	2554.85	2082.40	3313.64	1231.91	804.95	289.55	132.66	84.40	0.00	3
13	3501.60	3860.78	7054.00	2950.25	952.36	248.33	66.78	0.00	0.00	0.00	2
14	4427.33	3921.15	2903.39	1495.46	746.45	218.82	88.78	60.31	0.00	0.00	1
15	3945.68	4235.83	4141.15	3648.90	1868.70	497.32	305.52	83.51	89.02	0.00	3
16	2632.30	2321.19	3082.51	2494.47	725.25	160.22	76.32	59.91		236.50	2
17	2288.61	1536.36	1831.34	1629.08	1248.00	474.70	249.62	116.73	68.37	0.00	3
18	2770.13	1924.85	1841.81	2355.31	2397.22	1103.52	653.84	290.23	103.61	70.44	1
19	3236.28	2902.59	3347.46	3234.37	695.96	131.02	86.01	71.44	0.00	0.00	2
20	4808.90	3827.23	3210.31	3303.91	1285.72	239.36	122.57	72.02	60.31	0.00	3
21	3615.16	4640.18	2517.43	1693.82	1134.31	423.52	241.18	108.84	0.00	0.00	1
22	1551.80	1250.43	1190.44	1434.80	858.69	250.32	163.90	125.31	54.77	0.00	2
23	1190.62	1286.86	1426.73	1727.69	1380.77	804.10	501.62	250.90	129.24	70.08	1
24	1004.03	1103.49	944.11	2039.62	753.95	348.76	209.63	13353.92	173.72	88.83	3
25	8404.38	6856.04	8895.85		1506.31	1088.33		628.56	99.44	60.75	2
26	5787.33	5503.81	3699.83		1751.31	556.08	1541.33	281.66	299.68	233.54	3
27	5397.31	5401.65	4798.67	3290.79	1019.07	284.00	403.29	156.27	81.33	63.44	1
28	2308.25	2362.80	4973.99	3421.55	3124.59	564.88	188.51	98.92	0.00	0.00	2
29	3202.50	2353.52	3736.25	1872.41	1713.68	462.81	149.84	58.55	63.15	0.00	3
30	2698.24	3362.85	5138.22	3857.89	2388.98	423.32	147.63	108.36	0.00	0.00	1
31	836.73	901.80	1409.85	1752.47	614.82	131.49	51.43	0.00	0.00	0.00	1
32	328.31	352.19	455.48	506.30	379.77	148.90	121.37	61.20	0.00	0.00	2
33	586.42	497.11	810.85	941.87	692.08	176.09	179.28	104.39	0.00	0.00	3
34	1399.14	1151.23	1837.45	1079.25	565.74	80.64	60.03	0.00	0.00	0.00	2
35	1926.38	1406.69	1542.81		786.15	469.26	114.97	76.99	0.00	0.00	3
36	1246.49	1192.13	1353.81		480.38	134.24	72.84	0.00	0.00	0.00	1
37	3339.99	5080.07	11327.18	4631.00	1738.47	431.99	427.61	238.53		56.03	1
38	4801.45	4536.52	4199.58	2553.55	1223.31	425.19	271.35	138.25	60.75	0.00	2
39	4744.18	4064.35	4116.16	2486.02	1318.25	1032.00	336.68	144.62	80.70	0.00	3
40	1036.49	925.35	1475.60	1331.15	1610.47	280.45	114.56	80.50	0.00	0.00	2

Obs	c15	c16	c17	c18	c19	c20	c21	c22	c23	c24	trt
41	691.69	750.68	769.49	1742.83	1815.24	1009.18	588.07	219.99	136.57	0.00	3
42	1035.72	902.22	860.67	1852.01	1028.83	849.08	359.46	217.70	83.16	0.00	1
43	10034.87	8361.89	7241.68		2261.74	451.48		109.04	70.26	50.27	2
44	7091.17	6682.32	7608.95		3277.05	579.93	306.43	140.87		109.77	3
45	6941.72	6622.13	8384.78	8556.77		1115.41	372.56	231.93	221.91	129.72	1
46	3037.29	2714.48	3216.82	3736.92		169.83	120.46	82.89	0.00	0.00	2
47	1975.73	2202.21	2473.58	1756.93		489.63	147.22	0.00	0.00	0.00	1
48	2686.37	2329.06	3221.96	2937.17	1277.91	238.42	119.61	53.55	53.47	0.00	3
49	7024.76	5504.53	7457.00	3662.91	1826.29	223.19	162.40	189.90	0.00	0.00	1
50	7335.79	4584.14	5262.92	2586.89	1158.00		39284.85		135.12	63.86	2
51	4635.15	2628.90	4597.43			220.59	160.13			0.00	3
52	2447.34	2334.05	1551.11	1422.23	737.10	134.92	108.51	50.81	0.00	0.00	2
53	1355.21	1290.21	1369.78	836.69	661.93	292.04	130.46	82.07	0.00	0.00	3
54	1783.55	1718.95	1242.81	1168.65	803.25	312.41	220.96	64.60	0.00	0.00	1
55	1995.15	1642.37	1757.73	1492.79	919.23	105.66	112.75	76.90	97.82	0.00	2
56	1500.38	1398.46	1528.30	1458.06	591.25	228.99	124.75	58.00	0.00	0.00	1
57	1634.43	1122.50	713.21	493.37	189.51	107.13	74.75	53.62	122.14	51.70	3
58	4347.63	4058.50	3567.15	690.95	337.95	120.69	0.00	0.00	0.00	0.00	1
59	2585.19	3273.61	2146.85	1277.38	667.72	235.79	88.82		0.00	0.00	2
60	3613.04	3529.64	2293.18	1555.35	945.25		121.44	75.06	67.46	0.00	3
61	4974.49	4405.77	4411.78	3738.85	895.34	325.97	215.17	137.73	52.33	62.30	2
62	3333.28	3516.42	3811.99	2379.42	1196.80	693.22	513.46	291.97		128.01	1
63	3565.99	5119.01	4632.94	1871.57	1265.83	625.39	247.24		96.07	0.00	3
64	2582.72	1860.97	1409.62	650.32	480.73	156.53	103.71	102.93	70.88		2
65	1326.42	999.58	749.48	797.65	622.88	266.94	146.50	57.09		0.00	3
66	1607.45	1512.07	2061.83	1152.82	592.74	253.72	147.37	111.61	0.00	0.00	1
67	3956.23	3861.25	3868.27				142.42	96.14			2
68	3909.56	2492.94	2504.88	2545.76	1747.19	576.71	216.69	140.41		75.74	1
69	2396.18	1938.70	2981.90	2792.28	1606.57		282.79	161.05	92.32	56.77	3
70	1951.39	1879.80	2505.67	1101.14	378.72	304.90	148.66	149.43	56.37	50.50	2
71	1519.50	1830.30	1559.08	2158.56	1398.38	587.36	210.89	304.59	84.26	69.65	3
72	2322.47	2164.15	1988.23	4892.99	2047.10	1159.95	300.50	243.35	96.91	76.58	1
73	2742.04	2726.23	3156.73	2125.41		477.61	106.62	85.38	0.00	0.00	2
74	4052.57	2201.40	2042.11	1128.50	639.49	350.43	219.15		103.41	0.00	3
75	5223.78	3638.19	2926.83				197.53		0.00	0.00	1
76	3695.19	3547.49	4297.91	1973.16	1584.27	1037.04	323.46	207.64	91.56	0.00	1
77	2894.57	2742.22	1830.17	1549.75	1540.88	864.20	284.11	134.54	67.30	55.39	2
78	3305.28	2840.36	2431.99	1898.48	1198.10	356.22	192.67	103.89	73.07	56.86	3
79	3602.53	3583.66	6163.88	2631.30	1408.28	440.80	195.16	190.04	105.21	68.13	2
80	3270.19	2364.87	6290.70			1622.81	866.36		171.80	142.11	1

Obs	c15	c16	c17	c18	c19	c20	c21	c22	c23	c24	trt
81	2790.48	3283.20	2907.47		993.87	781.87	359.92	148.55	91.27		3
82	3643.77	3571.10	3368.03	3826.52	1577.53	385.76	451.45	196.09	208.92	99.71	2
83	1512.70	1725.53	1734.54	2137.21	2018.08	582.74	252.61	115.32	98.50	0.00	3
84	2457.82	2476.00	2278.35		2630.22		599.37	307.16	178.68	98.17	1
85	7154.95	4665.99	5085.75	15548.02	3594.79	2013.72	730.88	754.22	199.79	93.58	1
86	7857.13	5594.68	5254.74	2456.69	2119.20	721.57	372.46	196.66	100.54	60.47	2
87	4637.41	4100.57	5645.56	3977.85	2232.08	579.18	464.41	520.31	172.30	66.47	3
88	2922.39	4265.71	3689.74	1424.44	646.24	326.29	178.09	97.66		51.92	1
89	6955.72	5244.23	4537.48	3140.03	807.09	335.34	337.91		60.78	0.00	2
90	1706.29	1781.95	1939.20	1286.52	696.39	584.80	361.10	103.00	61.43	0.00	3
91	3464.04	3801.69	1785.98	1499.79	1438.29	90.21	149.48	92.54	0.00	0.00	2
92	1644.10	1172.14	1374.83	834.51	665.05	280.08	193.89	118.22	70.53	65.77	3
93	3515.55	2495.81	2086.88	1892.04	1346.44	644.45	462.41	291.38	143.79	73.09	1
94	2270.21	1048.46	1760.79	1177.99	356.77	108.04	66.28		62.76	0.00	2
95	1613.46	991.42	2090.55	978.33	864.11	438.43	249.59	89.12	59.60	403.58	3
96	1492.83	1535.76	1555.37	1277.16	307.71	125.98	0.00	0.00	0.00	0.00	2
97	2264.27	2080.57	1780.49	2432.74	650.88	404.80	145.77	71.67	0.00	0.00	1
98	2386.06	698.61	1897.79	1465.41	757.69	230.49	104.08	0.00	0.00	0.00	3
99	1426.98	1246.06	1517.79	2740.52	1551.81	562.95	200.49	132.90	52.22	84.97	1
100	630.78	594.71	717.10	1230.38	1233.92	3286.51	1434.04	529.96	311.39	95.48	2
101	716.54	2060.83	966.86	1911.00	585.23	688.34	203.42	106.88	0.00	0.00	3
102	1424.29	1199.81	1413.95	2485.84	764.00	272.97	125.58	78.32	0.00	0.00	2
103	1664.76	1338.17	1369.19	1912.98	1237.30	835.24	434.88	121.86	0.00	0.00	3
104	1337.04	1248.69	1743.10	1568.48	1167.95	671.89	310.03	132.86	135.23	56.60	1
105	2191.74	2267.93	3024.78	1644.11	841.00	504.41	280.90	58.57	0.00	0.00	1
106	2390.55	2294.50	2002.67	1825.00	943.34	658.90	172.89	58.53	0.00	0.00	2
107	1973.92	1691.84	2364.06	2261.77	554.83	606.59	256.18	145.58	0.00	0.00	3
108	1207.64	928.71	1187.61	789.43	485.20	206.95	71.05	59.65	0.00	0.00	2
109	1723.07	1354.20	1927.60	917.35	681.20	123.15	65.40	0.00	0.00	0.00	1
110	1689.12	1358.71	1949.03	1805.47	535.31	161.51	65.20	53.51	0.00	0.00	3
111	1375.16	1362.16	1719.76	2495.58	771.53	291.52	114.27	52.65	0.00	0.00	1
112	996.24	834.19	1643.53	1385.77	604.61	449.76	177.66	67.42	0.00	0.00	2
113	1739.67	1481.96	2087.86	1957.73	1280.28	609.17	232.80	108.64	0.00	0.00	3
114	2221.74	1733.48	2418.32	1113.46	330.21	349.58	0.00	0.00	0.00	0.00	2
115	1780.34	1652.39	1829.44	890.78	496.89	136.86		0.00	0.00	0.00	3
116	1510.74	1236.14	2255.60	748.36	262.68	80.81	0.00	0.00	0.00	0.00	1

**FASTING PHARMACOKINETIC DATASET**

Obs	sub	seq	per	treat	AUC <sub>T</sub>	AUC <sub>I</sub>	C <sub>MAX</sub>	T <sub>MAX</sub>	KE	THALF	trt
1	(b) (6)	2	1	R2	308294.22	311056.13	6514.00	60.00	0.024	29.248	3

Obs	sub	seq	per	treat	AUCT	AUCI	CMAX	TMAX	KE	THALF	trt
2	(b) (6)	2	2	T	401603.07	403324.39	10234.37	32.00	0.049	14.240	1
3		2	3	R1	329665.72	331703.82	8356.34	36.00	0.031	22.620	2
4		3	1	R1	236394.93	249266.50	5446.51	16.00	0.013	55.007	2
5		3	2	R2	443917.71	446964.55	9514.46	32.00	0.031	22.008	3
6		3	3	T	463335.94	466902.29	8083.70	28.00	0.019	35.912	1
7		3	1	R1	170874.06	172257.39	3845.44	16.00	0.045	15.412	2
8		3	2	R2	64867.72	104388.21	2407.01	10.00	0.025	28.157	3
9		3	3	T	141047.79	143311.33	3275.12	28.00	0.039	17.603	1
10		1	1	T	337651.09	342101.04	5511.59	24.00	0.014	51.133	1
11		1	2	R1	263474.91	267036.48	3802.27	28.00	0.019	35.958	2
12		1	3	R2	235197.35	238604.00	5454.85	10.00	0.025	27.972	3
13		2	1	R2	294279.62	295485.57	7127.06	24.00	0.055	12.515	3
14		2	2	T	189749.99	191196.16	4427.33	32.00	0.042	16.617	1
15		2	3	R1	350533.80	353576.43	14380.61	28.00	0.029	23.686	2
16		3	1	R1	193631.40	205977.00	4399.05	20.00	0.019	36.175	2
17		3	2	R2	137055.47	139766.45	2288.61	32.00	0.025	27.479	3
18		3	3	T	223817.17	227095.37	2770.13	32.00	0.021	32.251	1
19		3	1	R1	202068.36	207721.36	4187.35	24.00	0.013	54.837	2
20		3	2	R2	290440.37	292321.71	5584.63	20.00	0.032	21.618	3
21		3	3	T	245990.09	249306.47	4723.31	28.00	0.033	21.116	1
22		2	1	R2	122330.79	125842.69	3373.44	10.00	0.016	44.436	3
23		2	2	T	170517.76	175791.70	3780.53	6.00	0.013	52.152	1
24		2	3	R1	606379.04	608079.90	13353.92	144.00	0.052	13.269	2
25		3	1	R1	590558.32	592965.34	11642.19	24.00	0.025	27.458	2
26		3	2	R2	396993.64	410558.33	8062.87	28.00	0.017	40.251	3
27		3	3	T	351212.33	357872.32	9238.47	28.00	0.010	72.752	1
28		3	1	R1	268512.30	270743.48	4973.99	48.00	0.044	15.631	2
29		3	2	R2	226392.87	228437.22	7566.24	24.00	0.031	22.434	3
30		3	3	T	274252.39	276662.51	5138.22	48.00	0.045	15.414	1
31		1	1	T	81200.52	82081.02	1752.47	60.00	0.058	11.865	1
32		1	2	R1	38531.36	41012.31	768.99	12.00	0.025	28.093	2
33		1	3	R2	60824.68	64816.23	941.87	60.00	0.026	26.498	3
34		3	1	R1	93589.22	94745.51	1840.75	28.00	0.052	13.348	2
35		3	2	R2	118425.49	121069.16	2374.77	28.00	0.029	23.796	3
36		3	3	T	85518.42	87258.92	1805.54	24.00	0.042	16.559	1
37		1	1	T	395337.98	398750.95	11327.18	48.00	0.016	42.213	1
38		1	2	R1	241788.39	244727.19	4801.45	32.00	0.021	33.524	2
39		1	3	R2	259522.79	262469.51	4898.25	28.00	0.027	25.305	3
40		3	1	R1	95815.47	98910.72	1610.47	72.00	0.026	26.646	2
41		3	2	R2	133530.95	139591.77	1815.24	72.00	0.023	30.755	3

Obs	sub	seq	per	treat	AUCT	AUCI	CMAX	TMAX	KE	THALF	trt
42	(b) (6)	3	3	T	120343.59	124441.27	1852.01	60.00	0.020	34.147	1
43		3	1	R1	630515.64	636769.50	19830.41	24.00	0.008	86.213	2
44		3	2	R2	485828.25	490313.51	9830.13	28.00	0.024	28.316	3
45		3	3	T	722295.56	727775.42	13907.22	24.00	0.024	29.275	1
46		2	1	R2	244531.60	250077.52	3736.92	60.00	0.015	46.367	3
47		2	2	T	156586.37	160395.65	2473.58	48.00	0.039	17.931	1
48		2	3	R1	205499.31	207282.97	3277.44	24.00	0.030	23.117	2
49		1	1	T	531633.50	536280.86	17495.00	24.00	0.041	16.960	1
50		1	2	R1	2848161.45	2849299.78	39284.85	122.05	0.056	12.353	2
51		1	3	R2	413323.61	416940.16	13460.72	20.00	0.044	15.651	3
52		3	1	R1	139012.15	140401.36	2577.86	28.00	0.037	18.948	2
53		3	2	R2	93259.26	96012.43	1377.12	28.00	0.030	23.248	3
54		3	3	T	123670.23	125898.12	2658.80	28.00	0.029	23.900	1
55		2	1	R2	149079.69	153295.60	3080.07	5.00	0.023	29.867	3
56		2	2	T	124895.48	126922.44	2695.87	16.00	0.029	24.219	1
57		2	3	R1	100228.40	103298.55	2335.18	28.00	0.017	41.153	2
58		1	1	T	241777.86	244309.03	6012.49	16.00	0.048	14.534	1
59		1	2	R1	173847.25	175960.31	4782.48	24.00	0.042	16.487	2
60		1	3	R2	243464.26	245748.09	5129.26	8.00	0.030	23.461	3
61		2	1	R2	290250.74	292721.62	6126.07	28.00	0.025	27.485	3
62		2	2	T	259448.59	270513.14	4717.95	28.00	0.012	59.899	1
63		2	3	R1	278219.07	281944.04	5996.21	24.00	0.026	26.870	2
64		3	1	R1	131261.06	133999.52	3877.18	24.00	0.026	26.774	2
65		3	2	R2	93025.21	94851.19	1766.26	28.00	0.031	22.165	3
66		3	3	T	117935.38	124449.33	2150.05	28.00	0.017	40.446	1
67		2	1	R2	353629.67	356403.60	6738.88	10.00	0.035	19.995	3
68		2	2	T	207115.59	216471.46	3909.56	32.00	0.008	85.604	1
69		2	3	R1	231611.80	236837.56	3581.25	24.00	0.011	63.792	2
70		3	1	R1	168040.06	170414.56	4599.21	8.00	0.021	32.585	2
71		3	2	R2	182395.43	186513.58	3489.56	8.00	0.017	40.975	3
72		3	3	T	252823.47	259069.17	4892.99	60.57	0.012	56.520	1
73		3	1	R1	202108.44	204205.43	3742.60	28.00	0.041	17.021	2
74		3	2	R2	156627.46	165110.96	4052.57	32.00	0.012	56.852	3
75		3	3	T	295107.97	300553.07	10141.01	28.00	0.036	19.103	1
76		1	1	T	287982.12	293193.27	4899.80	24.00	0.018	39.442	1
77		1	2	R1	179962.87	182560.15	2894.57	32.00	0.021	32.495	2
78		1	3	R2	184829.57	193884.18	3637.46	28.00	0.006	110.356	3
79		2	1	R2	329439.60	335799.06	8812.20	20.00	0.011	64.687	3
80		2	2	T	423293.46	430308.03	6290.70	48.00	0.020	34.207	1
81		2	3	R1	236496.05	240308.31	4378.90	24.00	0.024	28.946	2

Obs	sub	seq	per	treat	AUCT	AUCI	CMAX	TMAX	KE	THALF	trt
82	(b) (6)	3	1	R1	268098.91	278563.91	3826.52	60.00	0.010	72.733	2
83		3	2	R2	176281.89	180237.92	3281.52	10.00	0.025	27.833	3
84		3	3	T	285739.23	293999.84	3763.10	10.00	0.012	58.313	1
85		1	1	T	626792.06	631119.94	15548.02	60.00	0.022	32.050	1
86		1	2	R1	451274.65	456196.15	15301.41	20.00	0.012	56.402	2
87		1	3	R2	508914.11	512014.69	14182.35	28.00	0.021	32.326	3
88		1	1	T	244147.40	246297.80	4836.33	20.00	0.024	28.702	1
89		1	2	R1	309034.41	311996.97	6955.72	32.00	0.021	33.778	2
90		1	3	R2	149704.43	152398.87	2422.86	24.00	0.023	30.396	3
91		3	1	R1	206000.51	208484.06	4707.11	28.00	0.037	18.598	2
92		3	2	R2	127651.94	131401.12	3072.56	5.00	0.018	39.504	3
93		3	3	T	232924.32	237997.13	3940.44	24.00	0.014	48.098	1
94		3	1	R1	91122.11	93672.09	2270.21	32.00	0.025	28.157	2
95		3	2	R2	126493.28	159979.81	2090.55	48.00	0.012	57.501	3
96		2	1	R2	88066.19	90319.93	1710.48	28.00	0.056	12.398	3
97		2	2	T	147227.13	149209.89	2500.93	20.00	0.036	19.172	1
98		2	3	R1	131173.61	133640.37	3207.43	24.00	0.042	16.425	2
99		1	1	T	155424.73	159559.79	2740.52	60.00	0.021	33.725	1
100		1	2	R1	217619.45	221734.72	3286.51	96.15	0.023	29.869	2
101		1	3	R2	113667.56	116427.78	2060.83	36.00	0.039	17.897	3
102		3	1	R1	111474.83	114485.25	2485.84	60.00	0.026	26.637	2
103		3	2	R2	138012.85	142007.29	1912.98	60.00	0.031	22.716	3
104		3	3	T	141318.94	144613.42	1942.35	28.00	0.017	40.337	1
105		1	1	T	161859.63	163438.37	3024.78	48.00	0.037	18.680	1
106		1	2	R1	147774.08	148934.30	2440.71	24.00	0.050	13.737	2
107		1	3	R2	155307.10	160221.22	3175.76	24.00	0.030	23.393	3
108		2	1	R2	74112.36	75900.48	1341.23	28.00	0.033	20.774	3
109		2	2	T	103809.30	105153.51	2378.81	28.00	0.049	14.244	1
110		2	3	R1	110782.67	112066.45	2132.28	28.00	0.042	16.626	2
111		1	1	T	114454.33	115926.08	2495.58	60.00	0.036	19.372	1
112		1	2	R1	90842.97	92531.51	1643.53	48.00	0.040	17.356	2
113		1	3	R2	177608.38	180748.29	7988.47	16.00	0.035	20.029	3
114		3	1	R1	120005.57	130710.01	2636.46	28.00	0.033	21.220	2
115		3	2	R2	91728.12	94345.79	1884.04	28.00	0.052	13.255	3
116		3	3	T	96521.92	97720.29	2255.60	48.00	0.067	10.277	1

## 4.5.2 Fasting Study Codes

```

/*=====
=====
/ Program      : HVScale3Period.SAS
/ SubMacros    :
/ Updated      : 15 Aug 2009
/ Purpose      : To analyze three period reference-scaled bioequivalence
studies.
/
/ Notes        : EXCEL DATA FILE MUST BE OPEN WHEN RUNNING THIS PROGRAM.
/                : OUTPUT FILE (WORD DOCUMENT) CONTAINING SUMMARY TABLES IS
CREATED.
/
/=====
=====
/ PARAMETERS:  THE FOLLOWING COLUMNS SHOULD BE IN THE INPUT DATASET (EXCEL
FILE).
/-----name-----description-----
-----
NAME OF VARIABLE
      SUBJ          SUBJECT NUMBER
      TRT            TREATMENT - CHARACTER (EITHER A OR B) A=TEST; B=REF
      SEQ            SEQUENCE NUMBER - NUMERIC (EITHER 1, 2, OR 3)
      PER            PERIOD NUMBER - NUMERIC (EITHER 1, 2, 3, OR 4)
      AUCT           AREA UNDER CURVE 0-T
      AUCI           AREA UNDER CURVE 0-INF
      CMAX           CMAX
      TMAX           TMAX
      KEL            ELIMINATION RATE CONSTANT
      THALF          HALF LIFE

      sequence 1      T      R      R
      sequence 2      R      T      R
      sequence 3      R      R      T

/=====
=====
/ AMENDMENT HISTORY:
/ Init --Date--  -----Description-----
/
/=====
=====*/
options nofmterr nocenter nodate symbolgen mlogic macrogen mprint ps=65
ls=80;

*****STEP 1: ENTER ANDA INFORMATION *****;
%let drug= Diclofenac Sodium Gel;
%let anda=208077;
%let studytype=FASTING;

*****STEP 2: ENTER UNITS FOR PK PARAMETERS *****;
%let aucunit = pg hr/mL;
%let cmaxunit = pg/mL;
%let timeunit = hr;

```

```

***** STEP 3: ENTER LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT
REPORTS *****;
%let studydir=C:\Users\Yajun.Liu\Documents\SAS\ANDAs\ANDA208077 Diclofenac
Sodium Gel;

***** STEP 4: ENTER THE NAME OF THE DATASET FILE (EXCEL FILE) *****;
%let excelfile = &studydir\ANDA208077_fasting.xlsx;

***** STEP 5: ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING STUDY
DATA *****;
%let sheetname = pk;

proc import datafile="&excelfile"
            out=base
            dbms=xlsx replace;
            sheet="&sheetname";
            getnames=yes;
            mixed=yes;

run;

libname studylib "&studydir";

***** STEP 5: PROVIDE NAMES OF THE VARIABLES TO READ IN FROM EXCEL FILE
*****;
***** PROVIDE STANDARD VARIABLE NAMES FROM THE PARAMETER LIST ABOVE *****;
***** VARIABLE NAMES: SUBJ TRT(A,B) SEQ(1,2) PER(1,2,3) AUCT AUCINF CMAX TMAX
KEL THALF *****;

data base;
set base;
/*sequence 1          T      R      R
   sequence 2          R      T      R
   sequence 3          R      R      T
*/

IF SEQU="TR1R2" THEN SEQ=1;
ELSE IF SEQU="R2TR1" THEN SEQ=2;
ELSE IF SEQU="R1R2T" THEN SEQ=3;

IF TREAT="T" THEN TRT="A";
ELSE IF TREAT IN("R1", "R2") THEN TRT="B";

run;

proc print data=base;
run;

```

```

*****
;
      ***** DO NOT CHANGE ANYTHING BELOW THIS LINE *****
*****
;

data pk;
  set base;

  LAUCT=log(auct);
  LAUCINF=log(auci);
  LCMAX=log(cmax);

run;

data pkn;
  set pk;
run;

data full;
  set pkn;

run;

proc sort
  data=pkn;
  by seq subj per;
run;

data test; set pkn; if trt='A'; latt=LAUCT; lait=LAUCINF; lct=LCMAX;
run;

data ref; set pkn; if trt='B';
run;

/*sequence 1          T    R    R
   sequence 2          R    T    R
   sequence 3          R    R    T
*/
/** ORIGINAL DON'S CODE **
data ref1; set ref; if (seq=1 and per=1) or (seq=2 and per=2) or (seq=3 and
per=1); lat1r=LAUCT; lai1r=LAUCINF; lcl1r=LCMAX;
run;
***/
data ref1; set ref; if (seq=1 and per=2) or (seq=2 and per=1) or (seq=3 and
per=1); lat1r=LAUCT; lai1r=LAUCINF; lcl1r=LCMAX;
run;

data ref2; set ref; if (seq=1 and per=3) or (seq=2 and per=3) or (seq=3 and
per=2); lat2r=LAUCT; lai2r=LAUCINF; lc2r=LCMAX;
run;

```

```

title "ref1";
proc print data=ref1;
run;

title "ref2";
proc print data=ref2;
run;
title;

data scavbe; merge test ref1 ref2; by seq subj;
ilat=latt-(0.5*(lat1r+lat2r)); *auct;
ilai=lait-(0.5*(lailr+lai2r)); *auci;
ilc=lct-(0.5*(lc1r+lc2r)); *cmax;

dlat=lat1r-lat2r; *auct;
dlai=lailr-lai2r; *auci;
dlc=lc1r-lc2r; *cmax;
keep seq subj per trt ilat dlat ilai dlai ilc dlc;
run;

proc print data=scavbe;
title 'dataset for scaled average BE';
run;

%macro calc(param,no);

PROC MIXED data=pkn;
CLASSES SEQ SUBJ PER TRT;
MODEL &param = SEQ PER TRT/ DDFM=SATTERTH;
RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
REPEATED/GRP=TRT SUB=SUBJ;
ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.1;
lsmeans trt; /* DEV */
ods output lsmeans=lsm&param(keep=trt estimate); /* DEV */
ods output Estimates=unsc&no;
title 'unscaled BE 90% CI - guidance version';
run;

DATA UPARAM&NO(KEEP=PARAMETER LCI UCI);
SET UNSC&NO;

ESTIMATE = 100 * EXP(ESTIMATE);
PARAMETER = "&PARAM";
LCI = 100 * EXP(LOWER);
UCI = 100 * EXP(UPPER);
RUN;

*** for scaled dataset***;
DATA UNSC&PARAM;
SET UNSC&NO;
RUN;

%mend calc;

%calc(LCMAX,1);
%calc(LAUCT,2);
%calc(LAUCINF,3);

```

```

**** ESTIMATES ****;
DATA LSMLAUCT;
  SET LSMLAUCT;
  PARAMETER = "LAUCT";
RUN;

DATA LSMLAUCINF;
  SET LSMLAUCINF;
  PARAMETER = "LAUCI";
RUN;

DATA LSMLCMAX;
  SET LSMLCMAX;
  PARAMETER = "LCMAX";
RUN;

DATA UESTIMATE;
  SET LSMLAUCT LSMLAUCINF LSMLCMAX;
RUN;

DATA UESTIMATE;
  SET UESTIMATE;

  GEOMEAN = EXP(ESTIMATE);
RUN;

PROC SORT
  DATA=UESTIMATE;
  BY PARAMETER;
RUN;

PROC TRANSPOSE
  DATA=UESTIMATE
  OUT=TRANSUEST(DROP=__NAME__);
  VAR GEOMEAN;
  BY PARAMETER;
  ID TRT;
RUN;

DATA UEST;
  SET TRANSUEST;

  RATIO = ROUND((A/B), .01);
RUN;

DATA UALL;
  SET UPARAM1 UPARAM2 UPARAM3;
RUN;

PROC SORT
  DATA=UALL;
  BY PARAMETER;
RUN;

PROC SORT
  DATA=UEST;

```

```

    BY PARAMETER;
RUN;

DATA UPARAMS;
    MERGE UEST
        UALL;
    BY PARAMETER;
RUN;

*** PROPER ORDER AUCT, AUCI, CMAX ***;
DATA UPARAMS;
    SET UPARAMS;

    IF PARAMETER = "LAUCT" THEN ORDER=1;
    ELSE IF PARAMETER = "LAUCI" THEN ORDER=2;
    ELSE IF PARAMETER = "LCMAX" THEN ORDER=3;
RUN;

PROC SORT
    DATA=UPARAMS;
    BY ORDER;
RUN;

proc template;
define style mystyle1;
parent = styles.rtf;
REPLACE fonts /
    'headingFont' = ("Arial", 8pt,Bold)
    'docFont' = ("Arial", 8pt)
    'TitleFont2' = ("Arial",8pt,Bold)
    'TitleFont' = ("Arial",8pt,Bold)
    'StrongFont' = ("Arial",8pt,Bold)
    'EmphasisFont' = ("Arial",8pt)
    'FixedEmphasisFont' = ("Arial",8pt)
    'FixedStrongFont' = ("Arial",8pt,Bold)
    'FixedHeadingFont' = ("Arial",8pt,Bold)
    'BatchFixedFont' = ("Arial",8pt)
    'FixedFont' = ("Arial",8pt)
    'headingEmphasisFont' = ("Arial",8pt,Bold);

style SysTitleAndFooterContainer from Container /
outputwidth = 85%
cellpadding = 2
cellspacing = 2
borderwidth = 0;

REPLACE Body from Document /
    bottommargin = 1.0in
    topmargin = 1.0in
    rightmargin = 1in
    leftmargin = 1in;
END;
run;

```

```

/*
data unsc1; set unsc1; unscabe_lower=exp(lower); unscabe_upper=exp(upper);
keep unscabe_lower unscabe_upper; run;
*/

***** SCALED ANALYSIS *****;

%MACRO SCALE(parameter, ipar, dpar);

    proc glm data=scavbe;
        class seq;
        model &ipar =seq/clparm alpha=0.1;
        estimate 'average' intercept 1 seq 0.3333333333 0.3333333333
0.3333333333;
        ods output overallanova=iglm&ipar.1;
        ods output Estimates=iglm&ipar.2;
        ods output NObs=iglm&ipar.3;
        title1 'scaled average BE';
        title2 'intermediate analysis - &ipar glm';
    run;

title "dev iglm&ipar.1";
proc print data=iglm&ipar.1;
run;

    proc glm data=scavbe;
        class seq;
        model &dpar =seq;
        ods output overallanova=dglm&dpar.1;
        ods output NObs=dglm&dpar.3;
        title1 'scaled average BE';
        title2 'intermediate analysis - &dpar glm';
    run;

    data unsc&PARAMETER; set unsc&PARAMETER; unscabe_lower=exp(lower);
unscabe_upper=exp(upper);
    keep unscabe_lower unscabe_upper;
    run;

    data iglm&ipar.1; set iglm&ipar.1; if _n_=2; dfi=df; s2i=ms; keep dfi
s2i param;
        param = "&parameter";
    run;

    data iglm&ipar.2; set iglm&ipar.2; pointest=exp(estimate);
x=(estimate**2)-(stderr**2);
    boundx=(max((abs(LowerCL)),(abs(UpperCL))))**2;
    keep pointest x boundx stderr param;
    param = "&parameter";
    run;

```

```

        data iglm&ipar.3; set iglm&ipar.3; if _n_ = 2; ni=NobsUsed; keep ni
param;
        param = "&parameter";
run;

        data dglm&dpar.1; set dglm&dpar.1; if _n_=2; dfd=df; s2wr=ms/2; keep
dfd s2wr param;
        param = "&parameter";
run;

        data dglm&dpar.3; set dglm&dpar.3; if _n_ = 2; nd=NobsUsed; keep nd
param;
        param = "&parameter";
run;

        data idallglm&parameter;
        length method_used $15;
        merge unsc&parameter iglm&ipar.1 iglm&ipar.2 iglm&ipar.3 dglm&dpar.1
dglm&dpar.3;
        theta=((log(1.25))/0.25)**2; y=-theta*s2wr;
boundy=y*dfd/cinv(0.95,dfd); sWR=sqrt(s2wr);
        critbound=(x+y)+sqrt(((boundx-x)**2)+((boundy-y)**2));
        outcome='FAIL';
        if (s2wr < 0.086436) then method_used='Unscaled'; else
method_used='Scaled/PE';
        if ((s2wr < 0.086436) and (unscabe_lower ge 0.8) and (unscabe_upper le
1.25)) then outcome='PASS';
        if ((s2wr ge 0.086436) and (pointest ge 0.8) and (pointest le 1.25) and
(critbound le 0)) then outcome='PASS';
*     else outcome='FAIL';
run;

        proc print data=idallglm&parameter;
        title1 'output needed for mixed scaled av. BE - using glm';
run;

        data finalglm; set idallglm&parameter;
        keep param s2wr sWR unscabe_lower unscabe_upper pointest critbound
outcome method_used;
run;

        proc print data=finalglm;
        title1 'final output - &parameter - using glm';
run;

%mend scale;

%scale(LAUCT, ilat, dlat);
%scale(LAUCINF, ilai, dlai);
%scale(LCMAX, ilc, dlc);

data all;
set idallglmLAUCT
idallglmLAUCINF
idallglmLCMAX;

unscabe_lower = round((unscabe_lower*100),.01);

```

```

        unscabe_upper = round((unscabe_upper*100),.01);

run;

ods rtf file="&studydir\&ANDA.-ANALYSIS.doc" style=mystyle1 bodytitle;

**** ARITHMETIC MEANS *****;
/*
footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS - REPLICATE 1 (PERIODS 1 AND 2)";
proc report data=pkratio1 nowd split='\ ' box
    style(header)={background=lightorange
                    foreground=black}
    style(column)={background=white
                    foreground=black};

    column nname units ("Test" mean1 cv1 min1 max1)
           ("Reference" mean2 cv2 min2 max2)
           ("Ratio" rmean12);

    define nname /format=$12. spacing=2 "Parameter";
    define units /format=$12. spacing=2 "Unit";
    define mean1 /format=8.3 spacing=2 "Mean";
    define cv1 /format=8.2 spacing=2 "CV%";
    define min1 /format=8.2 spacing=2 "Min";
    define max1 /format=8.2 spacing=2 "Max";
    define mean2 /format=8.3 spacing=2 "Mean";
    define cv2 /format=8.2 spacing=2 "CV%";
    define min2 /format=8.2 spacing=2 "Min";
    define max2 /format=8.2 spacing=2 "Max";
    define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;

footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS - REPLICATE 2 (PERIODS 3 AND 4)";
proc report data=pkratio2 nowd split='\ ' box
    style(header)={background=lightorange
                    foreground=black}
    style(column)={background=white
                    foreground=black};

    column nname units ("Test" mean1 cv1 min1 max1)
           ("Reference" mean2 cv2 min2 max2)
           ("Ratio" rmean12);

    define nname /format=$12. spacing=2 "Parameter";
    define units /format=$12. spacing=2 "Unit";
    define mean1 /format=8.3 spacing=2 "Mean";
    define cv1 /format=8.2 spacing=2 "CV%";
    define min1 /format=8.2 spacing=2 "Min";
    define max1 /format=8.2 spacing=2 "Max";
    define mean2 /format=8.3 spacing=2 "Mean";
    define cv2 /format=8.2 spacing=2 "CV%";
    define min2 /format=8.2 spacing=2 "Min";
    define max2 /format=8.2 spacing=2 "Max";
    define rmean12 /format=8.2 spacing=2 "(T/R)";

```

```

run;
footnote;

footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS - ALL PERIODS (PERIODS 1, 2, 3, AND 4)";
proc report data=pkratio3 nowd split='\ ' box
  style(header)={background=lightorange
    foreground=black}
  style(column)={background=white
    foreground=black};

  column nname units ("Test" mean1 cv1 min1 max1)
    ("Reference" mean2 cv2 min2 max2)
    ("Ratio" rmean12);

  define nname /format=$12. spacing=2 "Parameter";
  define units /format=$12. spacing=2 "Unit";
  define mean1 /format=8.3 spacing=2 "Mean";
  define cv1 /format=8.2 spacing=2 "CV%";
  define min1 /format=8.2 spacing=2 "Min";
  define max1 /format=8.2 spacing=2 "Max";
  define mean2 /format=8.3 spacing=2 "Mean";
  define cv2 /format=8.2 spacing=2 "CV%";
  define min2 /format=8.2 spacing=2 "Min";
  define max2 /format=8.2 spacing=2 "Max";
  define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;

*/

*** UNSCALED ANALYSIS REPORT *****;
title1 "ANDA: &anda &drug STUDY TYPE: &STUDYTYPE";
title2 "SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA";

  proc report
    data=uparams
    headline
    headskip
    nowd
    split="|" box
  style(header)={background=lightorange
    foreground=black}
  style(column)={background=white
    foreground=black};

    column parameter ("Geometric Means|" a b) ratio ("90% CI|" lci uci);

    define parameter /display "Parameter" width=20 center;
    define a /display "Test" width=15 center
format=8.2;
    define b /display "Reference" width=15 center
format=8.2;
    define ratio /display "T/R Ratio" width=15 center
format=8.2;
    define lci /display "Lower CI" width=20 center format=8.2;
    define uci /display "Upper CI" width=20 center format=8.2;

```

```

run;

***** SCALED ANALYSIS REPORT *****;
title1 "SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA";

proc report
  data=all
  headline
  headskip
  nowd
  split='|' box
  style(header)={background=lightorange
    foreground=black}
  style(column)={background=white
    foreground=black};

  column param pointest unscabe_lower unscabe_upper s2wr swr critbound
method_used outcome;

  define param /display "Parameter" width=20 center;
  define pointest /display "T/R Ratio" width=15 center format=8.2;
  define unscabe_lower /display "Lower|90% CI" width=20 center
format=8.2;
  define unscabe_upper /display "Upper|90% CI" width=20 center
format=8.2;
  define s2wr /display "s2wr" width=15 center;
  define swr /display "sWR" width=15 center;
  define critbound /display "Criteria Bound" width=15 center;
  define method_used /display "Method Used" width=25 center;
  define outcome /display "OUTCOME" width=15 center;

run;

ods rtf close;

```

### 4.5.3 Fasting Study Output

ANDA: 208077 Diclofenac Sodium Gel STUDY TYPE: FASTING  
 SUMMARY OF STATISTICAL ANALYSIS - UNSCALED DATA

Parameter	Geometric Means		T/R Ratio	90% CI	
	Test	Reference		Lower CI	Upper CI
LAUCT	217402.5	222774.2	0.98	85.90	110.86
LAUCI	221125.6	232580.3	0.95	82.31	109.83
LCMAX	4360.56	4780.80	0.91	78.71	105.69

SUMMARY OF STATISTICAL ANALYSIS - SCALED DATA

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.98	85.90	110.86	0.424754	0.6517315	-0.241797	Scaled/PE	PASS
LAUCI	0.96	82.31	109.83	0.5422809	0.7363973	-0.305624	Scaled/PE	PASS
LCMAX	0.92	78.71	105.69	0.5330421	0.7300973	-0.291434	Scaled/PE	PASS

**4.6 Additional Attachments**

**4.6.1 16 Summary Tables of Failed Fasting Study**

**Table 1. Submission Summary**

<b>Drug Product Name</b>	Diclofenac Sodium Topical Gel, 1%
<b>Strength(s)</b>	1%
<b>Applicant Name</b>	Amneal Pharmaceuticals LLC
<b>Address</b>	85 Adams Avenue, Hauppauge, NY 11788, USA.
<b>Point of Contact</b>	
<b>Name</b>	Alpesh Patel Vice President, Global Regulatory Affairs
<b>Address</b>	Amneal Pharmaceuticals, 85 Adams Avenue, Hauppauge, New York 11788, USA.
<b>Telephone Number</b>	631-656-5007 Mobile: [REDACTED] (b) (6),
<b>Fax Number</b>	631-299-3995

**Table 2. Summary of Bioavailability Studies**

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters ( $\pm$ SD)						Study Report Location
					Cmax (pg/mL)	Tmax* (hr)	AUC0-t (pg·h/mL)	AUC $\infty$ (pg·h/mL)	T $\frac{1}{2}$ (hr)	Kel (hr <sup>-1</sup> )	
Study #120049	Randomised, Open-Label, 3-Way Reference-Replicate Crossover Bioequivalence Study of Diclofenac Sodium Topical Gel 1% (Test) and Voltaren Gel (Diclofenac Sodium Topical Gel; Reference) Following a Single Dose of 12 g in Healthy Subjects Under Fasting Conditions	Randomized single-dose, 3-way reference-replicate crossover	Diclofenac sodium 12g of 1% topical gel Topical gel [Batch # PW-ST-12001A]	48 completing (30M/18F) Healthy subjects Age (years) = 43 (19-68) Data set for statistical analysis = 46	33622.82 (154.42)	10.0 (3.00-48.0)	636901.16 (64.93)	634003.18 (64.80)	37.97 (48.11)	0.0211 (43.11)	Module 2.7
			Voltaren® Gel (diclofenac sodium) 12g of 1% topical gel Topical gel [Batch #10115876]		10912.42 (67.40)	22.0 (7.00-48.0)	373288.84 (44.59)	376176.03 (44.87)	38.11 (44.48)	0.0236 (40.25)	

\* Median (Range)

**Table 3A. Statistical Summary of the Comparative Bioavailability Data**

NOT APPLICABLE

<b>Drug</b> <b>Dose (# x mg)</b> <b>Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals</b>						
<b>Fasted Bioequivalence Study (Study No.)</b>						
Parameter	Test	N	Reference	N	Ratio	90% C.I.
AUC0-t						
AUC <sub>∞</sub>						
Cmax						
<b>Fed Bioequivalence Study (Study No.)</b>						
Parameter	Test	N	Reference	N	Ratio	90% C.I.
AUC0-t						
AUC <sub>∞</sub>						
Cmax						

**Table 3B. Statistical Summary of the Comparative Bioavailability Data for Reference-Scaled Average BE Studies.**

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	S2wr	Criteria Bound	Method Used	Outcome
LAUCT	160.82%	147.20%	175.70%	0.0404	20.30%	FDA Draft Guidance on Progesterone (Recommended Feb 2011)	The test Diclofenac Sodium Topical Gel 1% (Treatment A) is not comparable to the reference Voltaren Gel (Treatment B) following a single 120 mg dose under fasting conditions.
LAUCI	162.65%	148.93%	177.64%	0.0453	21.54%	FDA Draft Guidance on Progesterone (Recommended Feb 2011)	
LCMAX	226.24%	Not Applicable	Not Applicable	0.0897	30.63%	FDA Draft Guidance on Progesterone (Recommended Feb 2011)	

**Table 4 Bioanalytical Method Validation**

<b>Information Requested</b>	<b>Data</b>
<b>Bioanalytical method validation report location</b>	N/A
<b>Analyte</b>	Diclofenac
<b>Internal standard (IS)</b>	Diclofenac-d4
<b>Method description</b>	This method involves the extraction of diclofenac and the internal standard from human EDTA K <sub>2</sub> plasma by solid phase extraction. Samples are kept frozen at -20°C prior to analysis and 0.500 mL of human EDTA K <sub>2</sub> plasma was used for analysis.
<b>Limit of quantitation (pg/mL)</b>	49.76 Partial validation 7
<b>Average recovery of drug (%)</b>	69.42, 67.11 and 68.08% Partial validation 7
<b>Average recovery of IS (%)</b>	71.40 Partial validation 7
<b>Standard curve concentrations (pg/mL)</b>	50.00, 100.00, 1000.00, 2000.00, 4000.00, 8000.00, 16000.00 and 20000.00 Partial validation 7
<b>QC concentrations (pg/mL)</b>	LLQC: 49.76, QC1: 149.28, QC2: 9952.00 and QC3: 14928.00 Partial validation 7
<b>QC Intraday precision range (%)</b>	%CV: 0.64 to 8.47 Partial validation 7
<b>QC Intraday accuracy range (%)</b>	%Bias: -8.75 to 0.06 Partial validation 7
<b>QC Interday precision range (%)</b>	%CV: 1.59 to 9.40

Information Requested	Data
	Partial validation 7
<b>QC Interday accuracy range (%)</b>	%Bias: -3.41 to 0.83 Partial validation 7
<b>Bench-top stability (hrs)</b>	22 Hours and 50 Minutes at room temperature Partial validation 6
<b>Stock stability (days)</b>	Analytes: 105 days at -20°C IS: 265 days at -20°C Partial validation 7 and partial validation 3 respectively
<b>Processed stability (hrs)</b>	120 hours and 16 minutes at room temperature Partial validation 7
<b>Freeze-thaw stability (cycles)</b>	4 cycles at -20°C Partial validation 6
<b>Long-term storage stability (days)</b>	133 days at -20°C Partial validation 8
<b>Dilution integrity</b>	QC3 diluted 1/2: CV (%) 1.41 %Nominal (%) 102.03% DQC diluted 1/20: CV (%) 3.07% Nominal (%) 99.69% Partial validation 4
<b>Selectivity</b>	No interfering peaks noted in blank plasma samples Partial validation 7

**Table 5. Summary of In Vitro Dissolution Studies**

**NOT APPLICABLE**

<b>Dissolution Conditions</b>		<b>Apparatus:</b>									
		<b>Speed of Rotation:</b>									
		<b>Medium:</b>									
		<b>Volume:</b>									
		<b>Temperature:</b>									
<b>Firm's Proposed Specifications</b>											
<b>Dissolution Testing Site (Name, Address)</b>											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)					Study Report Location
Study Report #:		Test Product	mg Tablet Capsule	12	Mean						
					Range						
					%CV						
Study Report #:		Reference Product	mg Tablet Capsule	12	Mean						
					Range						
					%CV						

**Table 6. Formulation Data**

Ingredients	Quantity in %w/w	Quantity mg/g	Quantity mg/day <sup>1</sup>
Diclofenac Sodium EP/USP	1.00	10.00	320.00
Isopropyl Alcohol USP	(b) (4)		
Carbomer Homopolymer Type C USP/NF (b) (4)			
Strong Ammonia Solution NF			
Cocoyl Caprylocaprate/ (b) (4)			
(b) (4) Mineral Oil USP			
Polyoxyl 20 Cetostearyl Ether/PH (b) (4)			
Propylene Glycol USP			
(b) (4) Fragrance			
(b) (4)			
Purified Water USP			
<b>Total</b>			
<p>(b) (4)</p> <p>QS = Quantity Sufficient</p> <p><sup>1</sup>Calculated based on the maximum daily dose of 32 g of gel.</p>			

**Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study**

Study No. 120049			
		Treatment Groups	
		Test Product N =46	Reference Product N =46
Age (years)	Mean ± SD	43 ± 13	43 ± 13
	Range	19 - 68	19 - 68
Age Groups	< 18	0	0
	18 – 40	20 (43.5%)	20 (43.5%)
	41 – 64	24 (52.2%)	24 (52.2%)
	65 – 75	2 (4.3%)	2 (4.3%)
	> 75	0	0
Sex	Male	17 (37.0%)	17 (37.0%)
	Female	29 (63.0%)	29 (63.0%)
Race	Asian	0	0
	Black	2 (4.3%)	2 (4.3%)
	White	44 (95.7%)	44 (95.7%)
	Other	0	0
Ethnicity	Not Hispanic	40 (87.0%)	40 (87.0%)
	Hispanic	6 (13.0%)	6 (13.0%)
BMI	Mean ± SD	25.28 ± 2.49	25.28 ± 2.49
	Range	20.55 - 29.69	20.55 - 29.69
Height	Mean ± SD	169.4 ± 8.6	169.4 ± 8.6
	Range	148.0 - 185.5	148.0 - 185.5
Weight	Mean ± SD	72.93 ± 11.64	72.93 ± 11.64
	Range	51.30 - 96.40	51.30 - 96.40

BMI: Body Mass Index; n: Number of observations; SD: Standard deviation.

Other: Multi-racial, American Indian or Alaska native, Native Hawaiian or Other Pacific Islander.

Test (A) = Amneal Pharmaceuticals, U.S.A., diclofenac sodium 12 g of 1% topical gel.

Reference (B) = Novartis, U.S.A. (Voltaren Gel), diclofenac sodium 12 g of 1% topical gel.

**Table 8. Incidence of Adverse Events in Individual Studies**

Body System / Adverse Event	Reported Incidence by Treatment Groups			
	Fasted Bioequivalence Study Study No. 120049			
	Test N =47	Reference N =48	Reference (first application) N=48	Reference (second application) N=46
<b>Body as a Whole</b>	<b>10 (21.3%)</b>	<b>14 (29.2%)</b>	<b>11 (22.9%)</b>	<b>4 (8.7%)</b>
Fever	1 (2.1%)			
Flu synd		1 (2.1%)	1 (2.1%)	
Headache	6 (12.8%)	5 (10.4%)	5 (10.4%)	1 (2.2%)
Inject site react	3 (6.4%)	4 (8.3%)	3 (6.3%)	1 (2.2%)
Pain		2 (4.2%)		2 (4.2%)
Pain abdo	1 (2.1%)			
Pain back	2 (4.3%)	1 (2.1%)		1 (2.2%)
Pain inject site	3 (6.4%)	2 (4.2%)	2 (4.2%)	
<b>Cardiovascular System</b>	<b>1 (2.1%)</b>			
Vasodilat	1 (2.1%)			
<b>Digestive System</b>	<b>1 (2.1%)</b>	<b>4 (8.3%)</b>	<b>2 (4.2%)</b>	<b>2 (4.3%)</b>
Anorexia		1 (2.1%)		1 (2.2%)
Constip		1 (2.1%)	1 (2.1%)	
Diarrhea		2 (4.2%)	1 (2.1%)	1 (2.2%)
Nausea		1 (2.1%)	1 (2.1%)	
Vomit	1 (2.1%)			
<b>Hemic and Lymphatic System</b>		<b>1 (2.1%)</b>		<b>1 (2.2%)</b>
Wbc abnorm		1 (2.1%)		1 (2.2%)
<b>Musculoskeletal System</b>		<b>1 (2.1%)</b>		<b>1 (2.2%)</b>
Myalgia		1 (2.1%)		1 (2.2%)

Body System / Adverse Event	Reported Incidence by Treatment Groups			
	Fasted Bioequivalence Study Study No. 120049			
	Test N =47	Reference N =48	Reference (first application) N=48	Reference (second application) N=46
<b>Nervous System</b>	<b>10 (21.3%)</b>	<b>13 (27.1%)</b>	<b>10 (20.8%)</b>	<b>11 (23.9%)</b>
Dizziness	1 (2.1%)			
Hypesthesia	1 (2.1%)			
Neuritis periph		1 (2.1%)	1 (2.1%)	
Somnolence	8 (17.0%)	12 (25.0%)	9 (18.8%)	11 (23.9%)
<b>Respiratory System</b>		<b>7 (14.6%)</b>	<b>5 (10.4%)</b>	<b>2 (4.3%)</b>
Pharyngitis		1 (2.1%)	1 (2.1%)	
Rhinitis		6 (12.5%)	4 (8.3%)	2 (4.3%)
<b>Skin and Appendages</b>	<b>1 (2.1%)</b>	<b>3 (6.3%)</b>	<b>2 (4.2%)</b>	<b>1 (2.2%)</b>
Applicat site react	1 (2.1%)	2 (4.2%)	2 (4.2%)	
Derm contact		1 (2.1%)		1 (2.2%)
Rash	1 (2.1%)			
<b>Urogenital System</b>	<b>1 (2.1%)</b>	<b>1 (2.1%)</b>		<b>1 (2.2%)</b>
Albuminuria		1 (2.1%)		1 (2.2%)
Dysmenorrhea	1 (2.1%)			
<b>Total</b>	<b>17 (36.2%)</b>	<b>30 (62.5%)</b>	<b>23 (47.9%)</b>	<b>19 (41.3%)</b>

COSTART: Coding Symbols for a Thesaurus of Adverse Reaction Terms.

Test (A) = Amneal Pharmaceuticals, U.S.A., diclofenac sodium 12 g of 1% topical gel.

Reference (B) = Novartis, U.S.A. (Voltaren Gel), diclofenac sodium 12 g of 1% topical gel.

**Table 9. Reanalysis of Study Samples**

Study No. 120049AFIZ								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic <sup>1</sup>	0	0	0.00	0.00	0	0	0.00	0.00
Unacceptable internal standard response	1	1	0.03	0.03	1	1	0.03	0.03
Loss of sample during processing	1	4	0.03	0.12	1	4	0.03	0.12
Internal standard response lower than 5% of the mean internal standard response	1	1	0.03	0.03	1	1	0.03	0.03
Sample concentration above the upper limit of quantitation	100	16	2.98	0.48	100	16	2.98	0.48
Sample reanalyzed to obtain a confirming value	6	7	0.18	0.21	2	2	0.06	0.06
Sample volume insufficient for analysis	0	1	0.00	0.03	0	0	0.00	0.00
Sample reassayed or reinjected by error	0	4	0.00	0.12	0	0	0.00	0.00
Disregarded value	2	0	0.06	0.00	0	0	0.00	0.00
Total	111	34	3.31	1.01	105	24	3.13	0.72

1 - If no repeats were performed for pharmacokinetic reasons, insert "0.0."

Treatment A (Test): Diclofenac Sodium Topical Gel, 1% (Amneal Pharmaceuticals, USA)

Treatment B (Reference): Voltaren ® Gel (diclofenac sodium topical gel) (Novartis, USA)

**Table 10. Study Information**

<b>Study Number</b>	120049							
<b>Study Title</b>	Randomised, open-label, 3-way reference-replicated crossover, bioequivalence study of diclofenac sodium topical gel 1% (test) and voltaren gel (diclofenac sodium gel) (reference) following a single dose of 12 g in healthy subjects under fasting conditions							
<b>Study Type</b>	<input checked="" type="checkbox"/> In Vivo BE	<input type="checkbox"/> In Vitro BE	<input type="checkbox"/> Permeability	<input type="checkbox"/> Other (Specify)				
<b>Submission Location:</b>								
<b>Study Report</b>					N/A			
<b>Validation Report</b>					N/A			
<b>Bioanalytical Report</b>					N/A			
<b>Clinical Site (Name, Address, Phone #, Fax #)</b>	PharmaNet 2500, rue Einstein Québec (Québec), Canada G1P 0A2 Tel.: 418-527-4000 Fax: 418-527-3456							
<b>Principal Clinical Investigator (Name, Email)</b>	Josée Villeneuve, MD. josee.villeneuve@inventivhealth.com							
<b>Dosing Dates</b>	Period 1: 2012-03-20 (Subjects (b) (6))	2012-03-22 (Subjects (b) (6))	Period 2: 2012-04-10 (Subjects (b) (6))	2012-04-12 (Subjects (b) (6))				
	Period 3: 2012-05-01 (Subjects (b) (6))	2012-05-03 (Subjects (b) (6))						
<b>Analytical Site (Name, Address, Phone #, Fax #)</b>	(b) (4)							
<b>Analysis Dates</b>	2012-05-14 to 2012-05-26							
<b>Principal Analytical Investigator (Name, Email)</b>	(b) (4) B. Sc. (b) (4)							
<b>Sample Storage :</b>								
<b>(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)</b>	67 days (2012-03-20 to 2012-05-26)							
<b>(b) Temperature Range (e.g., -20° C to -80° C)</b>	-20°C							
<b>Long-Term Storage Stability Coverage (no. days @ temp °C)</b>	133 days at -20°C							
<b>LTSS Data Location</b>	N/A							

**Table 11. Product Information**

Product	Test		Reference	
<b>Treatment ID</b>				
<b>Product Name</b>	Diclofenac sodium		Voltaren® Gel (diclofenac sodium)	
<b>Manufacturer</b>	Amneal Pharmaceuticals		Novartis Pharma produktion GmbH, Germany	
<b>Batch/Lot No.</b>	PW-ST-12001A		10115876	
<b>Manufacture Date</b>	03/03/12		N/A	
<b>Expiration Date</b>	N/A		07/14	
<b>Strength</b>	1% w/w		1% w/w	
<b>Dosage Form</b>	Topical gel		Topical gel	
<b>Bio-batch Size</b>	N		N/A	
<b>Production Batch Size</b>	N/A		N/A	
<b>Potency</b>	102.5%		98.9%	
<b>Content Uniformity (mean, %CV)</b> <i>Uniformity in Containers</i>	Top	101.1%	Top	99.9%
	Middle	101.3%	Middle	99.0%
	Bottom	102.0%	Bottom	98.5%
	Mean	101.5%	Mean	98.8%
	RSD:	0.5%	RSD:	0.3%
<b>Dose Administered</b>	12 g of a 1% topical gel		12 g of a 1% topical gel	
<b>Route of Administration</b>	Topical		Topical	

**Table 12. Dropout Information**

Study No. 120049				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b) (6)	2012-04-11 11:50 / Reference / Subject elected to withdraw due to personal reason (work).	1	No	Not applicable
(b) (6)	2012-05-02 13:55 / Test / Subject elected to withdraw due to AE (Pain abdo).	2	No	Not applicable

Test (A) = Amneal Pharmaceuticals, U.S.A., diclofenac sodium 12 g of 1% topical gel.  
 Reference (B) = Novartis, U.S.A. (Voltaren Gel), diclofenac sodium 12 g of 1% topical gel.

**Table 13. Protocol Deviations**

Subject Number	Treatment	Protocol Deviation
<input type="checkbox"/> <b>Study medication, Dosing, and Randomisation</b>		
(b) (6)	B	<input type="checkbox"/> During Period 1 gel application procedures, a small amount of gel was lost since it was applied on the plate. Since the amount of gel could not be assessed because too small, the amount of lost diclofenac sodium should not be significant and this should have a minimal impact if any on the PK output of the study.
<b>Study Restrictions</b>		
(b) (6)	B	This subject consumed 25 mL of protein shake within 7 days prior to study drug application in Period 3. However, there is no impact since elimination of protein shake should be finished at the time of drug application.
(b) (6)	A	This subject left the clinic unit after his 48.0-hour blood draw without having his application sites washed by clinical staff in Period 3. The washing of the drug application site was aimed to prevent from transferring non-absorbed gel from subjects enrolled in the study to other people close to them, through direct contact. This action was scheduled to be done by study staff. Since this subject confirmed that he washed gel application sites (approximately a half hour late), this should not have any impact on the study output or jeopardised the safety of people close to him.
(b) (6)	A	This subject consumed 2 bites of chocolate cake between the 120 and 144-hour post-dose blood draws in Period 1. This deviation should have a minimal impact, if any, on the PK profile of diclofenac since median $T_{max}$ is expected within 24 hours post-gel application and this is a topical formulation.

Subject Number	Treatment	Protocol Deviation
(b) (6)	B	This subject reported the adverse event “Sunburn” at face and chest beginning 1 day prior to drug application in Period 1. However, dosing sites were not concerned by this adverse event. Therefore, there should be no significant impact on the study drug absorption. No impact on the study output for this subject.
	B	This subject consumed approximately 15 mL of pineapple juice between the 96.0 and 120-hour post-dose blood draws in Period 3. This should have minimal impact on the PK results of the study since the absorption phase of diclofenac was completed at that time and the elimination almost finished. Moreover, this was a very little amount of pineapple juice.
<input type="checkbox"/> <b>Study Samples (Pharmacokinetic)</b>		
(b) (6)	A, B	These subjects’ 1.00 and 36.0-hour post-dose blood samples were centrifuged as much as 119 minutes 16 seconds after blood collection in Period 1. As the bioanalytical method is not validated for this delay between samples collection and centrifugation, these samples would not be used for statistical analyses.
<input type="checkbox"/> <b>Safety measurements</b>		
(b) (6)	Study exit	This subject’s study exit procedures were performed 26 days after her last participation in the study. Subject’s laboratory results for study exit procedures were within normal range or judged not clinically significant by a physician. In addition, no adverse events were reported by the subject over the course of the study. Subject’s safety was not compromised.

PK: Pharmacokinetic.

Test (A) = Amneal Pharmaceuticals, U.S.A., diclofenac sodium 12 g of 1% topical gel.

Reference (B) = Novartis, U.S.A. (Voltaren Gel), diclofenac sodium 12 g of 1% topical gel.

Some deviations in the blood sampling schedule occurred during the study. A collection time was considered to be in deviation to the protocol if:

- Pre dose collection: not performed prior to drug application.
- Post dose collections during confinement (from 1.00 to 48.0 hour post dose): sample not collected, collected 30 seconds or more from scheduled time, or collection time considered inconclusive;
- Post-dose collections obtained during return visits (from 60.0 to 240-hour post-dose): sample not collected, collected more than 30 minutes from scheduled time, or collection time considered inconclusive.

There is no impact on the statistical analyses due to these time deviations since only the actual collection times were used in the PK calculations.

The QI judged the reported deviations were unlikely to have affected the results and conclusions of the study.

**Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses**

Bioequivalence Study No. 120049AFIZ Diclofenac								
Parameter	Standard Curve Samples							
Concentration (pg/mL)	50.00	100.00	1000.00	2000.00	4000.00	8000.00	16000.00	20000.00
Interday Precision (%CV)	6.19	6.31	2.37	1.53	1.83	1.90	1.86	2.40
Interday Accuracy (%)	1.08	-2.48	1.33	0.74	1.16	-0.99	-0.65	-0.53
Linearity	0.9932 to 0.9994							
Linearity Range (pg/mL)	250.00 to 50000.00							
Sensitivity/ LOQ (pg/mL)	250.00							
Bioequivalence Study No. 120049AFIZ Diclofenac								
Parameter	Quality Control Samples							
Concentration (pg/mL)	149.28	1492.80	9952.00	14928.00				
Interday Precision (%CV)	9.11	39.76	5.33	2.73				
Interday Accuracy (%)	0.64	3.89	0.77	-0.01				

**Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples**

SOP No.	Effective Date of SOP	SOP Title
	(b) (4)	Sample Reassays and Reporting of Final Concentrations

**Table 16. Composition of Meal Used in Fed Bioequivalence Study**

Not Applicable

<b>Standard FDA Meal Used?</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
<b>If No, then meal components and composition is listed in the tables below</b>					
<b>Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study</b>					
<b>Ingredients</b>	<b>Amount (g)</b>	<b>Energy (kcal)</b>	<b>Protein (kcal)</b>	<b>Fat (kcal)</b>	<b>Carbohydrate (kcal)</b>
<b>TOTAL</b>					
<b>PERCENTAGE</b>					

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 208077

APPLICANT: Amneal Pharmaceuticals

DRUG PRODUCT: Diclofenac Sodium Topical Gel, 1% w/w

The Division of Bioequivalence II has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns 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 Stier, Ph.D.  
Director, Division of Bioequivalence II  
Office of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**4.7 Outcome Page**

ANDA: 208077

**Reviewer:** Liu, Yajun

**Date Completed:**

**Verifier:** ,

**Date Verified:**

**Division:** Division of Bioequivalence

**Description:** Diclofenac Sodium Topical Gel, 1% w/w

---

*Productivity:*

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
25589	12/19/2014	Bioequivalence Study (REGULAR)	Fasting Study	1	1
25589	12/19/2014	Bioequivalence Study (REGULAR)	Failed Extra Study	1	1
				<b>Total:</b>	<b>2</b>

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 208077Orig1s000**

**OTHER REVIEWS**

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

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DATE: February 19, 2016

TO: Dale P. Conner, Pharm.D.  
Acting Director  
Office of Bioequivalence  
Office of Generic Drugs

FROM: Melkamu Getie-Kebtie, Ph.D., R.Ph.  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.  
Director  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Addendum** to Review of "For Cause" Clinical  
Establishment Inspection Report (EIR), covering **ANDA  
208077**, Diclofenac Sodium Topical Gel, 1%, sponsored  
by Amneal Pharmaceuticals

This is an addendum to the EIR Review memo finalized on January 27, 2016. This addendum is to update the list of subjects at the Andhra Medical College and their randomization numbers, who are recommended to be excluded in efficacy outcome determination (refer to Page 7-8 of this EIR memo). Please note that (b) (6) is added to the list.

**Inspection summary:** At the request of the Office of Bioequivalence, the Office of Study Integrity and Surveillance (OSIS) arranged "For Cause" inspections of the clinical portion of the following study at B.J Medical College & Hospital, Ahmedabad, India; Andhra Medical College, Visakhapatnam, India; and Centre for Knee Surgery, Vadodara, India. This is based on suspicion that the endpoint data appear "too good to be true." No form FDA 483 was issued at Andhra Medical College and Centre for Knee Surgery. A one-item FDA 483 was issued at Andhra Medical College & Hospital.

**Reviewer Recommendation:** This reviewer recommends that data from the BJ Medical College & Hospital are not acceptable for further Agency review, because it is not possible to confirm whether 101

of 103 study subjects enrolled in the study met the inclusion/exclusion criteria prior to randomization. The reviewer also recommends exclusion of data from the Andhra Medical College for 14 subjects due to insufficient verification of ages of subjects to confirm eligibility and to meet inclusion/exclusion criteria.

**Study Number:** AM-DCG-001

**Study Title:** "Multi-Center, Double-Blind, Vehicle-Controlled, Parallel-Group Study Comparing a Generic Diclofenac Sodium Topical Gel, 1% to Voltaren® Gel (Diclofenac Sodium Topical Gel), 1% in the Treatment of Subjects with Osteoarthritis of the Knee"

**Study dates:** 04/09/2014 - 09/03/2014

The Division of Clinical Review identified the following three sites for 'For Cause' inspection out of 19 clinical study sites:

**B.J Medical College & Hospital  
Ahmedabad, Gujarat, India  
Investigator: Dr. Ankit Kedia**

**Andhra Medical College  
Visakhapatnam, Andhra Pradesh, India  
Investigator: Dr. Pardha Saradhi**

**Centre for Knee Surgery  
Vadodara, Gujarat, India  
Investigator: Dr. Bharath Mody**

ORA Investigator Mrs. Janete Guardia conducted the inspection at the three sites. The audits compared the sites' source documents to data listed on the Case Report Forms (CRFs) and randomization schedule to test article dispensing log. The audit also included review of Informed Consent Forms (ICFs) for screened and enrolled subjects, procedures for handling and storage of test articles, IEC approval of protocol, site initiation visit report, site personnel responsibility and training log, clinical study agreement, Monitor visit confirmation letters and site qualification visit.

Mrs. Guardia collected reserve samples of Test article, Reference article, and Vehicle (Placebo) and sent the samples to CDER's Division of Pharmaceutical Analysis (DPA) laboratory in St. Louis, MO for testing.

**Clinical site 1: B.J Medical College & Hospital, Ahmedabad, Gujarat, India**

Mrs. Guardia performed the inspection at this site from 21-25 November 2015. Since Dr. Ankit Kedia, the Principal Investigator, has left the hospital, Mrs. Guardia conducted the inspection in the presence of Dr. Jalak Patel, the Clinical Research Coordinator. At the conclusion of the inspection, Mrs. Guardia issued FDA Form 483 (**Attachment 1**). The firm's response to the observations is attached (**Attachment 2**). The Form 483 observation, the Clinical Investigator's responses, and OSIS's evaluation follow:

**1) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specifically,**

- a) Subject (b) (6) was screened on 17/July/2014 and source documents show that a Target X-ray was conducted on 17/July/2014; however, the screening visit notes do not indicate that the subject provided an x-ray record of left and right view of knee (lower extremity) taken at another facility on 28/04/2014. The subject was enrolled, randomized and completed the study on 21/August/2014 as Subject number (b) (6)

Mrs. Guardia noted that, during the inspection, she requested a copy of the X-ray, but Dr. Patel stated that photocopies of the X-rays would not be visible. Mrs. Guardia exhibited a photograph of the X-ray to document the date and patient information for Subject (b) (6).

In response to Form FDA 483, Dr. Haresh Bhalodiya, the Sub-Investigator for this study, acknowledged that the X-ray evaluation statement released by the principal investigator on 17 July 2014 inadvertently failed to indicate the evaluation was based on the review of the 28 April 2014 X-ray result provided by the subject as a supportive source document. As a corrective action, a "Note to File" has been created for Subject (b) (6) describing a copy of knee X-ray taken at another facility was used during screening visit. The firm submitted a copy of the "Note to File" along with the written response.

**OSIS Evaluation:** The firm's response is acceptable.

- 1) b) Subject (b) (6) was screened and enrolled into the study on 09/June/2014. Source documents show the subject was

randomized with number (b) (6) on 16/June/2014 at Visit 2, but study records for Visit 3 and Visit 4 show that the subject was randomized with number (b) (6)

In his written response, Dr. Bhalodiya acknowledged that there was a typographic error in the Visit 2 source document for Subject (b) (6) and confirmed that the correct randomization number for Subject (b) (6) is (b) (6)

**OSIS Evaluation:** The firm's response is acceptable.

c) Your clinical facility screened 103 subjects for Study AM-DCG-001, 99 subjects were enrolled and randomized in the study and source records show that all 99 subjects completed the study with each subject missing 1 application dose in this 4-week study trial as noted in the "Patient Diary Part 1 and Part 2" booklets provided to the subjects upon enrollment into the study.

Mrs. Guardia noted that the subjects enrolled and randomized in the study were provided a Patient Diary Part I at baseline visit and Part II at Visit 3 and they were required to complete the diary four times daily for the course of the study. Mrs. Guardia observed that the dose application times recorded in several of the subject diaries were similar and the contents of the diaries showed similarity in handwriting raising suspicion that the diaries may have been completed by a single person. It was also interesting to note that no application dose was missing by any subject, except the first application, which was missing for all 99 subjects.

Dr. Bhalodiya stated that all the subjects enrolled at this site missed 1 application (first morning application on the day they started treatment) due to site specific outpatient department clinic schedule. A "Note to File" enclosed with the Form FDA 483 response clarifies that, on the day of the study visit, the subjects have to stay until around 12 pm at the clinic to complete their study specific activities. Their dosing schedule only allowed them to apply the medication three times on that day, i.e., around after lunch, after dinner, and before bed. Therefore, all 99 subjects enrolled at this site missed their first morning dose on the days of their scheduled study visits.

**OSIS evaluation:** Since the missed dose applies to all the treatment categories (Vehicle, Test, and Reference), its

impact to the study outcome is negligible. In addition, the study protocol AM-DCG-001, page 24, states: "Subjects will be considered compliant with the assigned study treatment if they used at least 75% and no more than 125% of study treatment doses." The occurrence of one missing application dose during the course of the study didn't violate the study protocol. However, it is concerning that several of the diaries might have been completed by a person other than the study subjects. The absence of missing applications, other than the first application, by all study subjects is contrary to observations at other sites and raises further doubt to the authenticity of the diaries. Nevertheless, this reviewer found no strong evidence of record falsification to recommend rejection of data from these subjects.

**Discussion items**

In addition to the FDA 483 observations noted above, Mrs. Guardia discussed the following items with the management at the close-out meeting.

**Discussion item 1. Inadequate documentation of "Note to File" regarding late laboratory reports for enrolled subjects.**

Mrs. Guardia noted that the laboratory report results of [REDACTED] (b) (6) [REDACTED] (b) (6) were dated a month or longer from when the subject was randomized into the study.

Examples include:

- Subject [REDACTED] (b) (6) - blood sample collected on 05/29/2014, reported on 07/04/2014 and reviewed by Dr. Kedia on 08/02/2014
- Subject [REDACTED] (b) (6) - blood sample collected on 06/02/2014, reported on 07/04/2014 and reviewed by Dr. Kedia on 08/02/2014
- Subject [REDACTED] (b) (6) - blood sample collected on 06/02/2014, reported on 07/04/2014 and reviewed by Dr. Kedia on 08/02/2014
- Subject [REDACTED] (b) (6) - blood sample collected on 06/02/2014, reported on 07/04/2014 and reviewed by Dr. Kedia on 08/02/2014

A "Note to File" obtained in the Investigator's binder dated 09/08/2014 states a delay in the Lab reports and hard copies thereof for the 15 subjects mentioned above. Mrs.

Guardia stated that there was no documentation to indicate that the Lab reports were submitted via telephone or otherwise to Dr. Kedia prior to randomization of subjects.

**Discussion item 2. Inadequate identification of the X-rays for all 103 subjects enrolled in the study. X-rays were labeled using "hospital" tape or "post-it" sticky notes with the subject number. The X-rays did not include a date it was taken and subjects who provided third party X-rays, the information was not adequately documented in the subject's study record.**

Mrs. Guardia stated the labeling procedure of the subjects' X-rays was inadequate in that several X-rays were not labelled with subject identification and the date that the X-ray was taken. This reviewer was informed by Mrs. Guardia via e-mail that all 103 subjects except for two (Subjects (b) (6) X-ray records did not have adequate identification. Subjects' (b) (6) X-rays were taken at another facility prior to enrollment and the X-ray indicated the date, time, and patient information. These subjects' X-rays were the only that had detailed information about when/where the X-rays were taken. The remaining X-rays had only a sticky tape or post-it note as shown on **Attachment 3**. Dr. Patel was not able to provide neither the date the X-rays were taken nor a legible copy thereof.

**OSIS Evaluation:** The Lab reports of the 15 subjects noted above (Discussion item 1) couldn't be verified by source document. All X-ray records, except 2, don't show subject identification and date the X-rays were taken (Discussion item 2). Based on the available evidence, it is not possible to confirm whether proper assessment was conducted to ensure 101 of 103 subjects enrolled in the study met the inclusion/exclusion criteria prior to randomization.

**Clinical site 2: Andhra Medical College, Visakhapatnam, Andhra Pradesh, India**

Mrs. Guardia conducted inspection at this site from 14-18 December 2015. At the conclusion of the inspection, no FDA 483 was issued. However, the following items were discussed with the management.

**Discussion item 1. Subject (b) (6) dispensing log was a copy and not able to be un-blinded. A "Note to File" documented that the**

dispensing log for this subject was inadvertently lost and a copy of the blinded dispense log previously submitted to the sponsor was obtained to remain in the Master File.

Mrs. Guardia noted that Dr. Saradhi, Principal Investigator, claimed the dispensing log might have been lost along with other records after a cyclone hit the town in October 2015. The site informed the Sponsor about the lost document and the Sponsor sent a copy of the original blinded record. According to the randomization schedule, the subject received the Test treatment and has a change in WOMAC score of -1 (13 to 12).

**OSIS Evaluation:** This reviewer believes that this is an isolated incident and inclusion of this subject's data is unlikely to affect the overall study outcome.

Discussion item 2. Source documents for 13 subjects did not contain identification records and a "Note to File" dated 02/SEP/2014 indicated repeated attempts to obtain subject id's. However, subjects completed the study but no documentation of how or when subjects were asked to provide id's for any of the 4 visits. In addition, Subject (b) (6) was enrolled in the study and ID provided states year of birth (b) (6)

and there were no other documents to verify this discrepancy in the subject's age. A "Note to File" dated 02/SEP/2014 states that date of birth recorded in signed ICF was considered the actual date of birth for the purpose of the study. (u) (u)

Mrs. Guardia noted that identification records include personal information, such as age, which is a crucial component of the inclusion/exclusion criteria. She indicated no source document, such as government issued ID, was available for these subjects to verify their age. Information including age was recorded on the Informed Consent, but not verifiable by source document. The subjects that were enrolled based on the date of birth documented on the Informed Consent include: (b) (6)

The Principal Investigator stated that it was difficult to obtain proper documentation from these subjects. Mrs. Guardia indicated that some subjects had identifications that stated a different year of birth from the year of birth the subject would enter on the Informed Consent Form. (b) (6)

**OSIS Evaluation:** The absence of source document to verify the personal identification information is a major concern as it is

not possible to ascertain a large number of study subjects at this site indeed met the inclusion criteria. Subject (b) (6) completed the study despite his/her age according to the ID made him/her ineligible. Therefore, this reviewer recommends that data from these 14 subjects be excluded from efficacy outcome determination. The Randomization number corresponding to each Subject number is listed in the table below.

Subject No.	Randomization No.
(b) (6)	

**Discussion item 3. Three subjects enrolled in the study were illiterate and signed the ICF with a thumbprint. However, the Patient Diaries were completed and source documents did not indicate how or who completed the diaries.**

(b) (6) ed that Dr. Saradhi explained when subjects (b) (6) were identified to be illiterate; each subject was accompanied by a family member who completed the diary. However, the subject source documents did not document the identity of the person who assisted the subjects in completing the diaries. It is not clear whether this procedure was employed across all study sites. The study Protocol didn't define a specific procedure as to who should help subjects apply the investigational products and/or complete their diaries in situations when they couldn't. Note that information recorded on the diaries include the date and time of study treatments, any missed treatments, rescue medication use, concomitant medication use, and the occurrence of adverse events (AEs) or intolerability to study medication. Information recorded on the diaries wasn't used for efficacy assessment. According to Mrs. Guardia, responses to the five efficacy assessment questions

were completed by study subjects except for those who are illiterate or otherwise unable to do by themselves. For these, clinic staff interviewed and completed the assessment.

**Discussion item 4. Three subjects [REDACTED] (b) (6) were enrolled in the study and completed the Patient Diaries. These subjects were enrolled on the same day (07/17/2014) and after reviewing the Patient Diaries all six diaries had similar handwriting.**

Mrs. Guardia noted that the hand-writing in the diaries did not match the hand-writing on the Informed Consent Form filled out and signed by subjects.

**OSIS Evaluation:** The diaries of the six subjects noted above (Discussion items 3 & 4) might have been completed by a person other than the study subjects raising concern about the authenticity of the diaries. The authenticity of the diaries doesn't necessarily impact the efficacy determination (OA assessment with WOMAC score) as the efficacy assessments weren't recorded in the diaries. However, it is not possible to ensure whether the investigational products were correctly applied especially by illiterate subjects.

**Clinical site 3: Centre for Knee Surgery, Vadodara, Gujarat, India**

Mrs. Guardia and Mr. Solomon Yimam, International Policy Analyst, conducted inspection at this site from 8-11 December 2015. No FDA 483 was issued. However, the following item was discussed with the management.

**Discussion item 1: A protocol violation occurred for one subject that did not meet inclusion/exclusion criteria but was enrolled and completed the study. The event was documented as a protocol deviation and noted it was due to laboratory results received late by the study site.**

Mrs. Guardia noted a record of protocol deviation on the Protocol Deviation Log noting that Subject [REDACTED] (b) (6) [REDACTED] (b) (4) value is more than 2 times the upper limit of normal and did not meet inclusion criteria of the protocol. The reason for the deviation was noted as the laboratory report being received late after the subject had completed the study. Upon review of the subject's source documents, the ORA Investigators observed that the blood sample was collected on 14 May 2014 and results were reported on 15 May 2014. Subsequently, the report was reviewed by the Sub-Investigator on 21 May 2014. The CRF indicates that

the subject received the first application dose on 22 May 2014 and the last application on 19 June 2014. Therefore, the timeline and documentation of the dates did not correlate with the reason noted in the Protocol Deviation Log. This subject's data were not submitted by the Sponsor

**OSIS Evaluation:** By enrolling a subject who doesn't meet the inclusion criteria; the Investigator violated the study protocol. However, data from this subject wasn't included in the efficacy assessment. Therefore, data integrity will not be affected by this protocol violation.

**Conclusions:**

Following the above inspections, this reviewer recommends that data from the BJ Medical College & Hospital are not acceptable for further Agency review, because it is not possible to confirm whether 101 of 103 study subjects enrolled in the study met the inclusion/exclusion criteria prior to randomization. The reviewer also recommends exclusion of data from the Andhra Medical College for 14 subjects due to lack of proper verification of age of subjects to confirm eligibility to meet inclusion/exclusion criteria.

**Final Classifications:**

**BJ Medical College & Hospital: VAI**

**Andhra Medical College: VAI**

**Centre for Knee Surgery: NAI**

CC:

OTS/OSIS/Kassim/Taylor/Kadavil/Fenty-Stewart/Nkah

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Cho

OTS/OSIS/DGDBE/Haidar/Skelly/Choi

OGD/OB/Conner

ORA/Guardia

Draft: 1/27/16, 2/19/16

Edit: MFS 1/27/16, 2/19/2016; SHH 02/03/2016

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good

Laboratory Practice Compliance/INSPECTIONS/BE Program  
/Clinical Sites

/BJ Medical College & Hospital, Ahmedabadrat, India

/Andhra Medical College, Visakhapatnam, India

/Centre for Knee Surgery, Vadodara, India

OSI file# BE6828

**FACTS: 11555101**

Melkamu Getie-Kehtie, Ph.D., R.Ph.  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance (OSIS)

Seongeun (Julia) Cho, Ph.D.  
Director  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance (OSIS)

# **Attachment 1**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER  7520 Standish Place (HFD-45) Rockville, MD 20855-2773 (301) 594-0020 Fax: (301) 594-1204  Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION  11/21/2015 - 11/25/2015
	FEI NUMBER  3007582225

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED  
**TO: Dr. Jalak Patel, Clinical Research Coordinator**

FIRM NAME  B.J. Medical College & Civil Hospital, Dept. of Orthopedics	STREET ADDRESS  Hospital Road, Haripura, Asarwa
CITY, STATE AND ZIP CODE  Ahmedabad, Gujarat 380016 INDIA	TYPE OF ESTABLISHMENT INSPECTED  Hospital/Clinical Facility

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) (WE) OBSERVED:

**OBSERVATION 1**

Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically,

a) Subject (b) (6) was screened on 17/July/2014 and source documents show that a Target X-ray date was conducted on 17/July/2014, however the screening visit notes do not indicate that the subject provided an x-ray record of left and right view of knee (lower extremity) taken at another facility on 28/04/2014. The subject was enrolled, randomized and completed the study on 21/August/2014 as Subject number (b) (6)

b) Subject (b) (6) was screened and enrolled into the study on 09/June/2014. Source documents show the subject was randomized with number (b) (6) on 16/June/2014 at Visit 2, but study records for Visit 3 and Visit 4 show that the subject was randomized with number (b) (6)

c) Your clinical facility screened 103 subjects for Study AM-DCG-001, 99 subjects were enrolled and randomized in the study and source records show that all 99 subjects completed the study with each subject missing 1 application dose in this 4-week study trial as noted in the "Patient Diary Part 1 and Part 2" booklets provided to the subjects upon enrollment into the study.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE ( <i>Print or Type</i> )	DATE ISSUED
		Janete F. Guardia, Investigator	11/25/2015

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."

# Attachment 2

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

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DATE: January 27, 2016

TO: Dale P. Conner, Pharm.D.  
Acting Director  
Office of Bioequivalence  
Office of Generic Drugs

FROM: Melkamu Getie-Kebtie, Ph.D., R.Ph.  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Acting Director  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of "For Cause" Clinical Establishment  
Inspection Report (EIR), covering **ANDA 208077**,  
Diclofenac Sodium Topical Gel, 1%, sponsored by Amneal  
Pharmaceuticals

**Inspection summary:** At the request of the Office of Bioequivalence, the Office of Study Integrity and Surveillance (OSIS) arranged "For Cause" inspections of the clinical portion of the following study at B.J Medical College & Hospital, Ahmedabad, India; Andhra Medical College, Visakhapatnam, India; and Centre for Knee Surgery, Vadodara, India. This is based on suspicion that the endpoint data appear "too good to be true." No form FDA 483 was issued at Andhra Medical College and Centre for Knee Surgery. A one-item FDA 483 was issued at Andhra Medical College & Hospital.

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**Study Number:** AM-DCG-001

**Study Title:** "Multi-Center, Double-Blind, Vehicle-Controlled, Parallel-Group Study Comparing a Generic Diclofenac Sodium Topical Gel, 1% to Voltaren® Gel (Diclofenac Sodium Topical Gel), 1% in the Treatment of Subjects with Osteoarthritis of the Knee"

**Study dates:** 04/09/2014 - 09/03/2014

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Investigator: Dr. Ankit Kedia**

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Visakhapatnam, Andhra Pradesh, India  
Investigator: Dr. Pardha Saradhi**

**Centre for Knee Surgery  
Vadodara, Gujarat, India  
Investigator: Dr. Bharath Mody**

ORA Investigator Mrs. Janete Guardia conducted the inspection at the three sites. The audits compared the sites' source documents to data listed on the Case Report Forms (CRFs) and randomization schedule to test article dispensing log. The audit also included review of Informed Consent Forms (ICFs) for screened and enrolled subjects, procedures for handling and storage of test articles, IEC approval of protocol, site initiation visit report, site personnel responsibility and training log, clinical study agreement, Monitor visit confirmation letters and site qualification visit.

Mrs. Guardia collected reserve samples of Test article, Reference article, and Vehicle (Placebo) and sent the samples to CDER's Division of Pharmaceutical Analysis (DPA) laboratory in St. Louis, MO for testing.

**Clinical site 1: B.J Medical College & Hospital, Ahmedabad, Gujarat, India**

Mrs. Guardia performed the inspection at this site from 21-25 November 2015. Since Dr. Ankit Kedia, the Principal Investigator, has left the hospital, Mrs. Guardia conducted the inspection in the presence of Dr. Jalak Patel, the Clinical Research Coordinator. At the conclusion of the inspection, Mrs.

Guardia issued FDA Form 483 (**Attachment 1**). The firm's response to the observations is attached (**Attachment 2**). The Form 483 observation, the Clinical Investigator's responses, and OSIS's evaluation follow:

**1) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specifically,**

**a) Subject (b) (6) was screened on 17/July/2014 and source documents show that a Target X-ray was conducted on 17/July/2014; however, the screening visit notes do not indicate that the subject provided an x-ray record of left and right view of knee (lower extremity) taken at another facility on 28/04/2014. The subject was enrolled, randomized and completed the study on 21/August/2014 as Subject number (b) (6)**

Mrs. Guardia noted that, during the inspection, she requested a copy of the X-ray, but Dr. Patel stated that photocopies of the X-rays would not be visible. Mrs. Guardia exhibited a photograph of the X-ray to document the date and patient information for Subject (b) (6)

In response to Form FDA 483, Dr. Haresh Bhalodiya, the Sub-Investigator for this study, acknowledged that the X-ray evaluation statement released by the principal investigator on 17 July 2014 inadvertently failed to indicate the evaluation was based on the review of the 28 April 2014 X-ray result provided by the subject as a supportive source document. As a corrective action, a "Note to File" has been created for Subject (b) (6) describing a copy of knee X-ray taken at another facility was used during screening visit. The firm submitted a copy of the "Note to File" along with the written response.

**OSIS Evaluation:** The firm's response is acceptable.

**1) b) Subject (b) (6) was screened and enrolled into the study on 09/June/2014. Source documents show the subject was randomized with number (b) (6) on 16/June/2014 at Visit 2, but study records for Visit 3 and V (b) (6) 4 show that the subject was randomized with number (b) (6)**

In his written response, Dr. Bhalodiya acknowledged that there was a typographical error in the Visit 2 source document for Subject (b) (6) and confirmed that the correct

randomization number for Subject [REDACTED] (b) (6)

**OSIS Evaluation:** The firm's response is acceptable.

**c) Your clinical facility screened 103 subjects for Study AM-DCG-001, 99 subjects were enrolled and randomized in the study and source records show that all 99 subjects completed the study with each subject missing 1 application dose in this 4-week study trial as noted in the "Patient Diary Part 1 and Part 2" booklets provided to the subjects upon enrollment into the study.**

Mrs. Guardia noted that the subjects enrolled and randomized in the study were provided a Patient Diary Part I at baseline visit and Part II at Visit 3 and they were required to complete the diary four times daily for the course of the study. Mrs. Guardia observed that the dose application times recorded in several of the subject diaries were similar and the contents of the diaries showed similarity in handwriting raising suspicion that the diaries may have been completed by a single person. It was also interesting to note that no application dose was missing by any subject, except the first application, which was missing for all 99 subjects.

Dr. Bhalodiya stated that all the subjects enrolled at this site missed 1 application (first morning application on the day they started treatment) due to site specific outpatient department clinic schedule. A "Note to File" enclosed with the Form FDA 483 response clarifies that, on the day of the study visit, the subjects have to stay until around 12 pm at the clinic to complete their study specific activities. Their dosing schedule only allowed them to apply the medication three times on that day, i.e., around after lunch, after dinner, and before bed. Therefore, all 99 subjects enrolled at this site missed their first morning dose on the days of their scheduled study visits.

**OSIS evaluation:** Since the missed dose applies to all the treatment categories (Vehicle, Test, and Reference), its impact to the study outcome is negligible. In addition, the study protocol AM-DCG-001, page 24, states: "Subjects will be considered compliant with the assigned study treatment if they used at least 75% and no more than 125% of study treatment doses." The occurrence of one missing application dose during the course of the study didn't violate the study protocol. However, it is concerning that several of

the diaries might have been completed by a person other than the study subjects. The absence of missing applications, other than the first application, by all study subjects is contrary to observations at other sites and raises further doubt to the authenticity of the diaries. Nevertheless, this reviewer found no strong evidence of record falsification to recommend rejection of data from these subjects.

**Discussion items**

In addition to the FDA 483 observations noted above, Mrs. Guardia discussed the following items with the management at the close-out meeting.

**Discussion item 1. Inadequate documentation of "Note to File" regarding late laboratory reports for enrolled subjects.**

Mrs. Guardia noted that the laboratory report results of (b) (6) were dated a month or longer from when the subject was randomized into the study.

Examples include:

- Subject (b) (6) - blood sample collected on 05/29/2014, reported on 07/04/2014 and reviewed by Dr. Kedia on 08/02/2014
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- Subject (b) (6) - blood sample collected on 06/02/2014, reported on 07/04/2014 and reviewed by Dr. Kedia on 08/02/2014

A "Note to File" obtained in the Investigator's binder dated 09/08/2014 states a delay in the Lab reports and hard copies thereof for the 15 subjects mentioned above. Mrs. Guardia stated that there was no documentation to indicate that the Lab reports were submitted via telephone or otherwise to Dr. Kedia prior to randomization of subjects.

**Discussion item 2. Inadequate identification of the X-rays for all 103 subjects enrolled in the study. X-rays were labeled using "hospital" tape or "post-it" sticky notes**

with the subject number. The X-rays did not include a date it was taken and subjects who provided third party X-rays, the information was not adequately documented in the subject's study record.

Mrs. Guardia stated the labeling procedure of the subjects' X-rays was inadequate in that several X-rays were not labelled with subject identification and the date that the X-ray was taken. This reviewer was informed by Mrs. Guardia via e-mail that all 103 subjects except for two (Subjects (b) (6) X-ray records did not have adequate identification. Subjects' (b) (6) X-rays were taken at another facility prior to enrollment and the X-ray indicated the date, time, and patient information. These subjects' X-rays were the only that had detailed information about when/where the X-rays were taken. The remaining X-rays had only a sticky tape or post-it note as shown on **Attachment 3**. Dr. Patel was not able to provide neither the date the X-rays were taken nor a legible copy thereof.

**OSIS Evaluation:** The Lab reports of the 15 subjects noted above (Discussion item 1) couldn't be verified by source document. All X-ray records, except 2, don't show subject identification and date the X-rays were taken (Discussion item 2). Based on the available evidence, it is not possible to confirm whether proper assessment was conducted to ensure 101 of 103 subjects enrolled in the study met the inclusion/exclusion criteria prior to randomization.

**Clinical site 2: Andhra Medical College, Visakhapatnam, Andhra Pradesh, India**

Mrs. Guardia conducted inspection at this site from 14-18 December 2015. At the conclusion of the inspection, no FDA 483 was issued. However, the following items were discussed with the management.

**Discussion item 1. Subject (b) (6) dispensing log was a copy and not able to be un-blinded. A "Note to File" documented that the dispensing log for this subject was inadvertently lost and a copy of the blinded dispense log previously submitted to the sponsor was obtained to remain in the Master File.**

Mrs. Guardia noted that Dr. Saradhi, Principal Investigator, claimed the dispensing log might have been lost along with other records after a cyclone hit the town in October 2015. The site

informed the Sponsor about the lost document and the Sponsor sent a copy of the original blinded record. According to the randomization schedule, the subject received the Test treatment and has a change in WOMAC score of -1 (13 to 12).

**OSIS Evaluation:** This reviewer believes that this is an isolated incident and inclusion of this subject's data is unlikely to affect the overall study outcome.

**Discussion item 2. Source documents for 13 subjects did not contain identification records and a "Note to File" dated 02/SEP/2014 indicated repeated attempts to obtain subject id's. However, subjects completed the study but no documentation of how or when subjects were asked to provide id's for any of the 4 visits. In addition, Subject (b) (6) was enrolled in the study and**

**and there were no other documents to verify this discrepancy in the subject's age. A "Note to File" dated 02/SEP/2014 states that date of birth recorded in signed ICF was considered the actual date of birth for the purpose of the study.**

Mrs. Guardia noted that identification records include personal information, such as age, which is a crucial component of the inclusion/exclusion criteria. She indicated no source document, such as government issued ID, was available for these subjects to verify their age. Information including age was recorded on the Informed Consent, but not verifiable by source document. The subjects that were enrolled based on the date of birth documented on the Informed Consent include:

(b) (6)  
(b) (6) The Principal Investigator stated that it was difficult to obtain proper documentation from these subjects. Mrs. Guardia indicated that some subjects had identifications that stated a different year of birth from the year of birth the subject would enter on the Informed Consent Form.

**OSIS Evaluation:** The absence of source document to verify the personal identification information is a major concern as it is not possible to ascertain a large number of study subjects at this site indeed met the inclusion criteria. Subject (b) (6) completed the study despite his/her age according to the ID made him/her ineligible. Therefore, this reviewer recommends that data from these 14 subjects be excluded from efficacy outcome determination.

**Discussion item 3. Three subjects enrolled in the study were illiterate and signed the ICF with a thumbprint. However, the Patient Diaries were completed and source documents did not indicate how or who completed the diaries.**

ed that Dr. Saradhi explained when subjects (b) (6) were identified to be illiterate, each subject was accompanied by a family member who completed the diary. However, the subject source documents did not document the identity of the person who assisted the subjects in completing the diaries. It is not clear whether this procedure was employed across all study sites. The study Protocol didn't define a specific procedure as to who should help subjects apply the investigational products and/or complete their diaries in situations when they couldn't. Note that information recorded on the diaries include the date and time of study treatments, any missed treatments, rescue medication use, concomitant medication use, and the occurrence of adverse events (AEs) or intolerability to study medication. Information recorded on the diaries wasn't used for efficacy assessment. According to Mrs. Guardia, responses to the five efficacy assessment questions were completed by study subjects except for those who are illiterate or otherwise unable to do by themselves. For these, clinic staff interviewed and completed the assessment.

**Discussion item 4. Three subjects (b) (6) were enrolled in the study and completed the Patient Diaries. These subjects were enrolled on the same day (07/17/2014) and after reviewing the Patient Diaries all six diaries had similar handwriting.**

Mrs. Guardia noted that the hand-writing in the diaries did not match the hand-writing on the Informed Consent Form filled out and signed by subjects.

**OSIS Evaluation:** The diaries of the six subjects noted above (Discussion items 3 & 4) might have been completed by a person other than the study subjects raising concern about the authenticity of the diaries. The authenticity of the diaries doesn't necessarily impact the efficacy determination (OA assessment with WOMAC score) as the efficacy assessments weren't recorded in the diaries. However, it is not possible to ensure whether the investigational products were correctly applied especially by illiterate subjects.

**Clinical site 3: Centre for Knee Surgery, Vadodara, Gujarat, India**

Mrs. Guardia and Mr. Solomon Yimam, International Policy Analyst, conducted inspection at this site from 8-11 December 2015. No FDA 483 was issued. However, the following item was discussed with the management.

**Discussion item 1: A protocol violation occurred for one subject that did not meet inclusion/exclusion criteria but was enrolled and completed the study. The event was documented as a protocol deviation and noted it was due to laboratory results received late by the study site.**

Mrs. Guardia noted a record of protocol deviation on the Protocol Deviation Log noting that Subject (b) (6) (b) (4) value is more than 2 times the upper limit of normal and did not meet inclusion criteria of the protocol. The reason for the deviation was noted as the laboratory report being received late after the subject had completed the study. Upon review of the subject's source documents, the ORA Investigators observed that the blood sample was collected on 14 May 2014 and results were reported on 15 May 2014. Subsequently, the report was reviewed by the Sub-Investigator on 21 May 2014. The CRF indicates that the subject received the first application dose on 22 May 2014 and the last application on 19 June 2014. Therefore, the timeline and documentation of the dates did not correlate with the reason noted in the Protocol Deviation Log. This subject's data were not submitted by the Sponsor

**OSIS Evaluation:** By enrolling a subject who doesn't meet the inclusion criteria; the Investigator violated the study protocol. However, data from this subject wasn't included in the efficacy assessment. Therefore, data integrity will not be affected by this protocol violation.

**Conclusions:**

Following the above inspections, this reviewer recommends that data from the BJ Medical College & Hospital are not acceptable for further Agency review, because it is not possible to confirm whether 101 of 103 study subjects enrolled in the study met the inclusion/exclusion criteria prior to randomization. The reviewer also recommends exclusion of data from the Andhra Medical College for 14 subjects due to lack of proper verification of age of subjects to confirm eligibility to meet inclusion/exclusion criteria.

**Final Classifications:**

**BJ Medical College & Hospital: VAI**  
**Andhra Medical College: VAI**  
**Centre for Knee Surgery: NAI**

CC:

OTS/OSIS/Kassim/Taylor/Kadavil/Fenty-Stewart/Nkah  
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Cho  
OTS/OSIS/DGDBE/Haidar/Skelly/Choi  
OGD/OB/Conner  
ORA/Guardia

Draft: 1/27/16

Edit: MFS 1/27/16, SHH 02/03/2016

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program  
/Clinical Sites  
/BJ Medical College & Hospital, Ahmedabadrat, India  
/Andhra Medical College, Visakhapatnam, India  
/Centre for Knee Surgery, Vadodara, India

OSI file# BE6828

**FACTS: 11555101**

Melkamu Getie-Kebtie, Ph.D., R.Ph.  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance (OSIS)

Sam H. Haidar, Ph.D., R.Ph.  
Acting Director  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance (OSIS)

# **Attachment 1**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER  7520 Standish Place (HFD-45) Rockville, MD 20855-2773 (301) 594-0020 Fax: (301) 594-1204  Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 11/21/2015 - 11/25/2015
	FEI NUMBER 3007582225

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED  
**TO: Dr. Jalak Patel, Clinical Research Coordinator**

FIRM NAME B.J. Medical College & Civil Hospital, Dept. of Orthopedics	STREET ADDRESS Hospital Road, Haripura, Asarwa
CITY, STATE AND ZIP CODE Ahmedabad, Gujarat 380016 INDIA	TYPE OF ESTABLISHMENT INSPECTED Hospital/Clinical Facility

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) (WE) OBSERVED:

**OBSERVATION 1**

Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically,

a) Subject (b) (6) was screened on 17/July/2014 and source documents show that a Target X-ray date was conducted on 17/July/2014, however the screening visit notes do not indicate that the subject provided an x-ray record of left and right view of knee (lower extremity) taken at another facility on 28/04/2014. The subject was enrolled, randomized and completed the study on 21/August/2014 as Subject number (b) (6)

b) Subject (b) (6) was screened and enrolled into the study on 09/June/2014. Source documents show the subject was randomized with number (b) (6) on 16/June/2014 at Visit 2, but study records for Visit 3 and Visit 4 show that the subject was randomized with number (b) (6)

c) Your clinical facility screened 103 subjects for Study AM-DCG-001, 99 subjects were enrolled and randomized in the study and source records show that all 99 subjects completed the study with each subject missing 1 application dose in this 4-week study trial as noted in the "Patient Diary Part 1 and Part 2" booklets provided to the subjects upon enrollment into the study.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE ( <i>Print or Type</i> )  Janete F. Guardia, Investigator	DATE ISSUED  11/25/2015
	(This area is intentionally left blank for the signature)		

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."

# Attachment 2

**OSIS Consult Request for Biopharmaceutical Inspections  
Addendum**

<b>Date</b>	July 24, 2015
<b>Subject</b>	<b>For Cause inspection request</b>
<b>To</b>	William H. Taylor, Ph.D. Director (Acting), Office of Study Integrity and Surveillance (OSIS), Office of Translational Sciences (OTS)
<b>Consulting Office/Division</b>	OGD/Division of Clinical Review/ANDA Team
<b>Project Manager</b>	Teena Thomas
<b>Application Type</b>	ANDA
<b>ANDA number</b>	208077
<b>Drug Product</b>	Diclofenac Sodium Topical Gel, 1%
<b>Applicant Name</b>	Amneal Pharmaceuticals
<b>Applicant Address</b>	85 Adams Ave, Hauppauge, NY 11788
<b>Original Submission Date</b>	12/19/2014
<b>GDUFA Due Date</b>	3/18/16
<b>Target Action Date</b>	10/15/2015
<b>OSI Review Requested by</b>	Lesley-Anne Furlong, Acting Director, Division Of Clinical Review, Office to Generic Drugs

<b>Inspection Request Detail</b>	
<b>Study Number</b>	AM-DCG-001
<b>Study Title</b>	A Multi-Center, Double-Blind, Vehicle-Controlled, Parallel-Group Study Comparing a Generic Diclofenac Sodium Topical Gel, 1% to Voltaren® Gel (Diclofenac Sodium Topical Gel), 1% in the Treatment of Subjects with Osteoarthritis of the Knee
<b>Study Type</b>	In Vivo Clinical Endpoint BE study
<b>Inspection Request Site</b>	<b>Clinical Sites</b>
<b>Facility</b>	<p><b>Study Site #24</b> Andhra Medical College, Department of Orthopaedics, Unit I, King George Hospital, Visakhapatnam, Andhra, Pradesh, 530002, India <b>Clinical Investigator:</b> Dr. Pardha Saradhi</p> <p><b>Study Site #33</b> Centre for Knee Surgery, Above Pizza Hut Near Vanijya Bhavan, RAC, Vadodara, Gujarat, 390007, India <b>Clinical Investigator:</b> Dr. Bharath Mody</p>

<b>Reason for inspection request</b>	<b>FOR CAUSE</b>
<b>Study Report</b>	\\cdsesub1\evsprod\anda208077\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoarthritis-of-knee\5351-stud-rep-contr\am-dcg-001\study-report-body.pdf

<b>Specific Items To Be Addressed During the Inspection</b>
<p>We suspect data fraud at fourteen clinical study sites because the efficacy data appear “to good to be true.” On 7/17/15, a For Cause Inspection was requested at Site #28 because this site enrolled the larger number of subjects. In addition to site #28, we request a For Cause Inspection to include two more clinical sites #24 and #33 that have not been inspected at a routine inspection. The primary endpoint of the clinical endpoint bioequivalence study (AM-DCG-001) is the mean change from baseline at week 4 in the Western Ontario McMaster Osteoarthritis Index (WOMAC) pain score (pain score = 0 to 20). At Site #24, #28, and #33, a <u>constant</u> change from baseline of WOMAC pain score of -1 was found among majority subjects (67/69 subjects) in reference listed drug (RLD, Voltaren®) treatment group.</p> <p>We note that historical NDA data for the reference listed drug (RLD) showed variable changes from baseline: the change from baseline of WOMAC pain score in RLD (Voltaren®) treatment group at week 4 was <u>varied</u> among subjects (n=127) (change from baseline of WOMAC pain score from -8 to 3) in the pivotal study (vosg-pe-310) of NDA022122 (original RLD approval NDA).</p> <p>Please look for evidence of data fraud. Assess whether the study was actually performed (look for subject’s knee X-ray films whether there was a knee problem, whether dated time on the X-ray film was within the screening time, whether lab reports were within corresponding study period, call subjects to confirm whether he/she participated the study). Evaluate source data, subject diaries, and case report forms. Please also look for evidence of unblinding.</p>

**Concern:**

**The reviewer has following concerns for 14 clinical sites (#5, #17, #19, #20, #22, #24, #26, #27, #28, #29, #30, #31 #32 and #33). However, only three study sites (#24, #28 and #33) are requested for inspection because site #28 contains the larger sample size among the study sites and sites #24 and #33 have not been inspected in a routine inspection.**

1. In the current clinical endpoint bioequivalence study (#AM-DCG-001), the primary endpoint for efficacy is the mean change from the baseline of Western Ontario McMaster Osteoarthritis Index WOMAC pain score (pain score = 0 to 20) at week 4 (completed 4 week treatment). In six study sites (#22, #24, #26, #28, #30, and #31), subjects (n=72) in reference drug group had a constant change from the baseline of WOMAC pain score equals -1 with no variation among subjects in the reference listed drug (RLD, Voltaren®) treatment group. For an example, for subject #28-2019 (at site 28, treated with RLD, Voltaren®), WOMAC pain score at baseline is 12, and WOMAC pain score at week 4 is 11. The change from the baseline of WOMAC pain score for this subject is 11 minus 12 = -1. The same change (-1) from baseline of WOMAC pain score was found in all the subjects (n=72) in all these six sites.
2. In eight study sites (#5, #17, #19, #20, #27, #29, #32 and #33), most subjects in the RLD group had a constant change from the baseline in WOMAC pain score equals to “-1” with lack of variability.
3. In the pivotal study (vosg-pe-310) of NDA022122 (original RLD approval NDA), the change from baseline of WOMAC pain score in RLD (Voltaren®) treatment group at week 4 was varied among subjects (n=127) from WOMAC pain score of -8 to 3. Comparing WOMAC pain scores of the RLD in Study vosg-pe-310 in NDA to those pain scores of the RLD in current clinical endpoint study (#AM-DCG-001) in this ANDA, it indicates that data fraud may occur in current clinical endpoint study (#AM-DCG-001) at sites (#5, #17, #19, #20, #22, #24, #26, #27, #28, #29, #30, #31 #32 and #33). The study sites (#24, #28 and #33) are selected for inspection because site #28 contains the larger sample size among the study sites and sites #24 and #33 have not been inspected in a routine inspection.

All subjects' data is located in the columns of the following dataset:

1. Data set subsumvt.xpt [\\cdsesub1\evsprod\anda208077\0001\m5\datasets\am-dcg-001\listings\subsumvt.xpt](#): WOMPA for WOMAC pain score (please noted that the VISITNUM= 2 is the baseline visit, and VISITNUM=4 is the week 4 visit).
2. Dataset sumlocf.xpt [\\cdsesub1\evsprod\anda208077\0001\m5\datasets\am-dcg-001\listings\sumlocf.xpt](#).: WOMPA\_B and WOMPA\_4 for WOMAC pain score at baseline and for WOMAC pain score at week 4, respectively.

The definition of the abbreviations used in these two dataset can be found in the following link:

[\\cdsesub1\evsprod\anda208077\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\osteoarthritis-of-knee\5351-stud-rep-contr\am-dcg-001\dfine.pdf](#)

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

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DATE: August 10, 2015

TO: Dale Conner, Pharm.D.  
(Acting) Director, Office of Bioequivalence  
Office of Bioequivalence (OB)  
Office of Generic Drugs

FROM: Kara A. Scheibner, Ph.D., Pharmacologist  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Acting Director  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance

SUBJECT: Inspection of Rathi Orthopedic and Research Centre,  
Ahmedabad, India, Malpani Multispecialty Hospital,  
Jaipur, India, and GMERS Medical College and Hospital,  
Ahmedabad, India, in support of ANDA 208077  
(Diclofenac Sodium Topical Gel, 1%), sponsored by  
Amneal Pharmaceuticals

**Summary:**

At the request of the Division of Generic Drugs, the Office of Study Integrity and Surveillance conducted inspections of the clinical portions of the following bioequivalence study at Rathi Orthopedic and Research Centre, Ahmedabad, India, Malpani Multispecialty Hospital, Jaipur, India, and GMERS Medical College and Hospital, Ahmedabad, India.

**Study Number:** AM-DCG-001

**Study Title:** "A Multi-Center, Double-Blind, Vehicle-Controlled, Parallel-Group Study Comparing a Generic Diclofenac Sodium Topical Gel, 1% to Voltaren® Gel (Diclofenac Sodium Topical Gel), 1% in the Treatment of Subjects with Osteoarthritis of the Knee"

**Study Dates:** 04/09/2014 to 09/03/2014

Inspections of clinical portions of study AM-DCG-001 were conducted by ORA Investigator Janete F. Guardia at GMERS Medical College and Hospital, Ahmedabad, India from March 26 to April 1, 2015, Rathi Orthopedic and Research Centre, Ahmedabad, India from April 6 to April 10, 2015, and Malpani Multispecialty Hospital, Jaipur, India from March 12 to March 20, 2015.

The audits included a thorough review and examination of facilities and equipment, personnel records, specimen handling and integrity, protocols, SOPs, subject consent, electronic records, IRB documentation, enrolled subject records, test article accountability, and record retention, as well as interviews and discussions with the firm's management and staff.

**Rathi Orthopedic and Research Centre:** FDA Form-483 was not issued at the conclusion of the inspection. There were two verbal discussion items at closing: 1) Hand written notes recording subject vital signs at screening were signed by the study PI, but not dated. 2) Several CRFs had cross-outs and changes that were dated and initialed several months after the PI signed that the subject had completed the study. For example, the musculoskeletal result for osteoarthritis knee subject 1198 was changed from normal to abnormal for Visits 2, 3, and 4.

**GMERS Medical College and Hospital:** Two-observation FDA Form-483 was issued at the conclusion of inspection (**Attachment 1**). The observations, the Firm's response to these observations (**Attachment 2**), and our evaluation of the responses follow.

**Observation 1:** An investigation was not conducted in accordance with the investigational plan. Specifically:

1. The following subjects were screened and randomized prior to receipt of laboratory results for exclusion/inclusion criteria
  - a. Subject (b) (6) - randomized on 23/Jun/2014 and IP dispensed (Kit #2117) prior to obtaining laboratory results reported on 26/Jun/2014 and reviewed on 28/Jun/2014 by the principal investigator
  - b. Subject (b) (6) - randomized on 24/Jun/2014 and IP dispensed (Kit #2122) prior to obtaining laboratory results reported on 27/Jun/2014 and reviewed on 30/Jun/2014 by the principal investigator
  - c. Subject (b) (6) - randomized on 24/Jun/2014 and IP dispensed (Kit #2119) prior to obtaining laboratory results reported on 26/Jun/2014 and reviewed on 30/Jun/2014 by the principal investigator

In the firm's response, they acknowledge the observation. Laboratory results for these subjects were delayed beyond the three to four expected days, and as the protocol involved washout of all pain medication for potential study subjects, the PI was concerned for the well-being of these subjects. The PI contacted the laboratory by telephone to request the results, and verified that "liver enzyme" test results were normal and negative for HBsAg reactivity. The PI then randomized these subjects. The PI confirmed the results upon receipt of the note to file has been added for Subjects (b) (6) documenting why the subjects were randomized prior to review of lab reports. In addition, new training has been implemented to emphasize recording all study information promptly.

We find the firm's response acceptable. This observation does not affect subject safety or study data.

**2. The Site Staff Signature and Responsibility Log, Version 01, Effective 19MAR2014 does not identify the tasks and duties performed and documented in the case history records for the following study participants:**

- a. CRC-1 performed UPT tests for 11 subjects (*Subjects* (b) (6))
- b. CRC-2 performed physical procedures such as height and weight on five (5) subjects (b) (6) and processed laboratory samples for two (2) subjects (b) (6).
- c. CRC-3 performed (b) (6) procedures such as height and weight on 15 subjects (b) (6) and processed laboratory samples for 13 subjects (b) (6)

The firm acknowledges the observations. The firm acknowledges that site staff did not include UPT tests on the Delegation Log for CRC-1. The firm acknowledges that CRC-2 and CRC-3 inadvertently performed height and weight measurements. However, the source template reflects that the PI performed the entire physical examination, including height and weight measurements. In regard to CRC-2 and CRC-3 processing (b) (4) re actually performed by (b) (4) as recorded in the subject (b) (6) ions do not affect subject safety or data integrity.

3. There is no "File Note" in the Master File to document that phlebotomy procedures not identified on the Site Staff Signature and Responsibility Log, Version 01, Effective 19MAR2014, will be conducted on-site by off-site phlebotomists from the contract laboratory assigned to conduct laboratory analysis for subject samples collected during the screening visit as required by the investigational plan.

The firm acknowledged the observation. A note to file has been added to clarify the phlebotomy and processing of blood samples.

The firm's response is acceptable. This observation does not affect data integrity.

**Observation 2:** Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. Specifically, the original color copy of the "Test Requisition Form (TRF)" was not maintained in the case history records for subject's [REDACTED] (b) (6)

(b) (6)

The firm acknowledged the observation. In their response, they stated that because lab reports were not provided in a timely manner, a print of the "soft" copy of the TRF from the lab was included in several patient files. A note to file has been added to source documents stating why original color copies were not included.

The firm's response is acceptable. This observation does not impact data integrity.

**Malpani Multispecialty Hospital:** FDA Form-483 was issued at the conclusion of inspection (**Attachment 3**). The observations, the firm's response to the observations (**Attachment 4**), and our evaluation of the responses follow.

**Observation 1:** Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation and informed consent. Specifically, the following records were not adequate:

- a. Source documents for subjects [REDACTED] (b) (6) note subjects obtained the Informed Consent Form, completed screening visit, completed physical exam and blood test conducted. However, the case history file does not document reason why subjects were not randomized and lost to follow up.

b. Case report forms for subjects (b) (6)  
do not indicate correct date of birth for the subjects  
according to source data.

The firm acknowledged the observations, and explained that subjects (b) (6) were not randomized because enrollment targets were met. Also, data clarification forms prepared on 03/SEP/2014 have corrected years of birth for both patients:  
(b) (6)

The firm's response is acceptable. Neither observation affects study data.

**Observation 2: Failure to assure that an IRB complying with applicable regulatory requirements was responsible for the initial and continuing review and approval of a clinical study. Specifically, the Protocol Deviation Log notes three (3) deviations pertaining to randomized subjects identified as (b) (6). However, there is no correspondence between the site and the Institutional Ethics Committee regarding these protocol deviations.**

The firm acknowledges the observation. They included a letter to the Institutional Ethics Committee on December 11, 2014 to notify them that the study had closed. In this letter, they described the protocol deviations for inclusion criteria for these three subjects. Receipt of the letter was acknowledged by the IEC.

The firm's response is acceptable. This observation does not affect subject safety or data integrity.

**Observation 3: An adequate final report was not provided to the sponsor shortly after completion of the investigator's participation in the investigation. Specifically, a letter dated 11/Dec/2014 regarding Protocol No. AM-DCG-001 regarding study closure status EC notification indicates that there were 10 screen failures and 02 patients screened but could not be randomized as recruitment target met. However, the Subject Screening and Enrollment Log documents that there are nine (9) screening failures and (3) subjects that signed ICF and were screened but not randomized.**

The firm acknowledged the observation. Subject (b) (6) also was a screen failure. The file has been updated. The response and corrective action are acceptable. There is no impact on data integrity.

**Conclusion:**

After evaluation of the EIRs, the Form-483 Observations, and the Firm's responses, we recommend that data from these three study sites, Malpani Multispecialty Hospital, GMERS Medical College and Hospital, and Rathi Orthopedic Research Centre, be accepted for further agency review. Inspections of two additional sites will be arranged soon and reviewed to OGD when EIRs are available.

Kara A. Scheibner, Ph.D.  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance

**Final Classification:**

**VAI - Rathi Orthopedic Research Centre, Ahmedabad, India  
(FEI# 3004427623)**

**VAI - GMERS Medical College and Hospital, Ahmedabad, India  
(FEI# 1000134234)**

**VAI - Malpani Multispecialty Hospital, Jaipur, India)  
(FEI# 3004613258)**

CC:

OTS/OSIS/Taylor/Dejernet/Nkah/Fenty-Stewart/Johnson

OTS/OSIS/DGDBE/Haidar/Skelly/Choi/Scheibner

OTS/OSI/DNDEB/Bonapace/Dasgupta/Cho

CDER/OGD/John Peters

ORA/Janete Guardia

Draft: KAS 8/7/2015

Edits: MFS 8/7/2015; SHH 8/10/2015

OSI: File#: BE6828

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical  
Sites/GMERS Medical College and Hospital, Ahmedabad, Gujarat,  
India

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical  
Sites/Rathi Orthopedic and Research Centre, Ahmedabad, Gujarat,  
India

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical  
Sites/Malpani Multispecialty Hospital, Rajasthan, India

**FACTS: 11510351**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 7520 Standish Place (HFD-45) Rockville, MD 20855-2773 (301) 594-0020 Fax:(301) 594-1204 Industry Information: <a href="http://www.fda.gov/oc/industry">www.fda.gov/oc/industry</a>	DATE(S) OF INSPECTION 03/26/2015 - 04/01/2015*
	FEI NUMBER 1000134234

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED  
**TO: Dr. Somesh P. Singh, Principal Investigator**

FIRM NAME GMERS Medical College & Civil Hospital	STREET ADDRESS Department of Orthopedics Near Gujarat Highcourt, S.G Highway
---	--

CITY, STATE, ZIP CODE, COUNTRY Ahmedabad 380061, India	TYPE ESTABLISHMENT INSPECTED Clinical Hospital
---	---

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:

1) The following subjects were screened and randomized prior to receipt of laboratory results for exclusion/inclusion criteria:

a) Subject (b) (6) - randomized on 23/Jun/2014 and IP dispensed (Kit #2117) prior to obtaining laboratory results reported on 26/Jun/2014 and reviewed on 28/Jun/2014 by the principal investigator

b) Subject (b) (6) randomized on 24/Jun/2014 and IP dispensed (Kit #2122) prior to obtaining laboratory results reported on 27/Jun/2014 and reviewed on 30/Jun/2014 by the principal investigator

c) Subject (b) (6) - randomized on 24/Jun/2014 and IP dispensed (Kit #2119) prior to obtaining laboratory results reported on 26/Jun/2014 and reviewed on 30/Jun/2014 by the principal investigator

2) The Site Staff Signature & Responsibility Log, Version 01, Effective 19MAR2014 does not identify the tasks and duties performed and documented in the case history records for the following study participants:

a) CRC-1 performed UPT tests for 11 subjects

b) CRC-2 performed physical procedures such as height and weight on five (5) subjects and processed laboratory samples for two (2) subjects

c) CRC-3 performed physical procedures such as height and weight on 15 subjects and processed laboratory samples for 13 subjects

3) There is no "File Note" in the Master File to document that phlebotomy procedures not identified on the Site Staff Signature & Responsibility Log, Version 01, Effective 19MAR2014, will be conducted on-site by off-site phlebotomists from the contract laboratory assigned to conduct laboratory analysis for subject samples collected during the screening visit as required by the investigational plan

<b>SEE REVERSE OF THIS PAGE</b>	EMPLOYEE(S) SIGNATURE Janete F. Guardia, Investigator	DATE ISSUED 04/01/2015
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**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 7520 Standish Place (HFD-45) Rockville, MD 20855-2773 (301) 594-0020 Fax:(301) 594-1204 Industry Information: <a href="http://www.fda.gov/oc/industry">www.fda.gov/oc/industry</a>	DATE(S) OF INSPECTION 03/26/2015 - 04/01/2015*
	FEI NUMBER 1000134234

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED  
**TO: Dr. Somesh P. Singh, Principal Investigator**

FIRM NAME GMERS Medical College & Civil Hospital	STREET ADDRESS Department of Orthopedics Near Gujarat Highcourt, S.G Highway
---	--

CITY, STATE, ZIP CODE, COUNTRY Ahmedabad 380061, India	TYPE ESTABLISHMENT INSPECTED Clinical Hospital
---	---

**OBSERVATION 2**

Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

Specifically the original color copy of the "Test Requisition Form (TRF)" was not maintained in the case history records for subjects (b) (6)

**\* DATES OF INSPECTION:**

03/26/2015(Thu), 03/27/2015(Fri), 03/28/2015(Sat), 03/30/2015(Mon), 03/31/2015(Tue), 04/01/2015(Wed)

<b>SEE REVERSE OF THIS PAGE</b>	EMPLOYEE(S) SIGNATURE Janete F. Guardia, Investigator	DATE ISSUED 04/01/2015
-------------------------------------	--	---------------------------

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

<small>DISTRICT ADDRESS AND PHONE NUMBER</small> 7520 Standish Place (HFD-45) Rockville, MD 20855-2773 (301) 594-0020 Fax: (301) 594-1204 Industry Information: www.fda.gov/oc/industry	<small>DATE(S) OF INSPECTION</small> 03/16/2015 - 03/20/2015
	<small>FEI NUMBER</small> 3004613258

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED  
**TO: Dr. Rajiv Gupta, M.B.B.S., M.S., Principal Investigator**

<small>FIRM NAME</small> Malpani Multi Speciality Hospital	<small>STREET ADDRESS</small> SP 6, road no 1, V.K.I, Sikar Rd
<small>CITY, STATE, ZIP CODE, COUNTRY</small> Jaipur 302013, India	<small>TYPE ESTABLISHMENT INSPECTED</small> Hospital and Clinical facility

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**

Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation and informed consent.

Specifically, the following records were not adequate:

a) source documents for subjects (b) (6) note subjects obtained the Informed Consent Form, completed screening visit, completed physical exam and blood test conducted. However, the case history files does not document reason why subjects were not randomized and lost to follow-up.

b) case report forms for subjects (b) (6) do not indicate correct date of birth for the subjects, according to source data.

**OBSERVATION 2**

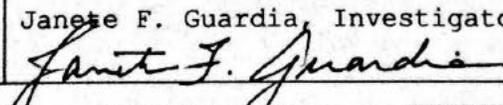
Failure to assure that an IRB complying with applicable regulatory requirements was responsible for the initial and continuing review and approval of a clinical study.

Specifically, the Protocol Deviation Log notes three (3) deviations pertaining to randomized subjects identified as (b) (6) (b) (6) However, there is no correspondence between the site and the Institutional Ethics Committee regarding these protocol deviations.

**OBSERVATION 3**

An adequate final report was not provided to the sponsor shortly after completion of the investigator's participation in the investigation.

Specifically, a letter dated 11/Dec/2014 regarding Protocol No. AM-DCG-001 regarding study closure status EC notification indicates that there were 10 screen failures and 02 patients screened but could not be randomized as recruitment target met. However, the Subject Screening & Enrollment Log documents that there are nine (9) screen failures and three (3) subjects that signed ICF and were screened but were not randomized.

<b>SEE REVERSE OF THIS PAGE</b>	<small>EMPLOYEE(S) SIGNATURE</small> Janete F. Guardia, Investigator 	<small>DATE ISSUED</small> 03/20/2015
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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER

7520 Standish Place (HFD-45)  
Rockville, MD 20855-2773  
(301) 594-0020 Fax:(301) 594-1204  
Industry Information: [www.fda.gov/oc/industry](http://www.fda.gov/oc/industry)

DATE(S) OF INSPECTION

03/16/2015 - 03/20/2015

FEI NUMBER

3004613258

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Dr. Rajiv Gupta, M.B.B.S., M.S., Principal Investigator

FIRM NAME

Malpani Multi Speciality Hospital

STREET ADDRESS

SP 6, road no 1, V.K.I, Sikar Rd

CITY, STATE, ZIP CODE, COUNTRY

Jaipur 302013, India

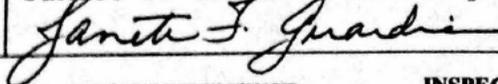
TYPE ESTABLISHMENT INSPECTED

Hospital and Clinical facility

SEE REVERSE  
OF THIS PAGE

EMPLOYEE(S) SIGNATURE

Janete F. Guardia, Investigator



DATE ISSUED

03/20/2015

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 208077Orig1s000**

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



<b>Food and Drug Administration</b> CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
<b>Document Status: Approved</b>		
<b>Title:</b> Approval Routing Summary Form	<b>Author:</b> Heather Strandberg	

<b>Approval Type:</b> <input checked="" type="checkbox"/> FULL APPROVAL <input type="checkbox"/> TENTATIVE APPROVAL <input type="checkbox"/> SUPPLEMENTAL APPROVAL (NEW STRENGTH)		
<b>RPM:</b> Andrew Coogan <b>Team:</b> Hennessey		<b>Approval Date:</b> 3/18/2016
<input checked="" type="checkbox"/> PI <input type="checkbox"/> PII <input type="checkbox"/> PIII <input type="checkbox"/> PIV (eligible for 180 day exclusivity) <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> MOU <input checked="" type="checkbox"/> RX or <input type="checkbox"/> OTC		
<b>ANDA #:</b> 208077 <b>Applicant:</b> Amneal Pharmaceuticals		<b>Established Product Name:</b> Diclofenac Sodium Topical Gel, 1%
<b>Basis of Submission (RLD):</b> NDA # 022122, Voltaren Gel (Is ANDA based on an approved Suitability Petition? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No)		
<b>Does the ANDA contain REMS?</b> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No (If YES, initiate approval action 6 weeks prior to target action date)		
<b>Regulatory Project Manager Evaluation:</b>		<b>Date:</b> 2/26/2016
<input type="checkbox"/> Date last Complete Response (CR) letter was issued -- Date _____		
<input type="checkbox"/> Previously reviewed and tentatively approved (if applicable) --- Date _____		
Date of Application 12/19/2014		Original Received Date 12/18/2014
Date Acceptable for Filing 12/19/2014		
<b>YES</b>	<b>NO</b>	
<input checked="" type="checkbox"/>	<input type="checkbox"/>	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A) Date of Acceptable Quality 2/11/2016 Date of Acceptable Dissolution 2/11/2016 Date of Acceptable Bioequivalence 2/24/2016 Date of Acceptable Labeling 9/10/2015
		If applicable: Date of Acceptable Microbiology N/A Date of Acceptable Clinical Review 2/26/2016 Date of Acceptable REMS N/A
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Are consults pending for any discipline?
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES → Verify a second filing review was completed and that all disciplines completed new reviews <input type="checkbox"/>
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Is there a pending Citizen Petition (CP)?
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Overall OC Recommendation is acceptable (EES is acceptable) Date Acceptable: 3/18/2016 Re-evaluation Date: _____
<input checked="" type="checkbox"/>	<input type="checkbox"/>	OSI Clinical Endpoint and Bioequivalence Site Inspections are acceptable
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff (OGDREQUEST) 30 to 60 days prior to approval, Date emailed _____
<b>Draft Approval/Tentative Approval Letter</b>		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Approval/Tentative Approval letter is drafted and uploaded to the Final Decision task
<b>Review Discipline/Division Endorsements</b>		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Division of Legal and Regulatory Support Endorsement completed, Date 3/17/2016
<input type="checkbox"/>	<input type="checkbox"/>	Paragraph IV Evaluation completed (if applicable), Date na
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Quality Endorsement completed, Date 3/18/2016
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Bioequivalence Endorsement completed, Date 3/16/2016
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Labeling Endorsement completed, Date 3/16/2016
<input checked="" type="checkbox"/>	<input type="checkbox"/>	REMS Endorsement (if applicable), Date na
<b>RPM Team Leader Endorsement and Action Package Verification</b>		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	RPM Team Leader Endorsement completed, Date 3/18/2016
<b>Final Decision and Letter Sign-off</b>		
<input type="checkbox"/>	<input type="checkbox"/>	Final Decision recommending approval/tentative approval completed, Date _____
<input type="checkbox"/>	<input type="checkbox"/>	Approval/Tentative Approval letter electronically signed, Date: _____
<b>Project Close-Out</b>		
<input type="checkbox"/>	<input type="checkbox"/>	Notify applicant of approval and provide a courtesy copy of the electronically signed letter
<input type="checkbox"/>	<input type="checkbox"/>	Is there a Post Marketing Agreement (PMA)? IF YES → Send email to PMA coordinator, Date emailed _____
<input type="checkbox"/>	<input type="checkbox"/>	Email OGD Approval distribution list (CDER-OGDAPPROVALS) with approval information

This page to be completed by the RPM

**Lead Division:** Program Management **Effective Date:** 10/1/2014 Page 1 of 8

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

Please ensure you are using the most current version of this Form. It is available at:  
[OGD QMS Approved Documents](#)



<b>Food and Drug Administration</b> CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
<b>Document Status: Approved</b>		
<b>Title:</b> Approval Routing Summary Form	<b>Author:</b> Heather Strandberg	

**ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION**

**1. Division of Legal and Regulatory Support Endorsement**

**Date:** 3/17/2016  
**Name/Title:** RTP

Contains GDEA certification: Yes <input type="checkbox"/> No <input type="checkbox"/>	
(required if sub after 6/1/92)	Pediatric Exclusivity System
Patent/Exclusivity Certification: Yes <input type="checkbox"/> No <input type="checkbox"/>	RLD = Voltren NDA# 22122
If Para. IV Certification- did applicant:	Date Checked _____
Notify patent holder/NDA holder Yes <input type="checkbox"/> No <input type="checkbox"/>	Nothing Submitted <input type="checkbox"/>
Was applicant sued w/in 45 days: Yes <input type="checkbox"/> No <input type="checkbox"/>	Written request issued <input type="checkbox"/>
Has case been settled: Yes <input type="checkbox"/> No <input type="checkbox"/>	Study Submitted <input type="checkbox"/>
Date settled:	
Is applicant eligible for 180 day	
Is a forfeiture memo needed: Yes <input type="checkbox"/> No <input type="checkbox"/>	
If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes <input type="checkbox"/> No <input type="checkbox"/>	
Date of latest Labeling Review/Approval Summary	
Any filing status changes requiring addition Labeling Review Yes <input type="checkbox"/> No <input type="checkbox"/>	
Type of Letter:	
<input checked="" type="checkbox"/> APPROVAL <input type="checkbox"/> TENTATIVE APPROVAL <input type="checkbox"/> SUPPLEMENTAL APPROVAL (NEW STRENGTH)	
<input type="checkbox"/> OTHER:	
Comments:	
BOS: NDA 22122 Voltren Gel 1%. ANDA submitted on 12/13/2014. ACK for filing on 12/19/2014 ( LO Date 02/03/2015) with a PI certification.	
This application is eligible for immediate full approval since there are no patents or exclusivities that protect the RLD. Application is considered a first generic.	



<b>Food and Drug Administration</b> CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
<b>Document Status: Approved</b>		
<b>Title:</b> Approval Routing Summary Form	<b>Author:</b> Heather Strandberg	

2. **Paragraph IV Evaluation (for ANDAs with PIV certifications or other controversial regulatory issues)**

**Date:** \_\_\_\_\_ **Name/Title:** \_\_\_\_\_ **Comments:**

*Or see corresponding endorsement task under the ANDA project within the platform*

3. **Quality Endorsement by the Office of Pharmaceutical Science**

**Date:** \_\_\_\_\_ **Name/Title:** \_\_\_\_\_ **Comments:**

*Or see corresponding endorsement task under the ANDA project within the platform*

4. **Bioequivalence Endorsement**

**Date:** \_\_\_\_\_ **Name/Title:** \_\_\_\_\_ **Comments:**

*Or see corresponding endorsement task under the ANDA project within the platform*

5. **Labeling Endorsement**

**Date:** \_\_\_\_\_ **Name/Title:** \_\_\_\_\_ **Comments:**

*Or see corresponding endorsement task under the ANDA project within the platform*

6. **REMS Endorsement**

**Date:** \_\_\_\_\_ **Name/Title:** \_\_\_\_\_ **Comments:**

*Or see corresponding endorsement task under the ANDA project within the platform*

7. **RPM Team Leader Endorsement**

**Date:** \_\_\_\_\_ **Name/Title:** \_\_\_\_\_ **Comments:**

*Or see corresponding endorsement task under the ANDA project within the platform*



<b>Food and Drug Administration</b> CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
<b>Document Status: Approved</b>		
<b>Title:</b> Approval Routing Summary Form	<b>Author:</b> Heather Strandberg	

**8. Final Decision**

**Date:** 3/18/2016  
**Name/Title:** WPR

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   
First Generic Approval   
PD or Clinical for BE   
Special Scientific or Reg. Issue

Date PETS checked for first generic drug \_\_\_\_\_

**Comments:**

BOS: NDA 22122 Voltren Gel 1%. There are no patents or exclusivities currently listed in the OB that protect the RLD. Chemistry acceptable 3/18/2016. QE 3/18/2016. Bio acceptable 2/23/2016. Clinical acceptable 2/25/2016. Labeling acceptable 9/8/2015. Facilities are approve. This ANDA is eligible for Full Approval.

**From:** Moore, Filita  
**Sent:** Friday, March 04, 2016 3:59 PM  
**To:** Herkenham, Kevin  
**Cc:** Coogan, Andrew  
**Subject:** RE: Comment on ANDA-208077-ORIG-1 (ref# 45914)

Hi Kevin,

I see that you are covering for Andrew next week. Andrew may have briefed you but ANDA 208077 has a GDUFA goal date of March 18, 2016. (b) (4)



Thank you,

Filita  
**Filita O. Moore, MBA, BSN, RN, NE-BC**  
**LCDR, U.S. Public Health Service Commissioned Corps**  
**Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)**  
**Office of Pharmaceutical Quality/CDER/FDA**



10903 New Hampshire Ave; Bldg #75 Room 4631; Silver Spring, MD 20993-0002  
(240) 402-9553 | ✉ [filita.moore@fda.hhs.gov](mailto:filita.moore@fda.hhs.gov)

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**From:** Coogan, Andrew  
**Sent:** Friday, March 04, 2016 3:51 PM  
**To:** Moore, Filita  
**Subject:** Automatic reply: Comment on ANDA-208077-ORIG-1 (ref# 45914)

Hello,

I will be out of the office for training until Monday March 21st. For any questions or issues that cannot wait until my return, Please contact Kevin Herkenham at [Kevin.herkenham@fda.hhs.gov](mailto:Kevin.herkenham@fda.hhs.gov) From Monday March 7th to Friday March 11th, and Scott Dallas at [Scott.Dallas@fda.hhs.gov](mailto:Scott.Dallas@fda.hhs.gov) from Monday March 14th to March 18th.

Thank you,  
Andrew Coogan



ANDA #208077

## INFORMATION REQUEST

Amneal Pharmaceuticals  
Attention: Candis Edwards  
Senior Vice President, Clinical Regulatory Affairs  
85 Adams Avenue  
Hauppauge, New York 11788

Dear Sir/Madam:

Please refer to your Abbreviated New Drug Application (ANDA) #208077 dated December 19, 2014 submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Diclofenac Sodium Topical Gel, 1% w/w.

We are reviewing the Quality sections of your submission and have the following comments and information requests. We request a prompt written response, no later than **September 21, 2015** in order to continue our evaluation of your ANDA.

Please note, submitting unsolicited information in your response to this Information Request may have an impact on your Target Action Date.

List of the deficiencies:

### **Chemistry deficiencies:**

#### **Drug Product**

- 1.
- 2.
- 3.
- 4.

(b) (4)

5.

6.

7.

8.

9.

10.

11.

12.

(b) (4)

**Process**

1.

(b) (4)

2.

3.

4.

5.

6.

7.

8.

9.

(b) (4)

If you do not submit a complete response by **September 21, 2015**, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

Please note, if information or data submitted exceeds the data requested in the IR/ECD this may result in a conversion to a Tier 2 Unsolicited Amendment (i.e., an amendment with information not requested by FDA).

If the submitted data is determined to be a Tier 2 Unsolicited Amendment, this may affect the goal date.

Send your submission through the Electronic Submission Gateway

<http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>. Prominently

identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST**

**Quality**

**REFERENCE # 152707**

If you have any questions, please contact Filita O. Moore, Regulatory Business Process Manager, at (240) 402-9553.

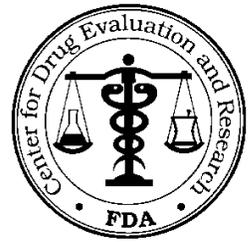
Sincerely,

Filita O. Moore, MBA, BSN, RN, NE-BC  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

# EASILY CORRECTABLE DEFICIENCY

ANDA 208077

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North VII  
7620 Standish Place  
Rockville, Maryland 20855



APPLICANT: Amneal Pharmaceuticals

TEL: (631) 656-5007

ATTN: Alpesh Patel, VP - Global Regulatory Affairs

Email: alpesh@amneal.com

FROM: Sunny Pyon

Dear Mr. Patel:

This communication is in reference to your abbreviated new drug application (ANDA) dated December 19, 2014 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Diclofenac Sodium Topical Gel, 1%.

We acknowledge receipt of your amendment(s) dated April, 14, 2015.

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 within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**EASILY CORRECTABLE DEFICIENCY  
LABELING  
REFERENCE # 152818**

If you do not submit a complete response within ten (10) U.S. business 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.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Labeling Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

If you have questions regarding these deficiencies please contact the Labeling Project Manager, Sunny Pyon, at sunny.pyon@fda.hhs.gov.

We have completed our review and have the following comments:

**LABELING DEFICIENCIES:**

1. CONTAINER LABEL

Please revise “Each gram contains 1% diclofenac sodium, USP.” to read “Each gram contains 1% w/w diclofenac sodium, USP.”

2. CARTON LABELING

Please refer to comment 1 above.

3. PRESCRIBING INFORMATION

- a. HIGHLIGHTS OF PRESCRIBING INFORMATION: Due to a recent change in policy, revise the presentation of the established name to appear in all upper case letters, in the following text as such: **“These highlights do not include all the information needed to use DICLOFENAC SODIUM TOPICAL GEL safely and effectively. See full prescribing information for DICLOFENAC SODIUM TOPICAL GEL.”**
- b. HIGHLIGHTS OF PRESCRIBING INFORMATION: The product title, immediately above the initial U.S. approval date, should be revised as below to comply with PLR format requirements. **DICLOFENAC SODIUM topical gel, 1%, for topical use only**
- c. HIGHLIGHTS OF PRESCRIBING INFORMATION: Revise the subsection title to read **“DOSAGE FORM AND STRENGTH”**.
- d. FULL PRESCRIBING INFORMATION/CONTENTS: Please revise “3 DOSAGE FORMS AND STRENGTHS” to read “3 DOSAGE FORM AND STRENGTH”.
- e. FULL PRESCRIBING INFORMATION/2 DOSAGE AND ADMINISTRATION/2.1 Dosing Card: Please revise “2.1 Dosing Card [*See the Instructions for Use*]” to read “2.1 Dosing Card [*See the patient Instructions for Use*]”.
- f. FULL PRESCRIBING INFORMATION/3 DOSAGE FORM AND STRENGTH: Please revise to read “3 DOSAGE FORM AND STRENGTH”. [Note the revision of “FORMS” to read “FORM” and “STRENGTHS” to read “STRENGTH”.]
- g. FULL PRESCRIBING INFORMATION/16 HOW SUPPLIED, first sentence: Please revise to read: “Diclofenac sodium topical gel 1% is available....”

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with all differences annotated and explained.

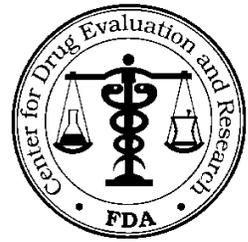
Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

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](http://service.govdelivery.com/service/subscribe.html?code=USFDA_17)

# EASILY CORRECTABLE DEFICIENCY

ANDA 208077

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North VII  
7620 Standish Place  
Rockville, Maryland 20855



APPLICANT: Amneal Pharmaceuticals

TEL: (631) 656 5007

ATTN: Alpesh Patel

Email: alpesh@amneal.com

FROM: Carol Yun

Dear Mr. Patel:

This communication is in reference to your abbreviated new drug application (ANDA), submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Diclofenac Sodium Topical Gel, 1%.

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 within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**EASILY CORRECTABLE DEFICIENCY  
LABELING  
REFERENCE # 109847**

If you do not submit a complete response within ten (10) U.S. business 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.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Labeling Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

If you have questions regarding these deficiencies please contact the Labeling Project Manager, Carol Yun, at carol.yun@fda.hhs.gov.

We have completed our review and have the following comments:

**LABELING:**

1. CONTAINER LABEL

- a. Please add “Use the dosing card attached inside carton” to the principal display panel (PDP).
- b. Please add “Store the dosing card with your diclofenac sodium topical gel, 1%.” after the storage statement in accordance with the reference listed drug (RLD).
- c. Please remove “w/w” from the established name.
- d. Please provide the space for the lot number and expiration date.

2. CARTON LABELING

- a. Please add “Use the dosing card attached inside the carton” to the PDP.
- b. Please add “Store the dosing card with your diclofenac sodium topical gel, 1%.” after the storage statement in accordance with the RLD.
- c. Please remove “w/w” from the established name on the PDP and back label.

3. DOSING CARD

- a. Please add “Dosing card for” prior to the established name.
- b. Please add “(2.25 inches)” and “(4.5 inches)” directly below “2 grams” and “4 grams”, respectively.
- c. Please revise “Please see patient medication guide for instructions.” to read “Please see instructions for use.”

4. PRESCRIBING INFORMATION

- a. Revise your labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Voltaren® Gel, NDA 022122/S-007, approved 11/25/14.
- b. HIGHLIGHTS OF PRESCRIBING INFORMATION: Please revise the first paragraph to read: “These highlights do not include all the information needed to use diclofenac sodium topical gel safely and effectively. See full prescribing information for diclofenac sodium topical gel.
- c. HIGHLIGHTS OF PRESCRIBING INFORMATION/Title: Please revise to read: **“DICLOFENAC sodium topical gel, 1%, for topical use only”**.
- d. HIGHLIGHTS OF PRESCRIBING INFORMATION/DOSAGE AND ADMINISTRATION: Please revise the first sentence to read: “Total dose should not exceed 32 g per day, over all affected joints.”
- e. HIGHLIGHTS OF PRESCRIBING INFORMATION/ Revision date: The date in this section does not correlate with the date at the end of the insert. Please comment and/or revise this date.
- f. FULL PRESCRIBING INFORMATION/5 WARNINGS AND PRECAUTIONS/5.6 Renal Effects: In the third paragraph of this subsection, please revise “...dosedependent...” to read “...dose-dependent...”.
- g. FULL PRESCRIBING INFORMATION/ 5 WARNINGS AND PRECAUTIONS/5.10 Corticosteroid Treatment: Please revise the second sentence of this subsection to read: “Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness.”
- h. FULL PRESCRIBING INFORMATION/ 5 WARNINGS AND PRECAUTIONS/5.13 Preexisting Asthma: Please revise the second sentence to read: “The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal.”

- i. FULL PRESCRIBING INFORMATION/12 CLINICAL PHARMACOLOGY/12.3  
Pharmacokinetics: Directly below Table 2, please revise "...tmax time of Cmax..." to read "tmax = time of Cmax".
- j. FULL PRESCRIBING INFORMATION/13 NONCLINICAL TOXICOLOGY/13.1  
Carcinogenesis, Mutagenesis, Impairment of Fertility: Please revise the first sentence to read: "Carcinogenicity studies in mice and rats administered diclofenac sodium as a dietary constituent for 2 years at doses up to 2 mg/kg/day resulted in no significant increases in tumor incidence corresponding to a human equivalent dose approximately 0.5- and 1-fold (mouse and rat, respectively) of the maximum human topical dose of diclofenac sodium topical gel (based on bioavailability and body surface area comparison)."
- k. FULL PRESCRIBING INFORMATION/16 HOW SUPPLIED: Please add the following statement: "Store the dosing card with your diclofenac sodium topical gel." after the storage statement.

5. MEDICATION GUIDE (MG)

- a. Revise your Medication Guide (MG) to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Voltaren® Gel, NDA 022122/S-007, approved 11/25/14.
- b. Ensure a sufficient number of Medication Guides is available for dispensing and distribution to patients receiving a prescription for your drug product, per 21 CFR 208.24.
- c. **Who should not take Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?/Tell your healthcare provider:** Please revise the third bullet to read: "if you are pregnant. NSAID medicines should not be used by pregnant women late in their pregnancy."
- d. **NSAID medicines that need a prescription** chart: Please add "®" to Flector, Voltaren gel, Arthrotec, Zipsor, Duexis, Oruvail, Toradol, Treximet, and Vimovo. Please relocate the "®" placed after Tolectin DS to the space after Tolectin. Lastly, please add "™" to Zorvolex.
- e. Please submit final printed labeling of the stand-alone MG; and ensure the font size is at least 10 font type.

6. PATIENT INSTRUCTIONS FOR USE

Revise your patient labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Voltaren® Gel, NDA 022122/S-007, approved 11/25/14.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling 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.

ANDA 208077

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[http://service.govdelivery.com/service/subscribe.html?code=USFDA\\_17](http://service.govdelivery.com/service/subscribe.html?code=USFDA_17)

Sincerely yours,

Carol Yun, Pharm.D.  
Labeling Project Manager  
Division of Labeling Review  
Office of Regulatory Operations  
Office of Generic Drugs  
Center for Drug Evaluation and Research