CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204623Orig1s000

MEDICAL REVIEW(S)

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA/BLA #	204623
Applicant Name	Mallinckrodt, Inc.
Date of Submission	May 4, 2012
PDUFA Goal Date	March 4, 2013
Proprietary Name / Established (USAN) Name	Pending/ Diclofenac Sodium Topical Solution, 2% w/w
Dosage Forms / Strength	Topical Solution, 2%
Proposed Indication(s)	1. For the (b) (4) (b) (4) of osteoarthritis of the knee
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Jacqueline Spaulding, M.D., Ellen Fields, M.D., MPH
Statistical Review	Feng Li, Ph.D., Dionne Price, Ph.D.
Pharmacology Toxicology Review	Jay H. Chang, Ph.D., Adam Wasserman, Ph.D.
CMC Review/OBP Review	Yong Hu, Ph.D., Prasad Peri, Ph.D.
Clinical Pharmacology Review	Ying Fan, Ph.D., Yun Xu, Ph.D.
OSI	Jyoti B. Patel, Ph.D., Sam H. Haidar, R.Ph., Ph.D.
CDTL Review	Ellen Fields, M.D., MPH
OSE/DMEPA	Anne Crandall Tobenkin, PharmD, Lubna Merchant, PharmD, M.S
OPDP/DCDP	L. Shenee Toombs, Eunice Chung-Davies, Pharm.D.
OMP/DMPP	Latonia Ford, RN, BSN, MBA, LaShawn Griffitns, MSHS-PH, BSN, RN
Other	

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication ErrorsPrevention
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion
DCDP=Division of Consumer Drug Promotion
OMP=Office of Medical Policy Initiatives
DMPP=Division of Medical Policy Programs

Signatory Authority Review Template

1. Introduction

This NDA represents a new formulation of topical diclofenac sodium and cross references Pennsaid, a topical solution of diclofenac sodium, 1.5%, approved on November 4, 2009. Pennsaid is dosed as 40 drops applied to the knee four times daily. The formulation under review is more concentrated, 2%, more viscous than the original Pennsaid formulation, and is intended to be dosed twice daily with administration via a metered-dose pump. (b) (4) [redacted] As discussed below, the findings of the clinical efficacy study (b) (4) [redacted] support an indication for the treatment of the pain of osteoarthritis of the knee.

Initially submitted as an efficacy supplement, the application was changed to a new NDA as the product is a new formulation. The application is a 505(b)(2) and relies on the Agency's prior findings for Pennsaid, a 505(b)(2) application which relied on prior findings for Solaraze and oral Voltaren.

Diclofenac is nonsteroidal anti-inflammatory drug currently approved in oral and topical formulations including a topical solution, topical gel and patch, and as an ophthalmic solution.

2. Background

The Applicant formulated the product under review, diclofenac topical solution 2%, with a different strength and a different dosing regimen than Pennsaid. As a result, the Applicant was advised that one adequate and well-controlled 12-week study was required to support a finding of efficacy, in addition to the relative bioavailability data required for a 505(b)(2) application. This advice was provided at an End-of-Phase 2 meeting in 2006 and at a guidance meeting in 2008. However, the only clinical efficacy study submitted in this NDA was a 4-week efficacy study originally intended to be an exploratory study. The Applicant presented an argument that the study was consistent with the study design described in the Office of Generic Drug's (OGD) *Draft Guidance on[Topical] Diclofenac Sodium*. The Guidance outlines that the clinical development approach for generic topical diclofenac products should consist of one bioequivalence (BE) study and one BE study with a clinical endpoint. The latter study design is a comparison of a generic diclofenac sodium topical gel, the reference listed drug, or placebo for the treatment of patients with osteoarthritis for 4 weeks. The Applicant's rationale was that diclofenac sodium topical solution 2% had similar diclofenac systemic exposure to Pennsaid and so, this guidance should apply. While this argument was initially considered inadequate, it was thought that if the pharmacokinetic data were the same, additional efficacy may not be necessary and, so, the application was filed. After reconsideration, the Applicant's argument that the studies required under the draft guidance were sufficient to support the application was found acceptable. As the exposure from the two products appeared to be

similar, it was decided that there was no need to hold this application to a substantially higher burden of evidence.

3. CMC/Device

Diclofenac sodium topical solution 2% w/w is proposed for twice daily administration provided in a metered-dose container. As described by Dr. Hu:

> The Applicant makes a reference to the DMF (b) (4) for the complete drug substance information. The DMF has been reviewed and found adequate for this application, which was initially submitted as NDA 20947/S-009. Refer to the DMF review #5 dated 6/20/2012.
>
> The composition of the 2% topical solution is similar to the marketed PENNSAID 1.5% topical solution. The 2% topical solution has a higher concentration of the active ingredient, diclofenac sodium, compared to PENNSAID 1.5% topical solution, as well as differences in inactive ingredients including elimination of glycerin and (b) (4) in ethanol concentration (b) (4) (b) (4). The 2% formulation possesses a higher product viscosity than PENNSAID 1.5% topical solution (b) (4), that would lead to more convenient product application.

Although proposed as a gel, a rheology study was performed by an independent lab and based on the data, Dr. Hu notes:

> … the 2% w/w diclofenac sodium topical formulation has been more appropriately classified as a viscous solution moving forward. (b) (4) .

The following is also from Dr. Hu's review:

> The container closure system is the (b) (4) container with a 1 mL (b) (4) metering pump. (b) (4) The target deliverable weight for the configuration (whole bottle) is 112 grams. The target dispensed weight per pump actuation is 1 gram, containing 20 mg of diclofenac sodium.
>
> …The safety of the container closure system is supported by the extractables and leachables data. The extractables observed above the analytical evaluation thresholds (AETs) calculated using the safety concern threshold of 1.5 µg/day are (b) (4) (b) (4)
>
> …The Applicant has provided 18 months leachables data for the 25 ºC/60%RH stability condition and 6 months leachables data for the 40 ºC/75%RH stability

condition for the three registration stability batches. Although some unknown leachable peaks were found above the analytical evaluation threshold (AET) calculated based on the safety qualification threshold of (b) (4) µg/day (the same qualification was recommended by the FDA for the Pennsaid 1.5% product) under the 40 ºC/75%RH stability condition, no leachables were observed above the AET at the 25 ºC/60%RH stability condition for 18 months.

It should be noted that although the to-be-marketed formulation is the same as that evaluated in the clinical program, the container closure system has evolved during development. The clinical supplies for the pivotal safety and efficacy study used the so-called (b) (4) container/pump system, which as shown by the controlled lab test data and the data from the clinicians, delivered very variable weights of the solution per actuation.

The proposed expiration dating period is 24 months and the storage statement is "Stored at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]." Considering that no significant changes have been observed based on 6 months stability data for the registration batches ((b) (4) (b) (4) pump configuration) at both 25 ºC/60% RH and 40 ºC/75% RH, the 18 months leachables data for the registration batches at 25 ºC/60% RH, and the supporting 18 months stability data for the phase 2 safety/efficacy study batch ((b) (4) container, not to-be-marketed) at 25 ºC/60% RH, this reviewer concurs with the proposed 24-month expiration dating period.

(b) (4) deficiency does not affect the quality of the product in the multi-dose container.

(b) (4)

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding CMC issues to preclude approval.

4. Nonclinical Pharmacology/Toxicology

The Applicant has cross-referenced all of the nonclinical pharmacology and pharmacokinetic literature previously submitted to NDA 20947, Pennsaid 1.5%. In addition, as noted by Dr. Chang:

> Additionally, a series of new nonclinical pharmacokinetic studies were submitted that compared the absorption and distribution of diclofenac to the knees of swine after single and repeated administrations of PENNSAID 2% vs. the marketed PENNSAID 1.5% product. Both formulations showed rapid absorption of diclofenac through the skin with plasma levels detected within 1 hour after dermal application and increasing concentrations with repeated administrations. The highest levels of diclofenac were detected in the epidermis and dermis of the skin followed by synovial fluid with levels diminishing distal to the application site.

Extraction studies were conducted to determine the safety of the container/closure system. With the exception of (b) (4) all of the compounds extracted were below the qualification threshold of 5 mcg/day. According to Dr. Chang:

> (b) (4) have been commonly used in pharmaceutical formulations and are included in the FDA Inactive Ingredient Guide with much higher listed potencies. Though there has been recent guidance from CDER to limit the use of certain (b) (4) in both marketed and investigational pharmaceutical products due to developmental and reproductive toxicity observed in nonclinical studies, the estimated TDE of (b) (4) /day is at least (b) (4) -fold lower than levels considered reasonably safe for (b) (4) by EPA.

Therefore, no further safety qualification of potential leachable compounds is necessary for this product.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The basis for approving diclofenac sodium topical solution 2% relies in part on the prior findings for Pennsaid. A relative bioavailability study comparing the two products is necessary to form not only a scientific bridge for relying on the Agency's prior findings, but to determine the systemic expsoure to diclofenac for both products. While these products are intended to act locally, the relative systemic exposure can provide important information about the ability of the diclofenac to penetrate from topical administration. This is based on the reasoning that if the same amount can penetrate into the blood, the same amount reaches local tissues. Initially, as no 12-week efficacy study was submitted, consideration was given to relying primarily on the pharmacokinetic data to support the application. As a result, the two relative bioavailability studies, Study COV05100070 and Study COV05100175, were initially considered pivotal studies in supporting the application and were submitted for inspection by the Office of Scientific Investigation (OSI). The OSI inspection found that reserve samples were not retained at the clinical study site and, therefore, the authenticity of the test and reference drug products administered cannot be confirmed for either study. As a result, OSI concluded that the data cannot be accepted for Agency's review and the Applicant must repeat the relative BA study with Pennsaid 1.5%.

As detailed in Dr. Fan's review, Study COV05100170 was a Phase 1, randomized, open-label, multiple-dose, 3-way crossover study. Diclofenac sodium topical solution 2%, 2 mL 40 (b)(4) mg/knee twice daily (original container-closure system), Pennsaid 1.5%, 1.2 mL 19.3 mg/knee four times daily and oral diclofenac (Sandoz, ANDA 74394) delayed-release tablets 75 mg twice daily were administered for 7 days with one dose on Day 8 (one dose on Day 8 for Pennsaid.)

Study COV05100175 was a Phase 1, randomized, open-label, multiple-dose, 2-way crossover study. Diclofenac sodium topical solution 2%, 2 mL, 40 (b)(4) mg/knee, twice daily (to-be-marketed container-closure system) and Pennsaid 1.5% 1.2 mL, 19.3 mg/knee, four times daily were administered for 7 days with one dose on Day 8 (two doses on Day 8 for Pennsaid.)

The steady state AUC and Cmax were similar for both topical diclofenac products and considerably lower than the oral product. Details of the results are not included based on the OSI recommendations.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that the relative bioavailability study must be repeated. It will be sufficient for the Applicant to conduct a study comparing diclofenac sodium topical solution 2% and Pennsaid, as noted in the addendum to the clinical pharmacology review. As Pennsaid (NDA 20947) referenced the Agency's prior findings for oral Voltaren tablet and Solaraze to support systemic safety and efficacy, and dermal safety and carcinogenicity, respectively, cross reference to Pennsaid and a relative bioavailability study with Pennsaid are sufficient to support reliance of these findings for diclofenac sodium topical solution 2%.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

A single 4-week efficacy study was submitted in support of this application. Initially intended as a Phase 2 study, COV05100031 was a randomized, double-blind, vehicle-controlled parallel group study in patients with OA of the knee. The study was a flare design; after prior analgesics were discontinued, when pain reached the minimum intensity of 5 out of 11 along with a 2 point increase, adult patients were randomized to diclofenac topical solution 2%, 40 (b)(4) mg (2 mL) or vehicle control. Acetaminophen was allowed as rescue medication. Details of the study are available in the reviews by Drs. Fields and Spaulding.

Ninety-two percent of the 260 subjects randomized completed the study. As discussed by Dr. Li, as the study was intended initially to be an exploratory, it was powered at 80% for the WOMAC pain endpoint with significance level 0.1. However, the study was submitted as the sole efficacy study. Dr. Li was able to replicate the Applicant's results of the primary efficacy

analysis, change from baseline in the Western Ontario and McMaster Universities (WOMAC) pain subscale, and secondary endpoints, change from baseline in WOMAC function and Patient Global Impression of Change are presented in Table 3 from his review.

Table 1: Efficacy Results at Week 4

		Least Square Means (Standard Error)			
Endpoint		**Diclofenac sodium 2% (N=130)**	**Vehicle (N=129)**	**Difference (95% CI)**	**P-value**
WOMAC pain	Baseline mean (SD)	12.4 (3.1)	12.6 (3.4)		
	Change from Baseline	-4.4 (0.4)	-3.4 (0.4)	-1.0 (-2.0, 0.0)	0.04
WOMAC function	Baseline mean (SD)	(b) (4)			
	Change from Baseline				
Patient's global	Baseline mean (SD)				
	Change from Baseline				

SD: standard deviation; CI: confidence interval.
Source: Clinical Study Report.

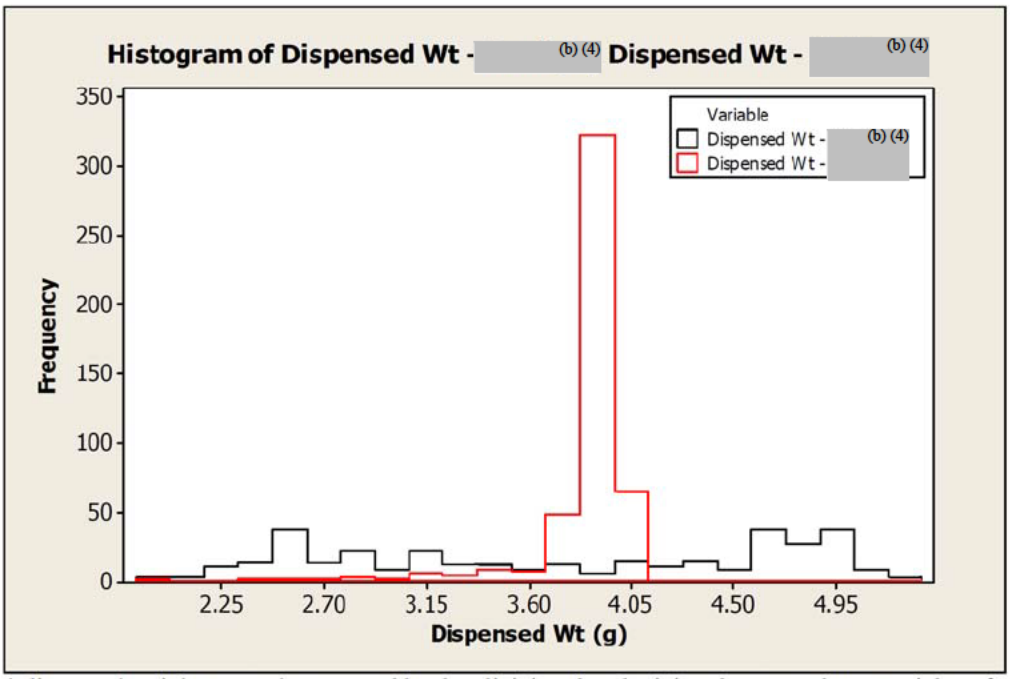
(b) (4) Using a significance level or 0.05, only the results of the WOMAC pain subscale demonstrate a statistically significantly greater reduction in pain intensity for the study drug compared to placebo. The effect size is small, but consistent with the results from topical analgesic studies in patients with OA. (b) (4) However, a successful outcome for the WOMAC pain subscale alone can support an indication for the treatment of the pain of osteoarthritis.

The Applicant did an analysis of the amount of study drug administered by subjects based on the weight of the returned bottles of study drug. This analysis, described in detail in Drs. Fields and Spaulding's reviews, found that there was a large amount of variability in the dosing among subjects, with an overall trend toward under dosing. The Applicant attributes this to subjects having difficulty using the dispensing system. The intended dose for the study was 2 grams in 2 mL, dispensed as two pumps of the metered dose pump dispenser. However, less than the full volume was delivered if the pump did not return to the full height prior to the second depression. This is important because under dosing during Study COV05100031 may have contributed to a smaller treatment effect.

The Applicant has changed the container/closure system in the final to-be-marketed product to a pump that delivers a much more consistent volume. A comparison of the dispensing weight for the two pump configurations from the two relative bioavailability studies is provided in the

figure from Dr. Hu's review below. The [(b) (4)] to-be-marketed device dispensed a much more consistent weight of drug product than the [(b) (4)] device used in Study COV05100031.

Figure 2. Histograms of dispensed weight from [(b) (4)] (Study COV05100070) and [(b) (4)] (Study COV05100175) containers*



* dispensed weights were documented by the clinicians by obtaining the pre-and post-weights of the containers

This 4-week efficacy study will be suitable to support efficacy as part of a weight of evidence argument, in conjunction with pharmacokinetic data once the relative bioavailability study is repeated. As long as the exposure to diclofenac is similar for the 1.5% and 2% diclofenac topical products in the repeat study, together with the results of Study COV05100031, there will be adequate evidence to support a finding of efficacy.

8. Safety

The safety of diclofenac sodium topical solution 2% was reviewed by Dr. Spaulding who found no new or unexpected findings. The safety database consists of 189 subjects and the Applicant is also relying on the safety of Pennsaid given the similarity of the products. As noted in Dr. Fields' review:

> The safety profile of diclofenac sodium topical solution 2% was assessed in 130 patients with primary OA of the knee, and 59 subjects in Phase 1 studies. Of the 130 subjects with OA, 129 received an average of 28 days of study drug BID on the study knee. Eighty-one subjects received an average of 28 days of BID treatment on the contralateral knee.

Dr. Spaulding reported that no serious adverse events or deaths were reported in the safety population. Early discontinuations were few, and discontinuations due to adverse events were predominantly local application site reactions. Approximately 40% of patients in both treatment groups had treatment emergent adverse events, the most common of the relevant events were application site dryness, application site exfoliation, and application site erythema.

9. Advisory Committee Meeting

No advisory committee meeting was held for this reformulation of an existing product with no new safety concerns.

10. Pediatrics

Pediatric studies under PREA for the entire age range of birth to <17 years were waived because the studies would be highly impracticable to conduct, since the number of pediatric patients with OA is too small to study. The Pediatric Research Committee (PeRC) agreed to this waiver on January 30, 2013.

11. Other Relevant Regulatory Issues

As noted in Section 5, as a result of the failure to retain study samples at the clinical pharmacology sites, OSI has recommended that FDA not rely on the data from the relative bioavailability studies.

There are no other unresolved relevant regulatory issues.

12. Labeling

As noted by Dr. Fields:

> Proprietary name
>
> At this writing a proprietary name has not been approved by the Agency. The Applicant proposed the proprietary name, "(b) (4)," at the time of NDA submission, however the Division of Medication Errors and Prevention Analysis (DMEPA) of the Office of Surveillance and Epidemiology (OSE) determined that while the modifier (b) (4)" conveys that the (b) (4), it does not convey the change in formulation, specifically the dose or frequency of administration. This was communicated to the Applicant via a teleconference in July, 2012, and the proposed name was withdrawn. Since then, the names (b) (4), and (b) (4) have been proposed by the Applicant and subsequently withdrawn. DMEPA recommended to the Applicant at a meeting held January 23, 2013, (b) (4)

[redacted], they propose the name Pennsaid, and highlight the differences from the original formulation in the labels and labeling. At this time, a new proprietary name has not been proposed by the Applicant.

Suggested edits for improving the package insert, medication guide, and the carton and container labels have been received from DMEPA, DMPP and DCDP and have been implemented.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action –Complete Response

- Risk Benefit Assessment

A complete response is required at this time because of the findings of the Office of Scientific Investigation, that the clinical samples were not retained at the clinical site where the relative bioavailability studies were conducted so that the authenticity of the test and reference drug products administered at could be confirmed. There was evidence of efficacy for diclofenac topical solution 2%, for the management of the pain of osteoarthritis in a 4-week adequate and well controlled clinical study based on the WOMAC Pain subscale. [redacted] No new safety concerns were identified in the clinical program. A repeat relative bioavailability study comparing diclofenac topical solution 2% with Pennsaid is required to complete the data required for approval.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Commitments

None

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/s/

SHARON H HERTZ
03/04/2013

Cross-Discipline Team Leader Review

Date	February 11, 2013
From	Ellen Fields, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA#	204623
Applicant	Mallinckrodt, Inc.
Date of Submission	May 4, 2012
PDUFA Goal Date	March 4, 2013
Proprietary Name / Established (USAN) names	TRADENAME/ Diclofenac sodium topical solution 2%
Dosage forms / Strength	Topical solution 2% (b) (4)
Proposed Indication(s)	(b) (4)
Recommended:	Complete Response

1. Introduction

Mallinckrodt, Inc. submitted a New Drug Application (NDA) for diclofenac sodium topical solution 2% seeking an indication for (b) (4) (OA) of the knee. The Applicant states that diclofenac sodium topical solution 2% is a modified formulation of PENNSAID (diclofenac sodium topical solution 1.5%), which was approved in November, 2009, for the treatment of signs and symptoms of OA. The Applicant's rationale for this product is that it will provide a more convenient dosing regimen, decreasing dosing frequency from four times daily for PENNSAID to two times daily.

Diclofenac a member of the nonsteroidal anti-inflammatory drug (NSAID) class, and is available as oral, ophthalmic, and topical formulations in the US in different salt forms. Other than PENNSAID, approved and marketed topical diclofenac products include Voltaren gel (NDA 22-122, diclofenac sodium 1%) indicated for the relief of the pain of OA, Flector patch (NDA 21-234, diclofenac epolamine 1.5%) indicated for topical treatment of acute pain due to minor strains, sprains, and contusions, and Solaraze gel (NDA 21005, diclofenac sodium 3%) indicated for the topical treatment of actinic keratoses.

This is a 505(b)(2) application that relies in part on previous findings of efficacy and safety for Voltaren oral tablets (diclofenac sodium enteric coated tablets, NDA 19201) and Solaraze (diclofenac sodium 3% gel, NDA 21005), and cross references the Applicant's product PENNSAID (diclofenac sodium topical solution 1.5%). The Applicant has submitted a Right of Reference letter to reference the diclofenac dermal carcinogenicity and dermal photocarcinogenicity for the Solaraze NDA.

(b) (4)

[redacted], the application is actually an original NDA and was resubmitted as such.

2. Background

Nuvo Research, Inc. was the Sponsor for the original PENNSAID formulation and initiated the development of the 2% formulation that is the subject of this NDA. In 2009, Mallinckrodt, Inc. purchased PENNSAID and entered into a licensing agreement with NUVO to continue development of topical 2% diclofenac sodium formulation initially referred to as PENNSAID Gel. The formulation was further assessed by Mallinckrodt and determined in 2011 to be a topical solution rather than a gel. The 2% solution may be referred to as Pennsaid Gel in parts of this review.

At a Type B meeting for IND 75,045 held September 25, 2006, the Division agreed that one adequate and well-controlled (AWC) clinical trial in patients with OA of the knee would be sufficient to support the efficacy of the 2% formulation if the Sponsor intended to cross reference findings of efficacy and safety of PENNSAID 1.5% (if approved), as well as provide comparative pharmacokinetic data demonstrating that exposure to the two products is similar. [redacted] In 2008 Nuvo inquired whether one AWC trial of 30 days duration would be sufficient to support efficacy, and the Division told the Sponsor that [redacted] efficacy must be assessed over 12 weeks. [redacted]

In May, 2010, Mallinckrodt submitted a protocol for a 4-week double-blind study of diclofenac sodium topical solution 2% to evaluate safety and efficacy in patients with OA of the knee. The submission stated that the purpose of this study was to confirm the efficacy, the safety profile, and BID dosing regimen of the 2% product. In that submission, Mallinckrodt also stated their intention to rely in part of the safety and efficacy of Solaraze Gel and Voltaren tablets, and to cross-reference to their NDA 20947 for PENNSAID solution. This four-week study is the single AWC study submitted in this NDA to support the efficacy and safety of diclofenac sodium 2% topical solution for the proposed indication.

This NDA submission included three clinical studies; two pharmacokinetic studies, Study COV05100070, a Phase 1, randomized, open-label, multiple-dose, three-way, crossover trial that evaluated the pharmacokinetics, relative bioavailability and safety of the 2% solution, PENNSAID 1.5% solution, and Voltaren 75mg (diclofenac sodium) tablets in healthy volunteers, Study COV05100075, a Phase 1, randomized, open-label, multiple-dose, 2-way crossover study that evaluated the pharmacokinetics, relative BA, and safety of the 2% solution and PENNSAID, and Study COV05100031, a randomized, double-blind, multiple-dose, vehicle-controlled, parallel group study of diclofenac topical solution 2% in adults with OA of the knee.

The Applicant referred to the Office of Generic Drug (OGD) *Draft Guidance on[Topical] Diclofenac Sodium* as their justification for conducting a four-week efficacy study in lieu of

the 12-week AWC study the Division had advised. The Guidance discusses the clinical development approach for generic drugs, that includes two studies; one bioequivalence (BE) study and one BE study with a clinical endpoint. The latter study would involve the treatment of patients with OA of the knee using a generic diclofenac sodium topical gel, the reference listed drug, or placebo for 4 weeks, with the primary endpoint being evaluated at the end of the four-week treatment. The Applicant's rationale was that since the 2% solution showed similar systemic exposure to PENNSAID, this guidance should apply.

At the time of NDA filing the Division did not agree with the Applicant regarding the applicability of the OGD guidance, however the application was filed because the Division's thinking at that time was that since the systemic exposure to PENNSAID and the 2% solution were similar, an approval could be primarily based on pharmacokinetic findings, with confirmation of efficacy based on the four-week clinical trial. Since the two PK studies would be the key determinants of the approvability of diclofenac sodium 2% topical solution, the Office of Scientific Investigation was consulted to inspect the clinical and analytical sites used for the studies COV05100070 and COV05100075. OSI, in their review, noted no issues with the analytical aspects of the studies, however due to lack of retention of test and reference drug samples at the clinical sites, the authenticity of these products could not be confirmed and, therefore, the data from these studies cannot be accepted for further Agency review.

Prior to receiving the results of the OSI inspections, the Division had determined that the four-week study could provide support for efficacy for diclofenac sodium 2% topical solution if the systemic exposure was in fact similar between the two topical solutions, using a weight of evidence approach. However, because the data from the clinical pharmacology studies could not be accepted for Agency review, evidence of similar PK exposure was not available, and the utility of the study results as a pharmacokinetic bridge for the Listed Drugs and PENNSAID was no longer possible.

3. CMC/Device

The CMC review was conducted by Yong Hu, Ph.D., with secondary concurrence by Prasad Peri, Ph.D.

Drug Substance

The drug substance, diclofenac sodium USP, is manufactured by ESTEVE QUIMICA, S.A. in Barcelona, Spain. The drug substance information is provided in the DMF (b) (4), which was found adequate by the review team.

Drug Product

Diclofenac sodium topical solution 2% w/w is to be administered twice daily. It is provided in a metered-dose container. The drug product is manufactured by Nuvo Manufacturing in Varennes, Quebec, Canada. The manufacturing process consists of (b) (4) .

The following table from Dr. Hu's review includes the composition of the drug product:

Table 3.2.P.1-1 Composition of Dosage Form and Function of Components

Component	Function	Reference Standard	2.0% Solution Quantity mg/g	2.0% Solution Percent (%) w/w	Max IID
Diclofenac Sodium	Active Ingredient	USP	20	2.0%	(b) (4)
Dimethyl Sulfoxide	(b) (4)	USP	(b) (4)	45.5%	
Ethanol 95% (v/v)		USP			
Purified Water		USP			
Propylene Glycol		USP			
Hydroxypropyl Cellulose		NF			
TOTAL			(b) (4)	**100.0%**	

Dr. Hu states the following in his review regarding the container closure system:

> The container closure system is the (b) (4) container with a 1 mL (b) (4) metering pump. (b) (4) . The target deliverable weight for the configuration (whole bottle) is 112 grams. The target dispensed weight per pump actuation is 1 gram, containing 20 mg of diclofenac sodium. As demonstrated by the characterization data, neither the applied force nor speed impacts the dispensed weight, as long as the minimum force is applied to complete a full actuation, and the (b) (4) pump is capable of delivering a consistent amount (1 gram) of drug product per actuation. The safety of the container closure system is supported by the extractables and leachables data.
>
> It should be noted that although the to-be-marketed formulation is the same as that evaluated in the clinical program, the container closure system has evolved during development. The clinical supplies for the pivotal safety and efficacy study used the so-called (b) (4) container/pump system, which as shown by the controlled lab test data and the data from the clinicians, delivered very variable weights of the solution per actuation. As per this reviewer's communications with Dr. Ellen Fields, the clinical team concluded that 2 pump actuations (2 grams of solution) per knee is the recommended dose despite the (b) (4) container/pump system used in the safety/efficacy clinical trial did not accurately deliver 2 gram dose. To this end, the proposed to-be-marketed

> container/closure ([redacted]/pump system) is fit for purpose as it consistently delivers 1 g of solution per pump actuation.

The Applicant initially submitted only 6 months of stability data with the NDA, which did not provide enough data to grant the proposed 24-month expiry for the drug product. A teleconference was held with the Applicant on January 24, 2013, in part to gain clarification on whether additional stability data was available. The Applicant stated that 18-month leachables data from the ongoing 25°C long term stability study was available and could be submitted. This data was submitted via email on January 25, 2013 and subsequently via CMC amendment on January 28, 2013. The new data showed that no unidentified compounds were identified above the analytic evaluation threshold (AET) from the [redacted] container with any of the three registration lots at 18 months under 25°C long term conditions.

Dr. Hu states in his review:

> The proposed expiration dating period is 24 months and the storage statement is "Stored at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]." Considering that no significant changes have been observed based on 6 months stability data for the registration batches ([redacted] pump configuration) at both 25 ºC/60% RH and 40 ºC/75% RH, the 18 months leachables data for the registration batches at 25 ºC/60% RH, and the supporting 18 months stability data for the phase 2 safety/efficacy study batch ([redacted] container, not to-be-marketed) at 25 ºC/60% RH, this reviewer concurs with the proposed 24-month expiration dating period.

Facilities review/inspection

The drug substance manufacturing establishment, Esteve Quimica, SA in Spain, was deemed acceptable by the Office of Compliance EES report dated August 2, 2012.

The drug product manufacturing and testing facilities were also deemed acceptable by the Office of Compliance EES report dated February 8, 2013.

Other

The pharmaceutical development data indicated that microbial testing was not necessary for this product.

[redacted]

CMC summary

According to the CMC review team, the Applicant has provided adequate information to ensure the identity, purity, strength, and quality of the drug product in the proposed multi-dose container with a metering pump. The review team has recommended approval from the CMC perspective.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by Jay Chang, Ph.D., with secondary concurrence by Adam Wasserman, Ph.D.

The following is a summary of the nonclinical findings as stated in Dr. Chang's review:

> As there is an extensive body of nonclinical pharmacology and pharmacokinetic literature on diclofenac, the Applicant conducted only a few new studies to support the PENNSAID 2% formulation. The Applicant has cross-referenced all of the nonclinical pharmacology and pharmacokinetic literature on diclofenac submitted to NDA 20-947 for PENNSAID 1.5%, which they own. Additionally, a series of new nonclinical pharmacokinetic studies were submitted that compared the absorption and distribution of diclofenac to the knees of swine after single and repeated administrations of PENNSAID 2% vs. the marketed PENNSAID 1.5% product. Both formulations showed rapid absorption of diclofenac through the skin with plasma levels detected within 1 hour after dermal application and increasing concentrations with repeated administrations. The highest levels of diclofenac were detected in the epidermis and dermis of the skin followed by synovial fluid with levels diminishing distal to the application site.

Extractables and Leachables

Dr. Chang states that the diclofenac sodium 2% product will employ a different container closure system than the approved PENNSAID 1.5% product. The new system is the (b) (4) (b) (4) container, which features a (b) (4) bottle design, with a 1 mL metering pump. The safety of the container/closure system was assessed via extraction studies followed by a literature-based toxicological evaluation of the substances that were extracted to determine the safe level of exposure for this topical solution. Estimated total daily exposures were calculated for the compounds extracted (see Dr. Chang's review for details), and all fell within the qualification threshold of 5 µg/day recommended by Product Quality Research Institute (PQRI) Leachables and Extractables Working Group except for (b) (4) However the TDE for (b) (4) was over (b) (4)-fold lower than levels considered reasonably safe by the EPA. Based on Dr. Chang's review of this data, no further qualification of these compounds for the proposed container closure system is considered necessary.

Leachables testing on the container/closure system was incorporated in stability studies under both long-term and accelerated conditions. As stated in the CMC section, only 6-month stability data was initially submitted with the NDA, however 18 months were submitted on January 28, 2013 which support the Applicant's proposed 24-month expiry.

The proposed label is essentially the same as the PENNSAID 1.5% label in terms of nonclinical information. The nonclinical team made changes to the label in the following sections: Pregnancy (8.1), and 13.1 (Carcinogenesis, Mutagenasis, Impairment of Fertility). Changes to the label were based on information in the Solaraze gel and Voltaren tablets labels. See Dr. Chang's review for details.

Approval of this NDA is recommended from the nonclinical perspective.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review was conducted by Ying Fan, Ph.D., with secondary concurrence by Yun Xu, Ph.D.

The pharmacokinetic diclofenac sodium topical 2% solution was evaluated in two relative bioavailability studies (Study COV05100070 and Study COV05100175). OSI inspection was requested on both relative bioavailability studies, COV05100170 and COV05100175, since at the time of NDA filing, these studies were determined to be the key bases for approval. Based on the OSI memo dated December 18, 2012, due to the lack of reserve samples, the authenticity of the test and reference drug products administered cannot be confirmed for both studies. Therefore, data cannot be accepted for further Agency's review. The Applicant will need to repeat the relative BA study with diclofenac sodium topical 2% solution, PENNSAID 1.5%, and oral diclofenac tablet.

Since the results from the two completed relative BA studies are not acceptable for review by the Agency due to the OSI inspection findings, the results are not discussed in this review.

The Office of Clinical Pharmacology finds NDA 204623 not acceptable from a Clinical Pharmacology perspective due to the failed OSI inspection results on Studies COV05100070 and COV05100175. The Applicant must repeat the relative bioavailability study with diclofenac sodium topical 2% solution, PENNSAID 1.5%, and oral diclofenac tablet

6. Clinical Microbiology

Clinical microbiology assessment was not necessary for this product as it is not an antimicrobial.

7. Clinical/Statistical- Efficacy

The clinical review of this NDA was conducted by Jacqueline Spaulding, MD.

The clinical development of diclofenac sodium 2% topical solution consisted of three studies, one efficacy and safety trial, and two relative bioavailability studies as shown in the Applicant's table below:

Table 1: Overview of Trials for Pennsaid Topical Solution 2% in Treatment of OA of the Knee

Category	COV05100031	COV05100070	COV05100175
Trial Design	Randomized, double-blind, multiple-dose, vehicle-controlled, parallel group	Randomized, open-label, multiple-dose, 3-way crossover	Randomized, open-label, multiple-dose, 2-way crossover
Subject Population	Males and females, 40-85 years with primary OA of the knee with moderate flare after washout of stable pain therapy	Healthy males and females, 18-55 years	Healthy males and females, 18-55 years
Objectives	Efficacy and safety	PK and BA vs 1.5% solution and tablet (bridging)	PK and BA vs 1.5% solution
Treatment Groups	PENNSAID solution 2%, 2 mL BID, topical Vehicle, 2 mL BID, topical	PENNSAID solution 2%, 2 mL BID, topical PENNSAID solution 1.5%, 1.2 mL QID, topical Diclofenac tablet, 75 mg, BID, oral	PENNSAID solution 2%, 2 mL BID, topical PENNSAID solution 1.5%, 1.2 mL QID, topical
Treatment Duration	4 weeks	7.5 days; each treatment period was separated by a 21-day washout period	7.5 days; each treatment period was separated by a 21-day washout period
Scheduled Visits During Treatment	Days 0, 7 (telephone), 10 (telephone), 14, 24 (telephone), 28	Days 1-8 (inpatient)	Days 1-8 (inpatient)
Countries	USA	USA	USA
Number of Subjects	260 total subjects PENNSAID 2%: 131 (130 treated) Vehicle control: 129	30 total subjects PENNSAID 2%: 22 PENNSAID 1.5%: 27 Diclofenac sodium tablets: 26	32 total subjects PENNSAID 2%: 32 PENNSAID 1.5%: 31

BA = bioavailability, BID = twice daily, OA = osteoarthritis, PK = pharmacokinetics, QID = 4 times daily, USA = United States of America

Note: The daily dose of diclofenac sodium for PENNSAID 2% topical solution BID is 80 mg (for each knee) and the daily dose of diclofenac sodium for PENNSAID 1.5% topical solution QID is 77.2 mg (for each knee).

Source: NDA 204623, Clinical Overview, Table 1-2 pg. 13 of 48

As discussed in Section 2 of this review, at the time of filing, the single AWC clinical study was deemed inadequate to support the safety and efficacy of the 2% formulation, since historically the Division has required a 12-week AWC efficacy trial to support a chronic pain indication such as OA; however, upon further internal deliberation and consideration of the generic guidance for topical diclofenac products, the Division determined that since the systemic exposure of the 1.5% and 2% products appeared similar, the study could be used to support efficacy and safety as part of a weight of evidence, that would also include the relative BA studies conducted by the Applicant.

Study COV05100031 was a flare design, Phase 2, randomized, double-blind, vehicle-controlled, parallel group clinical study to evaluate the safety and efficacy of Pennsaid Gel (designated by this name prior to determination that it is actually a solution) in the symptomatic treatment of osteoarthritis of the knee. The objectives were: 1) to characterize the analgesic effect and to determine the effect size for Pennsaid Gel by evaluating multiple efficacy endpoints to assist in planning the Phase 3 program, 2) To determine if an effective level of analgesia is maintained throughout the dosing interval, and 3) To evaluate the safety of Pennsaid gel in the treatment of OA of the knee. The study was powered to detect a difference in pain between diclofenac sodium 2% and the vehicle control with the significance level at 0.1. When this study was conducted, it was not intended to be the key study in support of efficacy for diclofenac sodium topical solution 2%, but rather an exploratory study to gather data to plan for the Phase 3 trial.

Subjects enrolled in the study were male and female patients aged 40-85 years with a history consistent with primary OA of the knee and radiologic evidence of OA of the knee within one year prior to screening, consistent with Grade 2 or 3 Kellgren-Lawrence grading scale. Enrolled subjects were required to be have been on a stable analgesic (oral or topical NSAID or acetaminophen), at least three days per week for the month prior to screening. Following washout of the subjects' stable pain treatment, they must have experienced a flare of pain resulting in a baseline minimum pain score of at least 5 on an 11-point Numerical Rating Scale (NRS), and at least a 2-unit worsening from the screening pain score. The baseline pain score was an average of the NRS pain scores reported over the last 24 hours for three days prior to randomization. Subjects were excluded who had underlying conditions including secondary OA of the knee, prior knee surgery, uncontrolled cardiac, renal, hepatic or other systemic diseases, rheumatologic conditions, documented GI ulcer or bleeding in last 6 months, or were taking prohibited medications.

Study treatments included diclofenac topical solution 2% and a vehicle control topical solution applied to the study knee for four weeks. Rescue medication was acetaminophen up to 1950mg/day during the treatment phase except the three days prior to clinic visits. Allowed concomitant medications included non-analgesic therapy for non-arthritis conditions, stable low-dose aspirin for cardiovascular prophylaxis, stable sedative hypnotics, stable therapy with antidepressants, and use of a cane if used for 30-days prior to screening. Prohibited medications included other NSAIDs (oral or topical), muscle relaxants, corticosteroids, opioid or other analgesics, topical products on the knees, intra-articular treatments for the knee, non-pharmaceutical therapy to relieve knee pain, sedatives for insomnia, chondroitan, glucosamine, herbal remedies, and heat.

Following screening, study subjects underwent a 3-14 day washout period when no analgesics were allowed. If at baseline the subject met the flare criteria (pain score of at least 5 on an 11-point NRS, and at least a 2-unit worsening from the screening pain score) they were randomized 1:1 to receive either study drug or vehicle control. Treatment consisted of 2 actuations (20mg diclofenac sodium/actuation) of study drug or vehicle to the index knee every 12-hours, at the same time each day. If the non-study knee became painful at any time during the study, the subject was to also treat that knee with study drug/vehicle. Subjects were to report pain intensity scores twice daily via an interactive voice response system (IVRS) using an 11-point NRS for the index knee and non-index knee if treated, and daily use of rescue medication. Subjects completed the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index questionnaire at baseline (Day 1 before treatment). Clinic visits were scheduled for Weeks 2 and 4, at which time physical examination and vital signs, application site skin irritation scores, adverse event evaluation, WOMAC OA Index (pain, physical function, stiffness each on a 5-point Likert scale), Patient Global Assessment (PGA, assessed 11-point NRS), and laboratory evaluation (only end of study) were collected.

The primary efficacy variable was the change in WOMAC pain subscale score from baseline to Week 4. Secondary efficacy endpoints included the daily pain intensity evaluated using NRS, subject's global assessment (PGA), WOMAC function, WOMAC stiffness, and use of rescue medication.

A total of 260 subjects were randomized, 131 to diclofenac 2% and 129 to the vehicle control. One subject was randomized to diclofenac 2% in error and did not receive any study drug. All other randomized subjects were included in the mITT population. The subject disposition is shown in Table 2 with percentages based on the number of subjects in the mITT population. Overall, approximately 8% of the subjects discontinued early. The dropout rates of the diclofenac sodium 2% and control groups were 6% and 9% respectively. There were four subjects (3%) from the diclofenac sodium 2% group and five subjects (4%) from the control group who discontinued because of adverse events. Two subjects (2%) from the control group dropped out due to lack of efficacy.

Table 2: Subject Disposition − Number (%) of Patients

	Diclofenac sodium 2%	**Vehicle control**	**Total**
Randomized	131	129	260
Received treatment (mITT)	**130**	**129**	**259**
Terminated prematurely	**8 (6%)**	**12 (9%)**	**20 (8%)**
Reason for discontinuation			
Adverse event	4 (3%)	5 (4%)	9 (3%)
Subject withdrew consent	1 (1%)	2 (2%)	3 (1%)
Lack of efficacy	0	2 (2%)	2 (1%)
Protocol non-compliance	1 (1%)	1 (1%)	2 (1%)
Withdrawal of subject by Sponsor	1 (1%)	0	1
Other	1 (1%)	2 (2%)	3 (1%)

Source: Clinical study report.

The demographic and baseline characteristics were similar between the two treatment groups. The majority of the subjects were female (65% in diclofenac sodium arm and 70% in vehicle control). Overall, the mean age was about 60 years. Approximately 85% of the subjects were white. The average WOMAC subscale scores at baseline were similar for pain (12.4 and 12.6), physical function (42.9 and 43.3), and stiffness (5.3 and 5.4) for the Pennsaid 2% and vehicle control group, respectively.

Analysis of Study Drug Compliance

The Applicant conducted an analysis of treatment compliance. Based on daily study drug administrations reported by subjects using the IVRS, the compliance for both treatment groups was greater than 80%. In addition to patient reports of dosing, bottle weights were measured at dispensing and return to determine the amount of study drug used between study visits. This amount was compared to the amount expected to have been used (based on the number of knees treated and the number of days between study visits) to determine the percentage of actual/expected used and from that to calculate the average dose weight administered for each subject. The following Applicant's table from Dr. Spaulding's review shows the results of this analysis.

Table 3: Average Weight of Study Drug Administered Per Dose Calculated from Dispensed and Returned Bottle Weights

Compliance Assessment	Study Treatment		
	PENNSAID Gel N=130 n (%)	Vehicle Control N=129 n (%)	Total N=259 n (%)
Week 2:			
0 – 1.2 mg	43 (33.1%)	43 (33.3%)	86 (33.2%)
> 1.2 mg - ≤ 1.6 mg	38 (29.2%)	41 (31.8%)	79 (30.5%)
> 1.6 - ≤ 1.8 mg	11 (8.5%)	12 (9.3%)	23 (8.9%)
> 1.8 - ≤ 2.2 mg	22 (16.9%)	22 (17.1%)	44 (17.0%)
> 2.2 - ≤ 2.4 mg	7 (5.4%)	9 (7.0%)	16 (6.2%)
> 2.4 mg	9 (6.9%)	2 (1.6%)	11 (4.2%)
Total non-missing	130 (100%)	129 (100%)	259 (100%)
Week 4:			
0 – 1.2 mg	41 (33.9%)	43 (36.8%)	84 (35.3%)
> 1.2 mg - ≤ 1.6 mg	36 (29.8%)	33 (28.2%)	69 (29.0%)
> 1.6 - ≤ 1.8 mg	9 (7.4%)	10 (8.5%)	19 (8.0%)
> 1.8 - ≤ 2.2 mg	16 (13.2%)	16 (13.7%)	32 (13.4%)
> 2.2 - ≤ 2.4 mg	7 (5.8%)	5 (4.3%)	12 (5.0%)
> 2.4 mg	12 (9.9%)	10 (8.5%)	22 (9.2%)
Total non-missing	121 (93.1%)	117 (90.7%)	238 (91.9%)

Note: The source table displays the average percentage of actual/expected weight of study medication used; from that the average dose weight used can be calculated, which is displayed above in mg/dose for ease of interpretation.

Source: CSR-COV05100031, Table 8, pg. 56 of 106

The Applicant stated that the results show a wide variability of dosing among subjects in both treatment groups. Of note, the above units for amount dispensed should be in grams, not milligrams, which was confirmed by the Applicant. The Applicant provided the following explanation for the dosing variability among the subjects:

> However, the average dose weight indicates that there was notable under-dosing in both treatment groups. This was likely due to subject difficulty using the dispensing system. Based on laboratory studies, it was known that the dispensing volume was very consistent per pump actuation unless the pump mechanism did not return to full stroke position. If drug product was dispensed before the pump mechanism returned to full stroke position, the dispensed weight of drug product would be below target specification. It was noted that the pumping mechanism would periodically stick and required manual manipulation to return it to full position before initiating another pump actuation. Instructions provided to each subject prior to first dose addressed these issues. However, given the wide variability in calculated study drug amounts, it is likely that the dispenser was not reliably dispensing the expected 2 [mg/dose]. Due to the difficulties previously identified with the dispensing system and in light of these findings, Mallinckrodt has undertaken to identify, qualify and select a different dispenser for future studies and marketing.

This finding is relevant since the Applicant has changed the container/closure system from the one used in the clinical trial so that there is less variability in dosing. The Applicant demonstrated that the revised system delivers a consistent amount (1 gram) of drug product per actuation (see CMC review). Since the data regarding dosing from the clinical trial show that more patients were underdosed rather than overdosed, the use of the new container/closure system that more reliably delivers 1 gm per actuation is acceptable, as the efficacy using this device is expected to be at least as good as the one used in the clinical trial.

Results of Efficacy Analyses

The statistical analysis was conducted by Feng Li, Ph.D., with secondary concurrence by Dionne Price, Ph.D. As stated in Dr. Li's review:

> The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model with baseline score as a covariate and factors for treatment and whether the contralateral knee was treated. The ANCOVA model was determined through a backward elimination process with the initial model including terms for baseline pain score, gender, age (categorized as < 65 or not), Body Mass Index (< 30 or not), and whether the contralateral knee was treated. Through the backward elimination process, terms that were not significant (p-value>0.1) in the initial model were removed. The same ANCOVA model was also used to analyze the continuous secondary efficacy points. The primary analysis was conducted on a modified intention-to-treat (mITT) population including all subjects who were randomized and applied at least one dose of study medication.
>
> In the primary analysis, missing WOMAC assessments for subjects who discontinued early due to lack of efficacy or adverse events were imputed using a baseline observation carried forward approach (BOCF). Missing WOMAC assessments due to other reasons were imputed using a last observation carried forward approach (LOCF). Sensitivity analyses were conducted based on a BOCF approach and a LOCF approach. For subjects who inappropriately used rescue medication within 3 days of a study visit, the WOMAC and PGA scores were replaced using the baseline values regardless of discontinuation status or reason.
>
> The comparison between diclofenac sodium 2% and the vehicle control was conducted at the 0.10 significance level. The statistical analysis plan stated that this would be an exploratory study, and no adjustment would be made for multiple comparisons.

Dr. Li replicated the Applicant's results for the primary efficacy analyses as stated in his review and shown in the following table.

> Table 4 shows the results for WOMAC assessments from an ANCOVA model with terms including treatment, whether the non-study knee was

treated, and the baseline value. The ANCOVA model was determined based on the pre-specified backward selection procedure. A negative value of change from baseline indicated an improvement as compared to baseline. The maximum possible values of the WOMAC pain and functions endpoints were 20 and 68 respectively as both were presented as the sum of responses to a number of questionnaires. The diclofenac sodium 2% group had numerically better response in WOMAC pain, function, and patient's global impression than the control group. (b) (4)

The protocol stated that a subject could initiate the treatment for the contralateral knee if painful anytime during the study. Thus, I was initially concerned about the inclusion of the treatment status of the contralateral knee as a factor in the ANCOVA model as the decision to initiate treatment on the contralateral knee could occur after baseline and be affected by the treatment received. My concern was alleviated after I found that only four subjects initiated treatment on the contralateral knee after baseline.

Table 4: Efficacy Results at Week 4

		Least Square Means (Standard Error)			
Endpoint		**Diclofenac sodium 2% (N=130)**	**Vehicle (N=129)**	**Difference (95% CI)**	**P-value**
WOMAC pain	Baseline mean (SD)	12.4 (3.1)	12.6 (3.4)		
	Change from Baseline	-4.4 (0.4)	-3.4 (0.4)	-1.0 (-2.0, 0.0)	0.04
WOMAC function	Baseline mean (SD)	(b) (4)			
	Change from Baseline				
Patient's global	Baseline mean (SD)				
	Change from Baseline				

SD: standard deviation; CI: confidence interval.
Source: Clinical Study Report.

The applicant conducted sensitivity analyses using BOCF and LOCF as imputation approaches for dropouts. According to Dr. Li's review, the results from the sensitivity analyses were similar to those of the primary analysis.

Dr. Li also conducted an analysis of rescue medication usage. The following table from his review demonstrates that overall, the percentage of subjects who took rescue during the study was similar between the treatment groups. More subjects in the control group than the diclofenac sodium group took rescue after Week 2. Approximately 21% of the patients in the control group and 12% of the patients in the diclofenac sodium 2% took rescue within 3 days of Week 4 visit. For these subjects, the Week 4 WOMAC assessments were replaced with baseline values per the pre-specified primary analysis. Dr. Li found that that if the observed WOMAC assessments were used instead of the baseline values the difference between the groups in the primary endpoint would not be significant, indicating that the control group might have had favorable responses after taking rescue.

Table 1: Percentage of Subjects Using Any Rescue Medication

Period	Diclofenac sodium 2% (N=130)	Vehicle Control (N=129)	P-value [1]
Week 1 and Week 2	89 (68%)	94 (73%)	0.4
Week 3 and Week 4	68 (52%)	82 (64%)	0.07
Overall	95 (73%)	99 (77%)	0.5

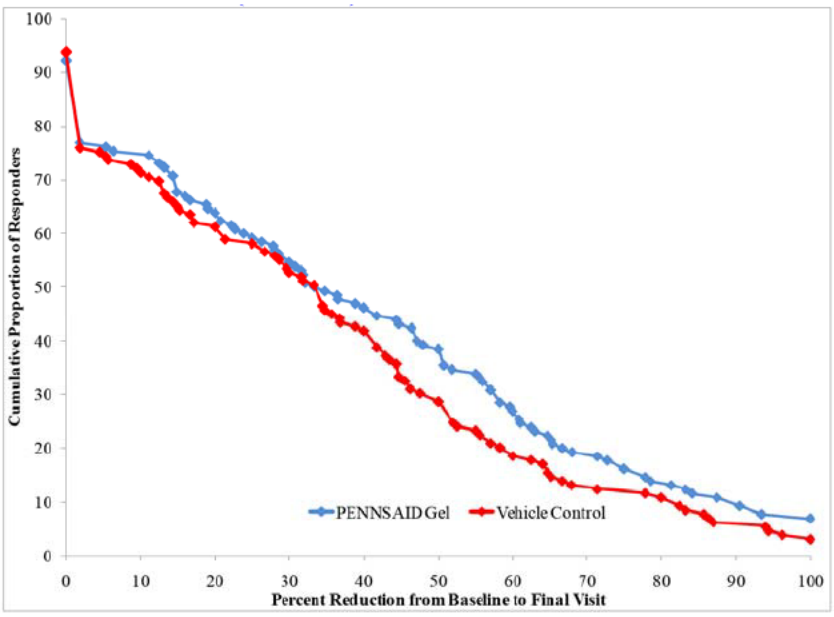
[1] Chi-Square test;
Source: Clinical Study Report

Subgroup analyses of the primary efficacy variable conducted by Dr. Li found that the results for subgroups by sex, age, BMI, and treatment status of the contralateral knee were generally consistent with the overall population.

(b) (4)

The Applicant's cumulative responder analysis of the average pain during the last 24-hours at the final study visit is shown here. There is some separation of the curves between treatment groups for approximately 35% and 75% reduction from baseline.

Figure 1: Cumulative Proportion of Responders Analysis: Average Pain During the Last 24 Hours at Final Visit



Efficacy Conclusions

Both Drs. Spaulding and Li concluded that the diclofenac sodium 2% group had a numerically better response in WOMAC pain, physical function, and patient's global assessment than the control group at Week 4. However, only the difference in WOMAC pain achieved statistical significance at level 0.05. (b) (4)

I am in agreement with these conclusions. The Division determined that this 4-week efficacy study can support findings of efficacy as part of a weight of evidence argument, since the pharmacokinetic exposure appears similar for the 1.5% and 2% diclofenac topical products, and, therefore, the applicability of the OGD guidance for topical diclofenac. (b) (4) However, the difference in WOMAC pain did achieve statistical significance at the 0.05 level, and despite the small treatment effect (-1) which is common in analgesic trials, the study supports an indication for the treatment of the pain of OA. That said, the results of the repeat pharmacokinetic studies are required confirm similar systemic exposure of the 2% and 1.5% diclofenac topical solutions in order for this four-week study to support efficacy.

8. Safety

Dr. Jacqueline Spaulding conducted the safety review for this NDA, and I am in agreement with her conclusions that there were no new or unexpected safety findings reported during the development of diclofenac sodium 2% topical solution, and the safety findings support the approval of the NDA.

A total of 189 subjects/patients were exposed to at least one dose of diclofenac sodium topical solution 2%. The safety profile of diclofenac sodium topical solution 2% was assessed in 130 patients with primary OA of the knee, and 59 subjects in Phase 1 studies. Of the 130 subjects with OA, 129 received an average of 28 days of study drug BID on the study knee. Eighty-one subjects received an average of 28 days of BID treatment on the contralateral knee.

The exact size required for the safety database was not formally discussed with the Applicant during drug development, however since the Applicant is cross-referencing the original Pennsaid NDA, safety data obtained in 911 subjects in controlled Phase 3 studies and 793 in an open-label study from that development program also support the safety of the 2% product, given the similar PK exposure from the two products (to be confirmed with the pending repeat PK study). Therefore, the total of 189 subjects exposed to the 2% product appears reasonable, as the major adverse events of interest are application site reactions, and since they are relatively common, would be observed in a database of this size.

The following summary of safety is from Dr. Spaulding's review:

> There were no serious adverse events (including deaths) reported in clinical studies in the Pennsaid (diclofenac sodium topical solution) 2% clinical development program. Twice as many patients in the placebo treatment arm were discontinued early secondary to a TEAE as compared to patients in the Pennsaid (diclofenac sodium topical solution) 2% treatment arm (6.2% vs. 3.1%, respectively). Of the Pennsaid (diclofenac sodium topical solution) 2% patients who discontinued secondary to a AE, 50% (2/4) of these patients had application site AEs whereas in the placebo group 100% of the patients who were discontinued (n=8/8) had application site AEs.
>
> The overall percentage of study patients who experienced any TEAE was 42.9% (n=111/259). The percentage of patients in the Pennsaid (diclofenac sodium topical solution) 2% treatment arm who experienced a TEAE was 40.0% (n=52/130) was lower as compared to the 45.7% (n=59/129) of placebo patients who experienced any TEAE.
>
> The most common adverse events reported in Pennsaid (diclofenac sodium topical solution) 2% patients for the placebo-controlled OA study were: application site dryness, application site exfoliation, application site erythema, and urinary tract infections.

There were no clinically significant adverse events related to laboratory assessments, vital signs or ECGs.

The following two tables from Dr. Spaulding's review show the treatment emergent adverse events leading to discontinuation of study drug by treatment group for Study xxxx, and the incidence of common treatment emergent adverse events by system organ class and preferred term for each treatment group. The most common adverse events in both cases were application site reactions.

Table 5: TEAEs Leading to Discontinuation of Study Drug

	Study Treatment		
	PENSAID Gel N=130 n (%)	**Vehicle Control N=129 n (%)**	**Total N=259 n (%)**
Number of subjects discontinuing study medication due to TEAE	**4 (3.1%)**	**8 (6.2%)**	**12 (4.6%)**
Cardiac Disorders	**1 (0.8%)**	**0**	**1 (0.4%)**
Tachycardia	1 (0.8%)	0	1 (0.4%)
General Disorders and Administration Site Conditions	**2 (1.5%)**	**8 (6.2%)**	**10 (3.9%)**
Application site dryness	0	3 (2.3%)	3 (1.2%)
Application site erythema	2 (1.5%)	4 (3.1%)	6 (2.3%)
Application site exfoliation	0	1 (0.8%)	1 (0.4%)
Application site induration	2 (1.5%)	0	2 (0.8%)
Application site pain	0	2 (1.6%)	2 (0.8%)
Application site pruritus	0	3 (2.3%)	3 (1.2%)
Application site rash	0	1 (0.8%)	1 (0.4%)
Application site scab	1 (0.8%)	0	1 (0.4%)
Infections and Infestations	**1 (0.8%)**	**0**	**1 (0.4%)**
Upper respiratory tract infection	1 (0.8%)	0	1 (0.4%)
Musculoskeletal and Connective Tissue Disorders	**0**	**1 (0.8%)**	**1 (0.4%)**
Joint swelling	0	1 (0.8%)	1 (0.4%)
Respiratory, Thoracic and Mediastinal Disorders	**1 (0.8%)**	**0**	**1 (0.4%)**
Throat tightness	1 (0.8%)	0	1 (0.4%)

Source: NDA 204623, CSR-COV05100031, Table 23, pg. 82 of 106

Table 6: Incidence of Common TEAEs by System Organ Class and Preferred Term

System Organ Class and Preferred Term	Study Treatment		
	PENSAID Gel N=130 n (%)	Vehicle Control N=129 n (%)	Total N=259 n (%)
General Disorders and Administration Site Conditions	**41 (31.5%)**	**50 (38.8%)**	**91 (35.1%)**
Application site dryness	28 (21.5%)	28 (21.7%)	56 (21.6%)
Application site exfoliation	9 (6.9%)	11 (8.5%)	20 (7.7%)
Application site erythema	5 (3.8%)	15 (11.6%)	20 (7.7%)
Application site pruritus	3 (2.3%)	18 (14.0%)	21 (8.1%)
Application site pain	2 (1.5%)	4 (3.1%)	6 (2.3%)
Infections or Infestations	**7 (5.4%)**	**6 (4.7%)**	**13 (5.0%)**
Urinary tract infection	4 (3.1%)	1 (0.8%)	5 (1.9%)

*Most common defined as incidence of > 3% in either treatment group

Source: NDA 204623, CSR-COV05100031, Table 20, pg. 77 of 106

The safety profile for diclofenac sodium 2% topical solution appears similar to that of the approved PENNSAID 1.5%.

9. Advisory Committee Meeting

An Advisory Committee meeting was not convened for this application.

10. Pediatrics

Pediatric studies under PREA for the entire age range of birth to <17 years were waived because the studies would be highly impracticable to conduct, since the number of pediatric patients with OA is too small to study. The Pediatric Research Committee (PeRC) agreed to this waiver on January 30, 2013.

11. Other Relevant Regulatory Issues

Financial disclosure

The Applicant has submitted the Financial Certification and Disclosure document as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*. These were no financial arrangements reported; at this time there does not appear to be a financial conflict of interest related to data integrity.

Office of Scientific Investigations Audit (OSI)

OSI was consulted to conduct audits of the clinical and analytical portions for the two pharmacokinetic studies, COV05100175 and COV05100070, as at the time of filing, these studies were determined to be the key determinants for approval of diclofenac sodium 2% topical solution. As stated previously in this review, based on the OSI memo dated December

18, 2012, due to the lack of reserve samples, the authenticity of the test and reference drug products administered cannot be confirmed for both studies. Therefore, data cannot be accepted for further Agency's review. Refer to the OSI memo for details regarding the inspection.

OSI was also consulted to inspect three clinical sites for the efficacy study COV05100031. The sites were John Hill, MD in DeLand, Florida, Albert Schreiner, MD, in Cincinnati, Ohio, and Douglas Schumacher, MD in Columbus, Ohio. These sites were chosen based on their enrollment of the largest number of patients per site. No significant deficiencies were noted at the sites and Forms FDA 483 were not issued. According to OSI, data from these three study sites appear reliable for review by the Agency.

12. Labeling

Proprietary name

At this writing a proprietary name has not been approved by the Agency. The Applicant proposed the proprietary name, (b) (4) at the time of NDA submission, however the Division of Medication Errors and Prevention Analysis (DMEPA) of the Office of Surveillance and Epidemiology (OSE) determined that while the (b) (4) it does not convey the change in formulation, specifically the dose or frequency of administration. This was communicated to the Applicant via a teleconference in July, 2012, and the proposed name was withdrawn. Since then, the names (b) (4), and (b) (4) have been proposed by the Applicant and subsequently withdrawn. DMEPA recommended to the Applicant at a meeting held January 23, 2013. (b) (4), they propose the name Pennsaid, and highlight the differences from the original formulation in the labels and labeling. At this time, a new proprietary name has not been proposed by the Applicant.

DMEPA label, labeling and packaging review

DMEPA conducted a review of the label, labeling and packaging that included a review of medical errors reported for the original Pennsaid formulation. They concluded that the product design for the 2% solution using a pump to apply the product instead of drops for the original Pennsaid is an improvement in terms of preventing dosing errors. However, they determined that the container label, carton and insert labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product and to mitigate confusion with the currently marketed Pennsaid product. Recommendations from DMEPA were communicated to the Applicant and incorporated into the label, labeling, and package.

Other issues with label

In general, the label will be similar to the Pennsaid 1% product. The Applicant (b) (4) (b) (4). However, as stated in Section 7 of this review, findings from Study COV05100031 support the indication, treatment of the pain of osteoarthritis, (b) (4)

(b) (4)

Medication Guide
The NSAID class medication guide is required for this product as it is a member of the NSAID class of drugs. This is currently under review by the patient labeling team.

The label is currently under review by the Office of Prescription Drug Promotion.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Complete Response

- Risk Benefit Assessment

Data to support approval of this NDA included the results of two pharmacokinetic studies to provide a bridge to the 505(b)(2) listed and cross referenced drug products, comparing diclofenac sodium topical solution 2% with Pennsaid 1.5%, Voltaren tablets, and Solaraze, and one adequate and well controlled, four week study comparing the study drug to placebo in the treatment of OA of the knee. Although the Division had conveyed to the Applicant several times during presubmission meetings that a single, adequate and well-controlled efficacy study of 12-weeks duration would be required to support the approval of diclofenac sodium topical solution 2%, the Applicant submitted the four-week study with the rationale that the OGD guidance for topical diclofenac products would apply to this application. The Guidance discusses the clinical development approach for generic topical diclofenac products, that includes two studies; one bioequivalence (BE) study and one BE study with a clinical endpoint. The latter study would involve the treatment of patients with OA of the knee using a generic diclofenac sodium topical product, the listed drug, or placebo for 4 weeks, with the primary endpoint being evaluated at the end of the four-week treatment. The Applicant's rationale was that since the 2% solution showed similar systemic exposure to PENNSAID, this guidance should apply.

Although on face the four-week efficacy study did not meet the Division's requirements the application was filed because at the time it was determined that an approval could be based on pharmacokinetic findings alone. Further internal discussions regarding the efficacy study resulted in the Division accepting Study COV05100031 as supportive of the efficacy of diclofenac sodium topical solution 2% because the pharmacokinetic studies showed similar systemic exposure between the Pennsaid 1.5% and diclofenac sodium topical solution 2% products. It was determined that the efficacy study could contribute to the weight of evidence for a regulatory decision along with the results of the pharmacokinetic studies.

Because the pharmacokinetic studies were initially determined to be key in the approval decision, OSI was consulted to audit the two studies at the clinical and analytical sites. The OSI memo dated December 18, 2012, stated that due to the lack of reserve samples, the authenticity of the test and reference drug products administered cannot be confirmed for both studies. Therefore, data cannot be accepted for further Agency's review. As a result, the

submitted studies could not be used to support efficacy or to provide a 505(b)(2) bridge to the listed drugs, the Applicant must repeat a relative BA study with diclofenac sodium topical 2% solution, PENNSAID 1.5%, and oral diclofenac tablet.

Study COV05100031 demonstrated that diclofenac sodium 2% group had a numerically better response in WOMAC pain, physical function, and patient's global assessment than the control group at Week 4. However, only the difference in WOMAC pain achieved statistical significance at level 0.05. (b) (4) Consequently, this study supports an indication for the treatment of the pain of OA, (b) (4)

Safety of diclofenac sodium topical solution 2% was demonstrated during the development of the product, and is similar to the approved Pennsaid 1.5%. There were no deaths or SAEs, by far the most frequently reported adverse events were application site reactions.

Therefore, based on the data available, diclofenac sodium topical solution 2% appears safe and effective for the treatment of OA of the knee, however, in the absence of reliable pharmacokinetic data that allows for bridging between diclofenac sodium topical solution 2% and the listed drugs, and demonstrates similar systemic exposure between the 1.5% and 2% products, this NDA cannot be approved. The Applicant must conduct a new pharmacokinetic study to provide the data needed to approve this NDA.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitment

None

- Recommended Comments to Applicant

In order to resolve the deficiencies documented by the Office of Scientific Investigations during inspection of the clinical sites for studies COV05100070 and COC05100175, you must conduct a relative bioavailability study with diclofenac sodium topical solution 2%, Pennsaid 1.5%, and oral diclofenac tablet. This will provide the data needed to bridge your product to the listed drugs and to demonstrate whether the systemic exposure to diclofenac sodium topical solution 2% is similar to Pennsaid 1.5%.

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

/s/

ELLEN W FIELDS
02/11/2013

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204623
Priority or Standard	Standard
Submit Date(s)	May 4, 2012
Received Date(s)	May 4, 2012
PDUFA Goal Date	March 4, 2013
Division / Office	Anesthesia, Analgesia & Addiction Products
Reviewer Name(s)	Jacqueline A. Spaulding
Review Completion Date	January 28, 2013
Established Name	Diclofenac sodium
(Proposed) Trade Name	Pennsaid
Therapeutic Class	NSAID
Applicant	Mallinckrodt/Covidien
Formulation(s)	Topical
Dosing Regimen	Twice daily
Indication(s)	[redacted] (b) (4) (OA) of the knee
Intended Population(s)	OA of the knee

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This new drug application (NDA 204623) seeks approval of Pennsaid (diclofenac sodium topical solution) 2% w/w for the treatment of (b) (4) of osteoarthritis (OA) of the knee in adults. This was a 505(b)(2) application relying on PENNSAID (diclofenac sodium topical solution) 1.5%, Voltaren and Solaraze. One multi-center, randomized, placebo-controlled, four-week trial in adult patients with moderate to severe OA of the knee (b) (4) The safety database consisted of 130 patients with OA of the knee treated with Pennsaid (diclofenac sodium topical solution) 2%. The adverse event profile of the drug appears similar to that of approved PENNSAID (1.5%) in that the most common adverse events in patients receiving Pennsaid (diclofenac sodium topical solution) 2% were application site skin reactions.

Pennsaid (diclofenac sodium topical solution) 2% has been reported to be a modified formulation of PENNSAID® (diclofenac sodium topical solution) 1.5% w/w which was approved by the Agency on November 4, 2009, for the treatment of signs and symptoms of OA of the knee. Pennsaid (diclofenac sodium topical solution) 2% is a new dosage strength and has a new dosing regimen. The Applicant's rationale for the formulation change was to provide a more convenient dose regimen (from 4 times a day to twice a day) with a similar performance to PENNSAID 1.5%.

Pennsaid (diclofenac sodium topical solution) 2% was originally submitted as an efficacy supplement (NDA 20947/S-009) on May 4, 2012. During the initial filing period, the Division in consultation with the User Fee Staff determined that in addition to change a from 1.5% to 2% diclofenac concentration, Pennsaid (diclofenac sodium topical solution) 2% also had a new container closure system, a pump instead of a bottle with a dropper, that would be used in the to-be-marketed 2 % formulation. The new container closure system was intended to ensure delivery of a consistent amount of drug per actuation making it a new dosage form, a metered pump. Therefore, clinical data would be required for approval making the submission a new NDA and not an efficacy supplement.

During a teleconference on June 19, 2012, the Applicant was informed that because Pennsaid (diclofenac sodium topical solution) 2% was a new dosage form (i.e., metered pump) and the former was quantitatively and qualitatively different from PENNSAID 1.5% it represented a new NDA. Subsequently, the application was given a new NDA #204623. Another key discussion during this teleconference involved the Applicant's

submission of a four-week Phase 2 exploratory efficacy/safety study instead of the required 12- week double-blind efficacy study to support the proposed indication as told to them doing previous regulatory meetings. The Applicant argued that:

> Pennsaid (diclofenac sodium topical solution) 2% is essentially a modified formulation intending to replace 1.5 % with 2 % diclofenac with a similar total daily dose (TDD) [TDD for PENNSAID 1.5% is 154 mg and for Pennsaid (diclofenac sodium topical solution }2% is 160 mg]. Hence provided comparability data for efficacy, PK and also concentration data

In addition, the Applicant referred to the Office of Generic Drug (OGD) *Draft Guidance on[Topical] Diclofenac Sodium* as their justification for conducting a four-week efficacy study adequate for filing of the NDA.

> Upon review of the [draft generic] guidance for [diclofenac], Mallinckrodt feels that the study design reflects the Sponsor's understanding of FDA's intent for comparability and in vivo bioequivalence. In agreement with the clinical objectives outlined in the guidance, COV05100031 evaluated the primary endpoint in patients with osteoarthritis of the knee after 4 weeks of treatment. The study demonstrated that Pennsaid 2% was efficacious and well tolerated.

Despite the Applicant's position, the review team initially determined that the four-week efficacy study was inadequate for filing. However, after preliminary review of pharmacokinetic (PK) data by the clinical pharmacology team the systemic exposure of Pennsaid (diclofenac sodium topical solution) 2% was shown to be higher than that of approved PENNSAID 1.5%. Based on the PK data results, the Division determined that the relative bioavailability study between Pennsaid (diclofenac sodium topical solution) 2% and PENNSAID 1.5% may be considered pivotal for approval of the product. Therefore, the Office of Scientific Investigation (OSI) inspection was consulted to inspect both relative BA studies (COV05100170 and COV05100175).

During the review cycle, the Applicant's rationale for conducting a four-week efficacy/safety study was discussed with Office of Drug Evaluation (ODE) upper management and it decided that the four-week efficacy study alone would be sufficient to demonstrate efficacy of the product. The relative bioavailability between 2% and 1.5% PENNSAID would be only be considered as supporting information.

Late in the review cycle results of the OSI inspection of clinical pharmacology sites revealed samples of the test and reference article were not retained at the clinical sites. OSI determined the authenticity of the test and reference drug products used in these studies could not be confirmed and recommended data from these studies not be accepted for further agency review. Even though Studies COV05100070 and COV05100175 were no longer considered pivotal, the results of the OSI inspections could not be ignored. Further, the clinical pharmacology review team stated these

studies provided important data to fulfill the 505(b) (2) requirement, and supporting information to demonstrate efficacy of the product.

In concurrence with OSI and the clinical pharmacology review team, the Division determined that secondary to failed OSI inspections data from relative BA studies, data could not be accepted for further agency review.

There are several deficiencies that potentially hinder the approval of Pennsaid (diclofenac sodium topical solution) 2% for the proposed indication:

1. At an End-0f-Phase 2 Meeting (September 25, 2006) and a Type B Guidance Meeting (August 28, 2008) the Division informed the Applicant that three endpoints (i.e., WOMAC pain, WOMAC function and PGA) would be required to support the indication (b) (4) of OA of the knee.
    a. Efficacy results from the Applicant's, Phase 2 four-week randomized, double-blind, placebo-controlled trial (b) (4) While the primary endpoint (reduction in WOMAC pain) at Week 4 was statistically better for patients receiving Pennsaid (diclofenac sodium topical solution) 2% as compared to patients receiving placebo topical solution, the treatment difference was small. (b) (4) The safety database consisted of 130 patients with OA of the knee treated with Pennsaid (diclofenac sodium topical solution) 2% and the safety profile of the drug appears to be similar to that of PENNSAID and other topical NSAIDs. The most common adverse events reported in the Pennsaid (diclofenac sodium topical solution) 2% group were skin reactions at the application site.

2. The Division has stated, in regulatory correspondence and at several milestone meetings, a 12-week clinical trial would be necessary to support approval of the Pennsaid (diclofenac sodium topical solution) 2% formulation (b) (4) of OA of the knee.
    a. The Applicant's rationale for conducting a four-week efficacy study in lieu of a 12-week efficacy study (as generally required by the Division) was based on the OGD *Draft Guidance on Diclofenac Sodium* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244644.pdf). The Applicant believes this guidance supports the design of their Phase 2 efficacy/safety study. The OGD *Draft Guidance for Topical Diclofenac Sodium* discusses the clinical development approach for generic drugs which essentially involves two studies. The two studies include: one bioequivalence (BE) study and one BE study with a clinical endpoint. The latter study would involve the

treatment of patients with OA of the knee using a generic diclofenac sodium topical gel, the reference listed drug, or placebo for 4 weeks, with the primary endpoint being evaluated at the end of treatment, study week 4. Because the comparative PK data showed a similar pattern of exposure for Pennsaid (diclofenac sodium topical solution) 2% and PENNSAID 1.5%, the Division is now of the opinion that the OGD guidance may be applicable in this situation. However, because of failed OSI inspections there is no relative BA data to support the efficacy of this application.

b. Approval of a prescription drug product for a chronic pain indication, such as osteoarthritis of the knee, generally requires adequate clinical trials that are at least 12 weeks in treatment duration.

3. At the EOP2 meeting the Division also informed the Applicant that approval would require that Pennsaid (diclofenac sodium topical solution) 2% be found to be safe and effective and if the Applicant intended to rely on evidence from clinical trials of PENNSAID to support a single clinical trial with Pennsaid (diclofenac sodium topical solution) 2% they would have to provide evidence that the two products resulted in similar exposure using comparative bridging pharmacokinetic (PK) data. The Division also noted that comparative PK studies should also be performed using the listed drugs relied upon for the PENNSAID NDA. The Applicant stated that they intended to submit a 505(b)(2) application relying on the Agency's findings of safety and effectiveness for PENNSAID, Voltaren, and Solaraze with plans to perform a bridging PK study comparing the PENNSAID and Pennsaid (diclofenac sodium topical solution 2%) formulations.
    a. The results of inspections of the clinical and analytical sites by the Office of Scientific Investigations show that in the Applicant's comparative PK studies, the samples of the test and reference articles were not retained. Therefore, according to OSI the authenticity of the test and reference drug products used in these studies cannot be confirmed and the data cannot be accepted for Agency review. A scientific bridge between PENNSAID and Pennsaid (diclofenac sodium topical solution) 2% cannot be established at this time. Further, a direct link to the listed drugs relied upon for the PENNSIAD NDA cannot be made as well.
    b. In order for the Applicant to rely on data from the Pennsaid 1.5% product, and oral diclofenac (which were the listed drugs for the Pennsaid 1.5%), the pharmacokinetic studies will have to be repeated. Whether this will occur during this review cycle (with an extended clock) or during a subsequent review cycle has yet to be determined.

4. The final to-be-marketed container-closure system was not used in the clinical efficacy/safety study, and one PK study (COV05100070). Therefore, there is no direct comparison data demonstrating the delivery performance is the same

between the two systems (e.g. deliver the same amount of drug etc.). The CMC review team and the clinical team are currently reviewing this issue.

Based on the previously mentioned deficiencies, I do not recommend approval of Pennsaid (diclofenac sodium topical solution) 2% for the treatment (b) (4) of OA of the knee, and recommend a Complete Response at this time.

Efficacy/safety study (COV05100031) demonstrated that after 4 weeks of treatment patients receiving Pennsaid (diclofenac sodium topical solution) 2% appeared to have a slightly better reduction of OA knee pain as compared to patients receiving placebo. However, the difference in the treatment effect was small as is the treatment effect size in premarketing controlled clinical studies involving approved PENNSAID 1.5%.

Regarding the approvability of Pennsaid (diclofenac sodium topical solution) 2% for the pain of knee OA, the general opinion of the Division appears to be positive. The four-week efficacy study demonstrated Pennsaid (diclofenac sodium topical solution) 2% was statistically better than placebo. The risk of using Pennsaid (diclofenac sodium topical solution) 2% appears similar in that its safety profile is similar to that of approved PENNSAID 1.5% A relative BA study showed similar exposure of Pennsaid (diclofenac sodium topical solution) 2% and PENNSAID 1.5% However, due to failed OSI inspections of the clinical pharmacology sites and considering the similar exposure between these two product, these results cannot be used to support approval. The applicant will have to submit data from a new relative BA study with oral diclofenac and PENNSAID 1.5%.

Therefore, the decision regarding the approval of Pennsaid (diclofenac sodium topical solution) 2% for pain of OA will depend on the results of a reliable PK study.

1.2 Risk Benefit Assessment

Overall, the benefit-risk profile of Pennsaid (diclofenac sodium topical solution) 2% is not favorable for the population of patients with knee OA.

Knee OA is the most common form of OA. It is estimated that knee OA affects approximately 18 million adults in the United States with 4.1 million reported difficulties in ambulation. Patients with symptomatic knee OA report disability in activities of daily living and significant declines in health-related quality of life. [1] Because of the potential toxicities (e.g., gastrointestinal and cardiovascular) associated with the use of systemic NSAIDs, there has been increasing interest in the development of topical NSAIDS for use in the treatment of OA of the knee.

In terms of efficacy, the study submitted in the NDA (i.e., Study COV05100031), a four-week, randomized, double-blind, placebo-controlled study in patients with OA of the knee (b) (4) .

1. Study COV05100031 (b) (4) While pain is the most common symptom associated with knee OA, the ability to perform activities of daily (relating to physical function) and overall quality of life are important factors in the treatment of patients with knee OA as well.
   - The clinical efficacy and safety study showed that Pennsaid (diclofenac sodium topical solution) 2% was statistically better than placebo (p value = 0.04) for the Applicant's primary endpoint (i.e., WOMAC pain); the statistical significance does not translate into clinical meaningfulness. The observed treatment effect size should be assessed in the context of the theoretical maximal treatment effect size. A 0-4 point rating scale was used to assess 5 items for the pain subscale; therefore the maximum potential improvement is 20 for the pain subscale. The actual difference in the means in patients treated with Pennsaid (diclofenac sodium topical solution) 2% and placebo was 1 for WOMAC pain. This difference is small in magnitude, and represents a small treatment benefit for knee OA patients.

2. The Applicant conducted a four-week efficacy study in lieu of the Division's requirement that for a prescription drug intending to seek an indication for the "treatment of (b) (4) pain of OA, adequate trials must be at least 12 weeks in duration". Generally, a 4-week efficacy/safety study is not adequate duration to evaluate a drug product for a chronic pain indication. At the time of filing, the Division questioned whether the Applicant's reference to the OGD Guidance for Topical Generic Diclofenac as their rationale for conducting a four-week study would be acceptable. Since the PK exposure of Pennsaid (diclofenac sodium topical solution) 2% appears to be similar to that of PENNSAID 2% the Division is currently of the opinion that a four-week study may be applicable to this NDA. However, a reliable comparative PK study will have to be submitted to support the efficacy of this product at four weeks.

In terms of safety, the most common adverse effects associated with the use of Pennsaid (diclofenac sodium topical solution) 2% are related to the skin. Despite the modest number of patients exposed to Pennsaid (diclofenac sodium topical solution) in the efficacy/safety study, review of safety information from premarketing controlled studies, and postmarketing experience support the low risk of this drug product.

The risks associated with the use of Pennsaid (diclofenac sodium topical solution) 2% appear to be minimal and similar to that of approved PENNSAID 1.5%. However, the potential benefits for the millions of patients suffering with chronic OA of the knee appear to be minimal as well.
(b) (4) there is data to support the modest analgesic efficacy of Pennsaid (diclofenac sodium topical solution) in the treatment of the pain of knee OA, (b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategies are recommended at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

In order to comply with the Pediatric Research Equity Act of 2007, the Applicant submitted a Pediatric Plan and requested waiver of clinical studies in pediatric patients because OA does not occur in the pediatric population to an extent where it would be feasible to study. The Pediatric plan and waiver request will be reviewed by Pediatric Review Committee on January 30, 2013.

No additional postmarketing study commitments are recommended at this time.

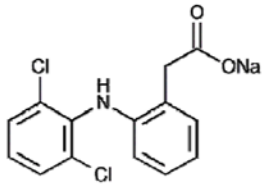
2 Introduction and Regulatory Background

2.1 Product Information

Pennsaid (diclofenac sodium topical solution) 2% is purported to be a modified formulation of Pennsaid 1.5% topical gel, which was approved by the Agency on November 4, 2009 (NDA 020947) for the treatment of the signs and symptoms of osteoarthritis.

Structural Formula:

Diclofenac Sodium, USP



Source: NDA 204623. Introduction, pg. 3 of 3

Description of product: clear, colorless to pink or orange solution containing 2% w/w diclofenac sodium. Each 1 mL of solution contains approximately 20 (b) (4) mg of diclofenac and the following inactive ingredients: dimethyl sulfoxide (DMSO) 45.5% w/w, propylene glycol, alcohol, purified water and hydroxypropyl cellulose (HPC)

Established name and proposed trade name: Established name: Diclofenac sodium topical solution 2% Initial proposed trade name {Pennsaid (b) (4)) was not accepted and no proposed trade name has been submitted at this writing.

Pharmacological class: nonsteroidal anti-inflammatory drug

Proposed indication: treatment (b) (4) of OA of the knee

Dosing regimen: (b) (4) (40 (b) (4) mg diclofenac) on each painful knee twice daily

2.2 Tables of Currently Available Treatments (b) (4)

There are multiple drug treatments approved for the indication for the treatment of the signs and symptoms of osteoarthritis including: naproxen, celecoxib, ibuprofen, ketoprofen, fenoprofen, diclofenac, etodolac, meloxicam, piroxicam, sulindac, oxaprozin, indomethacin, nabumetone and acetaminophen. There are currently no topical NSAIDs approved in the US for the treatment of (b) (4) of OA.

2.3 Availability of Proposed Active Ingredient in the United States

Diclofenac sodium is available as oral, intravenous and topical formulations in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID). The chronic use of NSAIDS like diclofenac has been associated with gastrointestinal (GI) and

cardiovascular (CV) side effects. Gastrointestinal adverse events associated with NSAIDS include dyspepsia and ulcers along with other more serious GI events such as life-threatening GI bleeding. In addition, this class of drugs has been showed to increase blood pressure.

There is a boxed warning for NSAIDS including diclofenac that describes the cardiovascular risks associated with taking the product such as serious cardiovascular thrombotic events, myocardial infarction, and stroke which can be fatal and the risk may increase with duration of use.

In addition to cardiovascular risks, the boxed warning on the label of diclofenac describes gastrointestinal risks associated with taking the product including: bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Also, elderly patients are at greater risk for serious gastrointestinal events.

Diclofenac and other NSAIDS are associated with known and potential serious adverse events including: anaphylactoid reactions, and skin reactions (Steven-Johnson Syndrome). Label warnings also advise caution in patients with hypertension, congestive heart failure and edema and avoidance of use in patients with moderate to severe renal impairment. Caution should be exercised when using NSAIDS like diclofenac in patients with hepatic disease, coagulation disorders and preexisting asthma. Drug overdose is also an important safety issue with diclofenac and as recommended in the label patients should be managed symptomatically and supportively following an NSAID overdose.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In 2009, Mallinckrodt Inc. purchased approved NDA 020947 PENNSAID (diclofenac sodium topical solution) 1.5% w/w from Nuvo Manufacturing. Along with that acquisition, Mallinckrodt entered into a licensing agreement with Nuvo to pursue the development of a topical 2% w/w diclofenac sodium formulation initially referred to as PENNSAID gel.

Key milestones in the Pennsaid (diclofenac sodium topical solution) 2% clinical development program are noted in Table 1:

Table 1: Pennsaid 2% Clinical Development Program

EOP2 Meeting (September 2006)	• For NDA, Sponsor proposes (b) (4) study in patients with symptomatic OA of the knee and clinical and pre-clinical data from Pennsaid topical solution 1.5% and published literature for submission as 505(b)(2) application o Efficacy Study: (b) (4) o Primary efficacy variables: (WOMAC pain. WOMAC function and Patient Global) o Division finds this proposal acceptable • (b) (4) • No dermal safety studies required; however submission will need to include data from Pennsaid 1.5% topical safety studies and rationale regarding adequacy and generalizabiltiy to support clinical studies of Pennsaid 2% • Approval will require the following: o Evidence that Pennsaid 2% is safe and effective o If relying on evidence from clinical trials of Pennsaid 1.5% to support single clinical trial for Pennsaid 2%, will also need to provide evidence two products are similar (e.g. comparative bridging PK data)
(b) (4)	

	(b) (4)
Type B Guidance Meeting (August 2008)	• Division informs Applicant that (b) (4) , adequate clinical trials must at least 12 weeks in duration." • All 3 endpoints (i.e. WOMAC pain, WOMAC function, Patient Global) required (b) (4) • Sponsor's patient's global does not reflect the effects of product on OA; advised to change • WOMAC subscale instrument for stiffness has not been established as a suitable stand-alone measure • Use conservative imputation. Proposed sensitivity analysis #1 (i.e. BOCF for lack of efficacy or any AEs and LOCF for others) may be acceptable as primary approach if reason for withdrawal is clearly documented
Transfer of NDA (2009)	• Transfer of NDA from Nuvo Research to Malincrokdt/Covidien
Submission of IND 075045 Pennsaid (diclofenac sodium topical gel) 2% w/w (May 2010)	• New Sponsor Mallinckrodt with understanding from previous Sponsor (i.e. Nuvo Research) that Pennsaid 2% is a topical gel • Applicant now asserts empirical evaluation and rheology study of Pennsaid demonstrates Pennsaid 2% is a topical solution

2.6 Other Relevant Background Information

The Applicant (i.e., Mallinckrodt/Covidien) provided their rationale for conducting a four week efficacy study in lieu of a 12-week study which is generally required for drugs intended for a chronic pain indication. Following are excerpts from their correspondence document:

> The Phase 2 clinical study (COV05100031) of Pennsaid 2% topical solution was designed and executed prior to release of the first draft guidance documents for topical Diclofenac Sodium. Upon review of the [draft generic] guidance for [diclofenac], Mallinckrodt feels that the study design reflects the Sponsor's understanding of FDA's intent for comparability and in vivo bioequivalence. In agreement with the clinical objectives outlined in the guidance, COV05100031 evaluated the primary endpoint in patients with osteoarthritis of the knee after 4 weeks of treatment. The study demonstrated that Pennsaid 2% was efficacious and well tolerated.
>
> (b) (4) Pennsaid 2% topical solution was developed to reduce the

dosing frequency from 4 times daily (QID) to twice daily (BID) while retaining a similar total daily dose of diclofenac with comparable product performance. These modifications fulfill the definition of "major changes" to the NDA, requiring a prior approval supplement, therefore leading Mallinckrodt to seek marketing approval of Pennsaid 2% topical solution in a sNDA.

In view of this, the previous discussions between Nuvo and FDA (2006-2009) on the development of a new dosage form (i.e., a change from a topical solution to a topical gel) by the 505[b](2) application pathway [have been]re-evaluated Mallinckrodt has implemented much of FDA's published guidance in support of the PENNSAID 2% topical solution sNDA. Where we have differed from previous advice, the Sponsor has justified why some of the issues and recommendations of the Division can be appropriately modified for this sNDA. Mallinckrodt has also bridged to FDA's finding of safety and efficacy of the initial PENNSAID 1.5% product (PENNSAID solution, NDA 020947) to support filing of this supplement for regulatory approval of PENNSAID 2% topical solution."

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the submission was adequate. The organization and the ability to navigate the NDA were acceptable as well. One information request was sent to the Applicant for additional information regarding the weight of study drug administration per dose calculated from dispensed and returned bottle weights and the response was timely and adequate.

3.2 Compliance with Good Clinical Practices

The Applicant has certified that all studies submitted were conducted in compliance with Good Clinical Practices.

The Office of Scientific Investigations (OSI) conducted routine inspections of three clinical study sites that participated in Study COV05100031 as noted in Table 2. The three sties were selected for large subject enrollment.

Table 2: Clinical Inspection Sites

	Clinical Investigator	Site & Subjects	Inspection Dates	Outcome
1	John M. Hill, MD Avail Clinical Research, LLC 860 Peachwood Drive DeLand, FL 32720	Site 01 28 subjects	Oct 15 - 19, 2012	Pending Preliminary NAI
2	Albert W. Schreiner III, MD Sterling Research Group, LTD 375 Glensprings Drive, Suite 400 Cincinnati, OH 45246	Site 04 28 subjects	Sep 24 - 28, 2012	NAI
3	Douglas R. Schumacher, MD Radiant Research, Inc. 1275 Olentangy River Road, Suite 202 Columbus, OH 43212	Site 22 27 subjects	Sep 10 - 12, 2012	NAI

NAI = no action indicated, no deviation from regulations; VAI = voluntary action indicated, deviation from regulations; OAI = official action indicated, significant deviation from regulations and/or data unreliable

Pending: This preliminary outcome classification is based on information on Form FDA 483 and communication with the field investigator; final inspection report has not been received from the field office and OSI's complete review of the report remains pending as of this clinical inspection summary.

Note: The numbers of subjects shown above (active and placebo groups) are approximately twice those shown on the original DPP consult form, *Request for Clinical Inspections* (active group only).

Source: Dr. John Lee's, OSI Clinical Inspection Summary Review, pg. 5

According to Dr. John Lee's clinical inspection summary review the criterion for study site selection was based on large subject enrollment; and site-specific study data for efficacy, adverse events, protocol deviations and investigator conflicts of interest did not appear to be significantly different among study sites.

Please refer to Dr. John Lee's review dated October 24, 2012 for a complete discussion of the OSI inspection. Below are Dr. Lee's conclusions (taken verbatim from his review) regarding the good clinical practice inspections of these sites:

> At all three study sites, no significant GCP deficiencies were observed and a Form FDA 483 was not issued. At Site 01 (Hill), minor deficiency observations included inconsistent WOMAC data between source records and eCRFs for four subjects. All observed deficiencies were minor and apparently isolated, and are not expected to have an important impact on the study outcome at this site. At Site 22 (Schumacher), inspectional observations included inconsistent WOMAC data between the NDA data listings and site study records. The discrepancies appear to have resulted from the sponsor's error in data handling, and not from deficiencies in study conduct at the study site. These discrepancies also were minor and apparently isolated, and are not expected to have an important impact on the study results. The study data from all three inspected study sites appear reliable as reported in the NDA.

In addition Dr. Feng Li, statistical reviewer from the Office of Biometrics 2 summarized the relevant efficacy findings for the eight subjects with inconsistent WOMAC data as noted in Dr. Lee's review. Table 3 shows the WOMAC data (source and eCRF) for these eight subjects.

Table 3: WOMAC data For Eight Subjects

Site	Subject	Treatment	Completer?	Visit	WOMAC Question	Data		WOMAC Pain	
						Source data	eCRF	Sum	Correction
01	007	Placebo	Yes	Week 4	**Pain** while standing	Moderate (2)	Mild (1)	8	9
	029	Placebo	Yes	Week 2	Function Question 16	Severe (3)	Missing	NA	NA
	016	PENNSAID	Yes	Week 2	Function Question 13	None (0)	Missing	NA	NA
	036	PENNSAID	Yes	Week 2	Function Question 23	Moderate (2)	Mild (1)	NA	NA
22	022	PENNSAID	Yes	Week 2	**Pain** while sitting	None (0)	Mild (1)	NA	NA
	027	Placebo	Yes	Baseline	Stiffness Question 6	Severe (3)	Extreme (4)	NA	NA
	013	Placebo	No	Week 2		Drop out due to AE		9	NA
	029	Placebo	No	Week 2				11	NA

Source: Dr. Feng Li

According to Dr. Li while there were some mistakes in recording the source data to the eCRF, only one subject (01-001) had Week 4 pain data recorded wrong (one among five pain questions) and the mistake was in favor of placebo. Overall, the Applicant's errors do not appear to affect the efficacy results for the primary endpoint (i.e., WOMAC pain).

In addition, OSI conducted inspections of the analytical and clinical portions of the relative bioavailability studies (COV05100070 and COV05100175). OSI reviewer, Jyoti Patel PhD, made the following conclusion and recommendations:

> For the analytical portions of the studies, no objectionable conditions were observed.
>
> For the clinical portions of the studies: due to the lack of reserve samples, the authenticity of the test and reference drug products administered at Comprehensive Clinical Development, Inc., Miramar, FL cannot be confirmed. Form FDA-483 was issued. The firm management acknowledged that they did not retain samples for Protocol COV05100070 and Protocol COV05100075 and corrective action would be taken to prevent these types of events in the future.
>
> Due to failed inspections at clinical portions of relative BA, the data cannot be verified and data cannot be accepted for further agency's review.

Please refer to Dr. Patel's review, dated December 12, 2012 for a complete discussion of the OSI inspection of the clinical pharmacology study sites.

3.3 Financial Disclosures

The Applicant has submitted the Financial Certification and Disclosure document as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*. These were no financial arrangements reported; at this time it does not appear to be financial conflict of interests related to data integrity.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry/Manufacturing and Controls (CMC) review was conducted by Yong Hu PhD.of the Office of New Drug Quality Assurance (NDQA). At the time of this writing, Dr. Hu's review had yet to be finalized. A brief summary of Dr. Hu's preliminary findings follow:

- Table 4 displays the composition of Pennsaid 1.5% and 2% (diclofenac sodium topical) formulations and the function of each component

Table 4: Composition of Pennsaid 1.5% and 2% Topical Solution Formulations

		Pennsaid 1.5% Quantity mg/g	Pennsaid 1.5% Percent per g	Pennsaid 2% Quantity mg/g	Pennsaid 2% Percent per g
Component	**Function**				
Diclofenac sodium	Active ingredient	15	1.5	20	2.0
Dimethyl Sulfoxide	(b) (4)	455	45.5	455	45.5
Ethanol 95% (v/v)		(b) (4)			
Purified Water					
Propylene Glycol					
Hydroxypropyl Cellulose					
Glycerin				(b) (4)	
Total			**100%**		**100%**

Source: NDA 204623 Submission, CMC, Tablet 2.3P.1-1 and Table 2.3.P.2-1, pp. 3-4 of 27

- During clinical development of Pennsaid (diclofenac sodium topical solution) 2% a change in packaging (i.e., container-closure system) occurred [redacted (b) (4)]
  1. Non-commercial container closure system - [redacted (b) (4)]
     - The dispensing weight/actuation for this pump was [redacted (b) (4)] and it was used in Studies COV05100031 and COV05100070
  2. Commercial container closure system- [redacted (b) (4)] (used in Study COV05100075).
     - The dispensing weight/actuation for this pump was 1.0 gm and it was used in Study COV05100075

Please refer to Dr. Hu's review for a complete discussion of the CMC aspects of the NDA.

4.2 Clinical Microbiology

There was no clinical microbiology review associated with this NDA.

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review was conducted by Jay Chang, Ph.D. At the time of this writing, Dr. Chang's review had yet to be finalized. A brief summary of Dr. Chang's preliminary findings follows:

- The maximum recommended daily dose (MRDD) of diclofenac remains approximately the same (154 to 162 mg/day)
- The impurity specifications for drug substance is the same as the marketed Pennsaid 1.5% formulation
- The impurity specifications for the drug product are within the recommended levels as required by ICH Q#B
- No apparent safety issues with respect to extractable and leachables from the new container closure system

Please refer to Dr. Chang's review for a complete discussion of the preclinical pharmacology/toxicology aspects of the NDA.

4.4 Clinical Pharmacology

The Clinical Pharmacology review was conducted by Yun Xu Ph.D. At the writing of this review, Dr. Xu's review had yet to be finalized.

Two relative bioavailability studies were submitted in support of the NDA. The Division requested OSI inspection of clinical pharmacology study sites since at filing, these studies were considered key as support for approval, as the four-week efficacy trial was

at that time determined to be of inadequate duration to support efficacy.. OSI found that both sites failed to retain samples of the test and reference drug products, and therefore, recommended that the studies not be relied upon to support the application.

Study COV05100070 was a Phase 1, randomized, open-label, multiple-dose, three-way, crossover trial that evaluated the PK, PA and safety of Pennsaid 2% in Comparison with Sandoz 75 mg

Study COV05100075 was a Phase 1, randomized, open-label, multiple-dose, 2-way crossover study that evaluated the PK, BA and safety of Pennsaid (diclofenac sodium topical solution) 2%
price
Regarding OSI inspection of the clinical portions of the pharmacology studies COV05100070 and COV051000175, they note that reserve samples (as required by 21 CFR 320.38) of test and reference drug products were not retained at the clinical sites. Therefore, the authenticity of the test and reference drug products cannot be confirmed and recommend data not be accepted for further Agency review.

Please refer to Section 3.2 of this review for further discussion of the OSI inspection.

After extensive discussion with Dr Yu, clinical pharmacology team leader it was decided the study results could not be used to support the application due to failed OSI inspection. Therefore, the Sponsor will need to repeat the relative BA study. In this case, there will be no acceptable clinical pharmacology data to be discussed in the label

4.4.1 Mechanism of Action

The mechanism of action of diclofenac is believed to be due to inhibition of prostaglandin synthesis, primary via inhibition of the enzyme cyclooxgenase

4.4.2 Pharmacodynamics

Diclofenac has anti-inflammatory, analgesic and antiipyrectic properties.

4.4.3 Pharmacokinetics

Please see discussion above.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Three clinical trials, including 1 safety and efficacy trial, and 2 bioavailability and

pharmacokinetics (PK) trials, have been completed to support the marketing application for Pennsaid (diclofenac sodium topical solution) 2% and these studies are shown in Table 5.

Table 5: Overview of Trials for Pennsaid Topical Solution 2% in Treatment of OA of the Knee

Category	COV05100031	COV05100070	COV05100175
Trial Design	Randomized, double-blind, multiple-dose, vehicle-controlled, parallel group	Randomized, open-label, multiple-dose, 3-way crossover	Randomized, open-label, multiple-dose, 2-way crossover
Subject Population	Males and females, 40-85 years with primary OA of the knee with moderate flare after washout of stable pain therapy	Healthy males and females, 18-55 years	Healthy males and females, 18-55 years
Objectives	Efficacy and safety	PK and BA vs 1.5% solution and tablet (bridging)	PK and BA vs 1.5% solution
Treatment Groups	PENNSAID solution 2%, 2 mL BID, topical Vehicle, 2 mL BID, topical	PENNSAID solution 2%, 2 mL BID, topical PENNSAID solution 1.5%, 1.2 mL QID, topical Diclofenac tablet, 75 mg, BID, oral	PENNSAID solution 2%, 2 mL BID, topical PENNSAID solution 1.5%, 1.2 mL QID, topical
Treatment Duration	4 weeks	7.5 days; each treatment period was separated by a 21-day washout period	7.5 days; each treatment period was separated by a 21-day washout period
Scheduled Visits During Treatment	Days 0, 7 (telephone), 10 (telephone), 14, 24 (telephone), 28	Days 1-8 (inpatient)	Days 1-8 (inpatient)
Countries	USA	USA	USA
Number of Subjects	260 total subjects PENNSAID 2%: 131 (130 treated) Vehicle control: 129	30 total subjects PENNSAID 2%: 22 PENNSAID 1.5%: 27 Diclofenac sodium tablets: 26	32 total subjects PENNSAID 2%: 32 PENNSAID 1.5%: 31

BA = bioavailability, BID = twice daily, OA = osteoarthritis, PK = pharmacokinetics, QID = 4 times daily, USA = United States of America

Note: The daily dose of diclofenac sodium for PENNSAID 2% topical solution BID is (b) (4) (for each knee) and the daily dose of diclofenac sodium for PENNSAID 1.5% topical solution QID is (b) (4) (for each knee).

Source: NDA 204623, Clinical Overview, Table 1-2 pg. 13 of 48

5.2 Review Strategy

The strategy employed in reviewing the NDA involved:

- Evaluation of efficacy and safety data from Study COV05100031 submitted to support the Applicant's claim that Pennsaid (diclofenac sodium topical solution) 2% is safe and effective for the treatment (b) (4) of OA of the knee
- Evaluation of safety data from premarketing controlled clinical trials and postmarketing experience for approved PENNSAID and;
- Review of the published medical literature

5.3 Discussion of Individual Studies/Clinical Trials

Study COV05100031

Title
A Phase 2, Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Clinical Study to Evaluate the Safety and Efficacy of Pennsaid Gel in the Symptomatic Treatment of Osteoarthritis of the Knee

Objectives
The objectives of this study were to have been:

- To characterize the analgesic effect and to determine the effect size for Pennsaid gel by evaluating multiple efficacy endpoints to assist in planning the Phase 3 program;
- To determine if an effective level of analgesia is maintained throughout the dosing interval; and
- To evaluate the safety of Pennsaid gel in the treatment of OA of the knee.

Study Design
The design of the study was to have been Phase 2, 4-week, 2-arm, randomized, double-blind, vehicle-controlled, parallel group

Study Population/N
The study was to have enrolled a minimum of 260 (130 in each treatment group) patients with primary OA of the knee

Study treatments
1. Pennsaid (diclofenac) topical solution 2%
2. Vehicle Controlled topical solution (was to have contained DMSO, propylene glycol, alcohol, purified water and hydroxypropyl)

Rescue Medications
Acetaminophen (up to 1,950 mg /day) during treatment phase of study except during the 3 calendar days before Visit 3 and Visit 4

Permitted concomitant medications/therapies – the following medications/therapies were to have been permitted during the study
- Acetaminophen (up to 1,950 mg/day) as rescue medication
- Non-analgesic therapy for non-arthritis conditions

- Stable low-dose aspirin (up to 81 mg/day) for cardiovascular prophylaxis if used regularly for at least 30 days prior to screening
- Stable therapy with sedative hypnotics (e.g., flurazepam, zolpidem) if used regularly for at least 14 days prior to screening
- Stable therapy with anti-depressant for treatment of depression if used regularly for at least 60 days prior to screening
- Use of cane if used continuously for 30 days prior to screening

Prohibited medications/therapy – the following medications/therapies were to have been prohibited during the study

- Any NSAID except for low dose ASA
- Muscle relaxants
- Corticosteroids
- Opioid analgesics
- Other oral analgesics (prescribed or OTC) except for dispensed rescue acetaminophen
- Acetaminophen and any other combination products that contain acetaminophen (e.g. cold medications)
- Topical medicinal products on the knees
- Intra-articular viscosupplementaton (e.g. hylan G-f 20) in the primary study knee
- Non-pharmaceutical therapy or device to relieve knee pain (e.g. physiotherapy, knee brace)
- Sedative therapy for insomnia
- Chondroitan or glucosamine
- Herbal remedies for pain
- Heating pads/bandages
- Exposure to sunlight or artificial light during study

Inclusion Criteria

Patients were to have met of the following criteria to be enrolled in the study:

1. Have a history consistent with primary OA of the knee
2. Radiologic evidence of OA of the knee within 1 year prior to screening must be consistent with a Grade 2 or 3 on the Kellgren-Lawrence grading scale.

   Grade 1: doubtful narrowing of joint space and possible osteophytic lipping
   Grade 2: definite osteophytes, definite narrowing of joint space
   Grade 3: moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour
   Grade 4: large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour

3. Must be on stable pain therapy (ie, at least 3 days per week for the previous month) with an oral or topical NSAID or acetaminophen prior to the screening visit.
4. Following washout of that stable pain therapy, must experience a "moderate flare" of pain in the designated study knee, defined as follows:
    a. Baseline minimum pain score of at least 5 using an 11-point NRS and at least a 2- unit worsening from the screening pain score. (NOTE: The baseline score was an average of the NRS knee pain scores reported for pain over the last 24 hours for 3 days prior to Visit 2)
5. Must be able to read and understand English or Spanish well enough to answer the questions in the corresponding version of the WOMAC LK3.1 OA Index, without any translation or explanation by the Investigator or any other individual.
6. If female:
    a. Is surgically sterile (hysterectomy or tubal ligation), or is postmenopausal for at least 12 months prior to the screening visit, or is postmenopausal for at least 6 months prior to the screening visit with a follicle stimulating hormone (FSH) level > 40 IU/L. or
    b. Is not pregnant, with a negative pregnancy test at the screening visit and baseline visit, and does not plan on becoming pregnant during the study as evidenced by her use of an acceptable method of contraception (including oral contraceptives, hormone implant, intrauterine device, spermicide with barrier method [condom or diaphragm], male sexual partner(s) surgically sterile, abstinence).
7. Be between 40 and 85 years of age, inclusive.
8. Except for OA, be in reasonably good general health as determined by the study Investigator.
9. Read and signed the informed consent form.

Exclusion Criteria

Patients who met any of the following criteria were not to have been enrolled in the study

1. Any subject who has secondary OA of the study knee will be excluded. NOTE: Any subject with a systemic disease that may affect bone or joints, including psoriasis, rheumatoid arthritis, syphilitic neuropathy, ochronosis, metabolic or other primary bone disease, need be excluded only if there is evidence of that disease in the study knee, such that the development of symptoms in the knee during the study might confuse the interpretation of the clinical response of the subject's OA to study therapy.
2. Any subject who exhibits chondrocalcinosis on the radiological examination of the knee AND gives a history of pseudogout or inflammatory flare-ups will be excluded. If it is clearly evident that the chondrocalcinosis is an "asymptomatic" radiological finding only, the subject may be included.

3. Any subject whose participation in the study would conflict with contraindications, warnings or precautions as stated in the prescribing information for oral or topical diclofenac will be excluded
4. Any subject who has severe, uncontrolled cardiac, renal, hepatic, or other systemic disease in the opinion of the Investigator will be excluded.
5. Any subject undergoing treatment or who has undergone treatment within the previous three years prior to the screening visit for any malignancy, except local therapy for superficial skin cancer not on the OA involved knee, will be excluded.
6. Any subject with known sensitivity to the use of diclofenac, aspirin (acetylsalicylic acid [ASA]) or any other NSAID, DMSO, or ethanol will be excluded. This includes subjects exhibiting aspirin or other NSAID-induced symptoms, including bronchospasm, rhinitis, urticaria, or other NSAID-induced allergic symptoms.
7. Any subject who on screening Medical History has an ongoing abnormality that could confound interpretation of the safety results in the opinion of the Investigator (eg, anemia, unresponsive GI reflux, etc) will be excluded.
8. Any subject with a documented (upper GI series or endoscopy) gastroduodenal ulcer or any GI bleeding (except hemorrhoidal) within the last 6 months prior to screening will be excluded. EXCEPTION: A subject with documented gastroduodenal ulcer disease, with or without overt bleeding, not associated with NSAID use, with evidence of Helicobacterpylori infection (biopsy, urease breath-test, or serum antibody), who had subsequently been treated with triple therapy (ie, a 7-day course of i) proton pump inhibitor and ii) two of the following: amoxicillin, clarithromycin, metronidazole) may be included if asymptomatic 90 days after that therapy.
9. Any subject with uncontrolled diabetes in the opinion of the Investigator will be excluded.
10. Any subject with any of the following laboratory test results at screening will be excluded:
    a. serum creatinine ≥ 1.5 x upper limit of normal (ULN)
    b. aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 x ULN
    c. gamma-glutamyltransferase (GGT) ≥ 3 x ULN
    d. hemoglobin ≤ lower limit of normal (LLN)
11. Any subject with a documented history of alcohol or drug abuse within one year prior to the screening visit will be excluded.
12. Any female subject who is breast-feeding will be excluded.
13. Any subject who has had major surgery or previous damage to the study knee at any time, or minor knee surgery to the study knee within one year prior to screening, will be excluded: MAJOR KNEE SURGERY OR PREVIOUS DAMAGE: eg, total knee replacement, damage/reconstruction of the anterior or posterior cruciate ligaments. MINOR KNEE SURGERY: anything other than major surgery as defined above, eg, cartilage repair, collateral ligament repair, arthroscopic debridement. If the category of surgery (major or minor) or damage is not clear, the Investigator should contact the Medical Monitor for clarification.

14. Any subject (i) requiring oral or intra-muscular corticosteroids, or (ii) who has received an intra-articular corticosteroid injection into the primary study knee within 90 days of screening or into any other joint within 30 days of screening, or (iii) who is applying topical corticosteroids onto the study knee, will be excluded.
15. Any subject who has received intra-articular viscosupplementation (eg, hylan G-F 20 [Synvisc®]) in the primary study knee in the 6 months prior to screening will be excluded.
16. Any subject on prior stable therapy (ie, more than 3 days per week for the previous month) with an opioid analgesic prior to the screening visit will be excluded. Prior as-needed use of opioid analgesics for acute pain relief is allowed although subjects in this category should washout of opioid analgesics as directed in Appendix A.
17. Any subject who recently (ie, within 14 days prior to screening) started taking a sedative hypnotic medication for insomnia will be excluded. Subjects may be included if they have been on stable therapy with insomnia medication for at least 14 days prior to screening. See Section 10.5 for a list of common insomnia medications.
18. Any subject who is taking anti-depressants will be excluded from the study, unless the subject has been on stable therapy for treatment of depression for at least 60 days prior to screening and can maintain that dose for the duration of the study.
19. Any subject not willing to discontinue prohibited medications/therapies will be excluded (see Appendix A for list of prohibited medications and minimum washout times).
20. Any subject who cannot tolerate acetaminophen will be excluded. (NOTE: Only acetaminophen may be used as rescue medication to relieve residual pain).
21. A subject who has previously been randomized, applied product, and dropped out or been withdrawn from this study will not be allowed to re-enter.
22. Any subject who has used another investigational drug within the previous 30 days prior to screening will be excluded.
23. Any subject on or currently applying for disability benefits on the basis of knee OA will be excluded.
24. Any subject with fibromyalgia will be excluded.
25. Any subject with other painful or disabling conditions affecting the knee or leg, or disabling condition of the hands (used to apply the study drug), will be excluded.
26. Any subject with a skin disorder with current involvement on the hands (used to apply the study drug) or the knee(s) (application site) will be excluded.
27. Any subject who has been referred to an orthopedic surgeon for consideration of, or been advised to have, knee replacement or knee reconstruction surgery will be excluded.
28. Any subject who has OA of the knee advanced to the point that all cartilage has been eroded such that on radiological examination the joint space has been eliminated in both lateral and medial tibia/femoral compartments (ie, bone on bone) will be excluded.
29. Any subject who has recently (ie, within 30 days of screening) started using a cane will be excluded. Use of a cane is allowed if used continuously for 30 days prior to

screening. Such therapy should be continued throughout the study, as withdrawal of therapy may result in a flare of pain unrelated to the study.

30. Any subject with a history of chronic headaches who, in the opinion of the Investigator, may require more than occasional use of rescue medication for headaches during the study will be excluded.

Study Schedule of Activities

Table 6 displays the study schedule of activities:

Table 6: Study COV05100031 Schedule of Events

SCHEDULE OF EVENTS	Screening		Treatment Period						
Study Visit	1		2		2a[a]	2b	3	3a	4
Days from Baseline Visit	-28 to -1		0		7	10	14	24	28
Interval from Baseline Visit			0		1 week (± 2 days)	4 days prior to Visit 3	2 weeks (± 2 days)	4 days prior to Visit 4	4 weeks (± 5 days)
			Pre-treatment	Post-treatment					
Informed Consent	X	Washout Period (3-14 days) Including Telephone Check-in [f,g] / Baseline NRS Pain Intensity Assessment (3 days)							
Inclusion/Exclusion	X		X						
Randomization			X						
Pregnancy Test [b]	X		X						X
Demographics	X								
Medical History	X		X						
Physical Examination	X[h]								X
Concomitant Medication/ Therapy	X		X	X			X		X
Vital Signs	X		X	X			X		X
Radiological Examination (Both Knees)[c]	X								
Clinical Laboratory Tests	X								X
New Study Medication/Rescue Meds Dispensed			X				X		
Study Medication/Rescue Meds Returned							X		X
NRS (Both Knees)	X								
NRS (Study Knee Only)				X[d]					
Report Use of Rescue Medication				X[d]					
WOMAC (Study Knee Only)			X				X		X
Patient Global Assessment			X				X		X
AE Evaluation				X	X		X		X[e]
Application Site Skin Evaluation (all Treated Knees)			X	X			X		X
Call subject to stop **rescue meds** and return study drug and rescue med bottles at the next office visit.						X		X	

[a] One telephone visit will occur 1 week ± 2 days after Visit 2 (baseline). See Section 12.5 for a list of items to be discussed with subject

Source: NDA 204623, Clinical Study Protocol COV05100031 Pg. 38 of 106

Study Conduct Summary

The study was to have consisted of a screening period, a washout period and treatment period.

Screening (Visit 1)

The following procedures and assessments were to have been conducted at screening: Informed consent, review of eligibility criteria, demographics, medical history, concomitant medication/therapy, pain intensity assessment in both knees using 11-point NRS, physical exam (including height and weight), vital signs, clinical labs (hematology, chemistry, urinalysis), serum pregnancy, radiological exam of both knees, patient

instruction on use of integrated voice response system and procedures for washout period.

Washout period
Patients eligible after screening were to have entered a 3-14-day pain medication washout period in which they were not to have taken acetaminophen or any prohibited medication. In addition, patients were to have reported knee pain intensity daily in both knees using the IVRS

Pretreatment/Baseline (Visit 2)
The average measure of knee pain intensity over the last 24 hours over 3 days was to have been used as the baseline assessment at Visit 2 to confirm subject eligibility and to select the study knee.

Procedures and assessments at this visit were to have included the following: assess patient eligibility using inclusion/exclusion criteria, urine pregnancy test, selection of study knee, medical history, concomitant medication/therapy, vitals, WOMAC assessment of study knee only, PGA assessment, application site evaluation, distribution of rescue medication, randomization and distribution of study drug

Treatment period
1. First application of study drug was to have been supervised at the study center.
    a. After ensuring that the study knee was clean and dry, patients were to have washed hands with soap and water
    b. Study drug was to have been pumped once into the hand and applied to the study knee
    c. The pump portion of the study bottle was to have inspected and if is was still compressed from the initial application, then the nozzle was to have been gently pushed up until it returned to its original position.
    d. Steps b and c were to have been repeated making sure the knee is completely covered with study drug
    e. Hands were to have been washed again with soap and water
    f. After application with study drug, patients were to have waited until study drug was dry before putting clothing over application site, waited at least 30 minutes prior to showering or bathing; were not to have used heating pads, bandages, or other tight fitting material or clothes to the application site and were not to have exposed application site to sunlight or artificial light
2. The following assessments were to be obtained after the first study application: vitals signs, concomitant therapy, AE evaluation and application site skin evaluation
3. Patients were to have applied 2 ml (ie.. 2 pumps of the study drug bottle) topically to study knee every 12 hours ± 2 hrs for 4 weeks at the same time each day
    a. If the non-study knee was to have become painful at any time during the study, study drug was to have initiated on this knee until the end of the study
4. Patients were to have reported daily NRS pain scores for study knees

5. Patients were to have reported daily on use of rescue medication
6. At Week 2 (Visit 3) the following procedures and assessments were to have been performed: vital signs, concomitant medications/therapy, AE evaluation, WOMAC, PGA, application site skin evaluation, return and dispensing of study drug and rescue medication
7. At Week 4 (Visit 4) the following procedures and assessments were to have been performed: pregnancy test, physical exam, vital signs, clinical lab tests, concomitant medication/therapy, WOMAC, PGA, AE evaluation, application site skin evaluation, return of study drug and rescue medication

Stopping Criteria
Study patients were to have been withdrawn from the study based on the following criteria

- Patient request
- Patient is unwilling or unable to comply with the protocol
- Patient develops application site skin irritation with a score > 2 on the ordinal scale used to assess skin irritation (0, 0.5, 1, 2, 3, and 4).
- Medical reason, at the discretion of the Investigator and/or the Medical Monitor

Patients who withdraw or who are withdrawn from the study by the Investigator before Visit 4 were to be required to complete the entire final efficacy NRS assessment following the last dose of study drug applied. Also, the patient was to have scheduled an early withdrawal visit as soon as possible (preferably within 3 calendar days of the last administration of study drug).

Patients that were withdrawn from the study were not to have been replaced.

Outcome Variables
Efficacy

- WOMAC LK3.1 Osteoarthritis (OA) Index – pain intensity assessed on 5 –point Likert scale from O (none) to 4(extreme)
- WOMAC LK3.1 OA Index – physical function pain intensity assessed on 5 –point Likert scale from O (none) to 4(extreme)
- WOMAC LK3.1 OA Index – stiffness pain intensity assessed on 5 –point Likert scale from O (none) to 4(extreme)
- Patient Global Assessment (PGA) – assessed on 11-point NRS from 0 (no pain) to 10 (pain as bad as you can imagine)
- Pain intensity (numerical rating scale)
- Use of rescue medication

Safety

- Adverse Events (AEs)

- Vitals (sitting blood pressure in non-dominant arm after 5 minutes of rest, pulse rate, respiratory rate and temperature)
- Physical examination
- Clinical laboratories (chemistry, urinalysis, hematology) and pregnancy test (serum & urine)
- Skin irritation assessment (ordinal scale of 0, 0.5, 1, 2, 3 and 4 where 0 represents no visible reaction and 4 represents erythema with induration and bullae)

Efficacy Endpoints

Primary

WOMAC pain

Secondary

WOMAC physical function
WOMAC stiffness
Pain intensity
Patient global
Use of rescue medication

Statistical Analysis Plan

Analysis Populations

Modified intent-to-treat (mITT): were to have been randomized subjects receiving at least one dose of study medication

Responders: two responder groups were to have been analyzed. Subjects who have pain relief of ≥ 30% from baseline by NRS and subjects who have pain relief of ≥ 50% from baseline by NRS.

Efficacy Analyses

These analyses were to have been conducted on the mITT population except specific analysis on the responder populations.

The primary efficacy analysis was to have been the analysis of the WOMAC LK3.1 pain intensity scale. The secondary efficacy analyses was to have been conducted on pain intensity evaluated twice daily using the NRS, the subject's global assessment of OA in the study knee, physical function, stiffness, and use of rescue medication.

The purposes of the above analyses were to have provided estimates of relative effect sizes to plan the appropriate Phase 3 program for Pennsaid topical 2% and to assess the duration of analgesia over the dosing interval. For assessing relative effect sizes, the results with Pennsaid were to have been compared to results with vehicle alone. The analyses were to have compared the mean change from baseline (Visit 2) to the final visit (Visit 4) using analysis of covariance (ANCOVA), with baseline score as a covariate, for pain on WOMAC, physical function, stiffness and subject's global

assessment. For each of the three NRS measurements taken each day (current pain at midday, current pain in the evening, and average pain over the prior 24 hours rated in the evening), the baseline and final assessments were to have been an average of 3 days of pain assessments (when no pain/rescue medication is allowed) prior to Visits 2 and 4. These pain intensity scores were to have been analyzed by ANCOVA. Plots of midday and evening pain intensity scores for each study day by treatment group were to have been generated. For these plots, pain scores reported within 4 hours of rescue medication use were to have been replaced by the pain score at baseline. The proportion of subjects needing rescue medication throughout the study was to have been compared using chi-square analysis. The number of tablets of rescue medication taken was to have been analyzed using analysis of variance (ANOVA). A responder analysis using the cumulative proportion of responders analysis (CPRA) approach was to have been conducted.

To assess the maintenance of analgesia over the dosing interval, the NRS current pain scores at midday and evening were to have been compared (as estimates of peak and trough pain relief) in the subset of PENNSAID Gel subjects who show pain relief (responders) using ANOVA. The variables analyzed were to have been the average of 3 days of pain assessments (when no pain/rescue medication is allowed) prior to Visit 4.

As this was to have been an exploratory study, where statistical tests were performed, they were to have been two-sided at the 0.10 level of significance with no adjustment for multiple comparisons.

Missing Values
Three separate imputation methods were to have been used to address missing data for subjects who discontinued early:

- Last observation carried forward (LOCF)
- Baseline observation carried forward (BOCF)
- Baseline observation carried forward for all subjects who discontinued early due to treatment failure (lack of efficacy or AE leading to discontinuation) and last observation carried forward for all other subjects who discontinued early

Safety Analyses
These analyses were to been conducted on the mITT population.

Adverse events were to have been classified using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs were to have been tabulated by system organ class (SOC) and by preferred term and SOC (overall and by relationship to study drug and by severity).

Summary statistics for clinical laboratory test results were to have been calculated at each assessment time point, by treatment group for each parameter as well as for their change from screening. Summary statistics for vital signs were to have been calculated

at each assessment time point, by treatment group for each parameter as well as for their change from baseline (pre-treatment Visit 2). Shift tables were to have been prepared for selected laboratory values and the occurrence of clinically significant laboratory values will be tabulated. Changes from screening in the physical examination findings were to have been summarized in data listings.

Sample size determination
A total of 260 subjects (130 in each group) were to have been enrolled in the study to provide estimates of relative effect sizes for Pennsaid (diclofenac sodium topical solution) and placebo control to assist in planning the Phase 3 program.

Protocol Amendments
The original protocol (dated February 5, 2010) was subsequently followed by two protocol amendments (Amendment #1 dated April 30, 2010 and Amendment #2 dated May 24, 2010).

According to the sponsor, Amendment #1 was an administrative amendment to align the background and rationale section of the protocol with other sections of the Pennsaid Gel Investigational New Drug (IND) Application, including the Investigator's Brochure. Study design changes were made including: 1) clarifying that the Screening Period will be no more than 28 days, including the 3 to 14 day washout period, and 3 days of baseline pain intensity measurements prior to Visit 2, 2) including language that self-reported AEs within the 30 days following the last dose should be recorded, and 3) removing the words "oral" and "topical" from Exclusion Criteria # 6 when referring to a sensitivity to diclofenac.

According to the sponsor, Amendment #2 was an administrative amendment completed prior to subject enrollment, for the purpose of revising the mechanics of study drug application, extending the period of time for data collection via the interactive voice response system (IVRS), and making the protocol consistent with final IVRS data collection

Since both amendments were submitted prior to subject enrollment, neither would be expected to affect the outcome of the study.

STUDY RESULTS

Patient Disposition
Table 7 shows the disposition of study patients.

Table 7: Disposition of Study Patients (Randomized Patients)

Disposition Categories	Study Treatment		
	PENNSAID Gel N=131 n (%)	Vehicle Control N=129 n (%)	Total N=260 n (%)
mITT Group	130 (99.2%)*	129 (100%)	259 (99.6%)
Status of mITT Subjects			
Completed (mITT)	122 (93.8%)	117 (90.7%)	239 (92.3%)
Withdrew Early (mITT)	8 (6.2%)	12 (9.3%)	20 (7.7%)
Adverse event	4 (3.1%)	5 (3.9%)	9 (3.5%)
Subject withdrew consent	1 (0.8%)	2 (1.6%)	3 (1.2%)
Lack of efficacy	0	2 (1.6%)	2 (0.8%)
Protocol non-compliance	1 (0.8%)	1 (0.8%)	2 (0.8%)
Withdrawal of subject by Sponsor**	1 (0.8%)	0	1 (0.4%)
Other***	1 (0.8%)	2 (1.6%)	3 (1.2%)

*Subject 13-015 did not receive study drug (Section 10.2)
**Subject 06-003 (PENNSAID Gel) did not qualify during the protocol-specified screening period (Section 10.2)
***Subject 19-004 (PENNSAID Gel) was withdrawn prior to planned hysterectomy. Subject 04-015 and Subject 11-014 (vehicle control) withdrew consent prior to completing study.

Source: NDA 204623, CSR COV05100031, Table 4, pp. 50 of 106

A total of 260 patients were initially randomized (131 Pennsaid 2% and 129 placebo control), however one patient in the Pennsaid (diclofenac sodium topical solution) 2% treatment arm was randomized in error and did not receive study drug. Therefore a total of 259 patients were randomized with 130 patients in the Pennsaid 2% treatment arm and 129 patients in the placebo control treatment arm. Overall, 92.3% (n= 239/260) of patients completed the study with 93.8% (n= 121/130) in Pennsaid 2% treatment arm and 90.7% (n= 117/129) in the placebo control treatment arm completing the study.

Discontinuations

The overall incidence of permanent discontinuations was 7.7% (n=20/259). The percentage of patients permanently discontinued was higher in the placebo group as compared to the Pennsaid (diclofenac sodium topical solution) 2% group [9.3% (n= 12/129) vs. 6.2% (n= 8130, respectively].

The overall incidence of adverse events (AEs) leading to discontinuation was 3.5%. In the Pennsaid 2% treatment arm, 3.1% (4/121) of patients were permanently discontinued from the study secondary to an adverse event as compared to 3.9% (5/129) of the vehicle control group. Further, three additional patients in the vehicle control treatment were discontinued from study drug due to AEs but completed the

study. This is unusual, as it is much more common that there is a higher rate of discontinuation in the study drug group due to adverse events. It is unclear why more subjects in the vehicle group discontinued due to AEs in this study.

In the Pennsaid 2% treatment group, the reported AEs leading to discontinuation from study included: tachycardia and throat tightness (n=1), upper respiratory infection leading to bronchitis requiring steroids (n=1), and application site erythema/induration (n=2). In the vehicle treatment group, the AEs leading to discontinuation from study included: bilateral application site dryness and erythema (n=1), study knee application site exfoliation, dryness and rash (n=1), contralateral knee application site dryness (n=1), contralateral knee application site erythema (n=1), study knee application site pruritus and erythema and joint swelling (n=1), study knee application site pain and pruritus (n=1), study knee application site pruritus (n=1) and application site pain and erythema (n=1). Of note, there were more skin reactions in the vehicle control treatment arm as compared to the Pennsaid 2% treatment arm which may be possibly due to the lack of the anti-inflammatory effect of diclofenac in the former group.

Demographics
Table 8 summarizes the demographics of the mITT population

Table 8: Demographics of mITT Population

Demographic Characteristics	Study Treatment			p-value
	PENNSAID Gel N=130	Vehicle Control N=129	Total N=259	
Mean Age (SD) (years)	60.2 (9.23)	61.9 (9.07)	61.1 (9.17)	0.136*
Mean Weight (SD) (kg)	93.3 (22.77)	89.8 (21.11)	91.6 (21.98)	0.201*
Mean Height (SD) (cm)	169.7 (10.40)	167.8 (9.87)	168.7 (10.16)	0.139*
Mean BMI (SD) (kg/m^2)	32.5 (7.68)	31.8 (6.79)	32.2 (7.24)	0.472*
Gender				
Male (%)	46 (35.4)	39 (30.2)	85 (32.8)	0.377**
Female (%)	84 (64.6)	90 (69.8)	174 (67.2)	
Ethnicity				
Hispanic or Latino (%)	2 (1.5)	0	2 (0.8)	0.498***
Not Hispanic or Latino (%)	128 (98.5)	129 (100)	257 (99.2)	
Race				
Asian (%)	1 (0.8)	0	1 (0.4)	0.799***
Black (%)	19 (14.6)	21 (16.3)	40 (15.4)	
White (%)	110 (84.6)	108 (83.7)	218 (84.2)	

Source: NDA 204523, CSR-COV05100031, Table 5, pg. 53 of 106

Generally, study patients had an average age of 61.1 years, and the majority were of white race (84.2%) and female gender (67.2%). Baseline demographics were similar between treatment groups.

Screening/Baseline disease characteristics

Table 9 displays screening and baseline disease parameters of patients in both treatment groups.

Table 9: Screening/Baseline Disease Characteristics of mITT population

Screening/Baseline Parameter	Study Treatment		p-value
	PENNSAID Gel N=130	Vehicle Control N=129	
Radiological Examination Study Knee Grade*			0.290
Grade 2, n (%)	62 (47.7%)	70 (54.3%)	
Grade 3, n (%)	68 (52.3%)	59 (45.7%)	
WOMAC Subscale Scores, mean (SD)			
Pain	12.4 (3.11)	12.6 (3.41)	0.754
Physical Function	42.9 (10.42)	43.3 (10.33)	0.735
Stiffness	5.3 (1.49)	5.4 (1.26)	0.519
PGA Global Assessment of OA within the past 48 Hours, n (%)			0.983
Very Good	0	1 (0.8%)	
Good	2 (1.5%)	2 (1.6%)	
Fair	23 (17.7%)	23 (17.8%)	
Poor	79 (60.8%)	76 (58.9%)	
Very Poor	26 (20.0%)	27 (20.9%)	
NRS Average Knee Pain During the Last 24 Hours, study knee, mean (SD)			
Screening	4.6 (1.58)	4.6 (1.65)	
Day 1, Pre-Treatment	7.6 (1.32)	7.6 (1.41)	
Change from Screening	3.0 (1.19)	3.0 (1.20)	0.918

*Based on Kellgren-Lawrence scores

Source: CSR-COV05100031, Table 6, pg. 54 of 106

The average WOMAC subscale scores at baseline were similar for pain (12.4 and 12.6), physical function (42.9 and 43.3), and stiffness (5.3 and 5.4) for the Pennsaid 2% and vehicle control group, respectively.

Protocol Violations

The Applicant reports that 24 study participants had major protocol deviations: 8.4% (11/130) of the Pennsaid 2% treatment group and 10.1% (13/129) of the vehicle control treatment group. The major protocol violations for the Pennsaid 2% treatment arm only are briefly summarized within the following categories:

1. Inclusion/Exclusion Criteria Violations
   - The washout period for one patient was extended to induce a flare to allow for inclusion on study. This patient did not qualify for the study during the protocol-specified screening period, and was withdrawn from the study by the Applicant
   - Three patients had exclusionary lab values at randomization.

2. Incorrect randomizations
   - One patient was ineligible for the study but was inadvertently randomized in error. This patient was not dosed and was not included in the mITT population.
   - The randomization of one patient was based on the left knee pain score when only the right knee qualified for study.
3. Inappropriate dosing of study drug
   - Two patients stopped treatment of the contralateral knee prior to study completion
4. Use of prohibited medications
   - Two patients used prohibited medication during the study
     - One patient used hydrocodone-acetaminophen, which was prescribed as an analgesic for unplanned dental surgery.
     - One patient used dexamethasone and methylprednisolone) to treat an upper respiratory infection. This patient was withdrawn from the study when the URI progressed to bronchitis. The discussion of this patient is found in Section 7.7.3 of this review. ?
5. Laboratory deviations
   - Prior to randomization, the urinalysis was not collected for one patient
6. Other deviations
   - One patient missed 3 doses of study drug and neglected to call the interactive voice response system (IVRS).

None of the above protocol deviations would be expected to affect the efficacy or safety outcomes of the study.

Measurement of Treatment Compliance

The Applicant assessed compliance based on patient reports of administration of study medication daily for each dose using IVRS as noted in Table 10.

Table 10: Study Drug Administration Compliance Based on Patient Self Reports of Dose Administration

Compliance Assessment	Study Treatment		
	PENNSAID Gel N=130 n (%)	Vehicle Control N=129 n (%)	Total N=259 n (%)
Week 2:			
0% - 60%	2 (1.6%)	4 (3.1%)	6 (2.3%)
> 60% - ≤ 80%	4 (3.1%)	0	4 (1.6%)
> 80% - ≤ 90%	6 (4.7%)	14 (10.9%)	20 (7.8%)
> 90% - ≤ 110%	117 (90.7)	111 (86.0%)	228 (88.4%)
> 110%	0	0	0
Total non-missing	129 (99.2%)	129 (100%)	258 (99.6%)
Week 4:			
0% - 60%	3 (2.5%)	0	3 (1.3%)
> 60% - ≤ 80%	2 (1.6%)	0	2 (0.8%)
> 80% - ≤ 90%	2 (1.6%)	5 (4.3%)	7 (2.9%)
> 90% - ≤ 110%	115 (94.3%)	112 (95.7%)	227 (95.0%)
> 110%	0	0	0
Total non-missing	122 (93.8%)	117 (90.7%)	239 (92.3%)

Source: CSR-COV05100031, Table 7, pg. 55 of 106

The Applicant's data shows that at both Weeks 2 and 4, patient compliance with drug administration in both treatment groups was >80%.

In addition to patient reports of dosing, bottle weights were measured at dispensing and return to determine the amount of study drug used between study visits. This amount was compared to the amount expected to have been used (based on the number of knees treated and the number of days between study visits) to determine the percentage of actual/expected used and from that to calculate the average dose weight administered for each subject.

Table 11 displays these results.

Table 11: Average Weight of Study Drug Administered Per Dose Calculated from Dispensed and Returned Bottle Weights

Compliance Assessment	Study Treatment		
	PENNSAID Gel N=130 n (%)	Vehicle Control N=129 n (%)	Total N=259 n (%)
Week 2:			
0 – 1.2 mg	43 (33.1%)	43 (33.3%)	86 (33.2%)
> 1.2 mg - ≤ 1.6 mg	38 (29.2%)	41 (31.8%)	79 (30.5%)
> 1.6 - ≤ 1.8 mg	11 (8.5%)	12 (9.3%)	23 (8.9%)
> 1.8 - ≤ 2.2 mg	22 (16.9%)	22 (17.1%)	44 (17.0%)
> 2.2 - ≤ 2.4 mg	7 (5.4%)	9 (7.0%)	16 (6.2%)
> 2.4 mg	9 (6.9%)	2 (1.6%)	11 (4.2%)
Total non-missing	130 (100%)	129 (100%)	259 (100%)
Week 4:			
0 – 1.2 mg	41 (33.9%)	43 (36.8%)	84 (35.3%)
> 1.2 mg - ≤ 1.6 mg	36 (29.8%)	33 (28.2%)	69 (29.0%)
> 1.6 - ≤ 1.8 mg	9 (7.4%)	10 (8.5%)	19 (8.0%)
> 1.8 - ≤ 2.2 mg	16 (13.2%)	16 (13.7%)	32 (13.4%)
> 2.2 - ≤ 2.4 mg	7 (5.8%)	5 (4.3%)	12 (5.0%)
> 2.4 mg	12 (9.9%)	10 (8.5%)	22 (9.2%)
Total non-missing	121 (93.1%)	117 (90.7%)	238 (91.9%)

Note: The source table displays the average percentage of actual/expected weight of study medication used; from that the average dose weight used can be calculated, which is displayed above in mg/dose for ease of interpretation.

Source: CSR-COV05100031, Table 8, pg. 56 of 106

The Applicant has made the following comments regarding the results in Table 11

> This table indicates wide variability of dosing among subjects in both treatment groups. Only approximately 1/3 of the subjects averaged using more than 1.6 mg/dose in either treatment groups or either study interval. The very high compliance rates based on self reports described in [Table 10] clearly indicate that subjects in general were self-dosing at the prescribed times.
>
> However, the average dose weight indicates that there was notable under-dosing in both treatment groups. This was likely due to subject difficulty using the dispensing system. Based on laboratory studies, it was known that the dispensing volume was very consistent per pump actuation unless the pump mechanism did not return to full stroke position. If drug product was dispensed before the pump mechanism returned to full stroke position, the dispensed weight of drug product would be below target specification. It was noted that the pumping mechanism would periodically stick and required manual manipulation to return it to full position before initiating another pump actuation. Instructions provided to each subject prior to first dose addressed these issues. However, given the wide variability in calculated study drug amounts, it is likely that the dispenser was not reliably dispensing the expected 2 [mg/dose]. Due to the

> difficulties previously identified with the dispensing system and in light of these findings, Mallinckrodt has undertaken to identify, qualify and select a different dispenser for future studies and marketing.

During the review process, an inconsistency was noted in the unit of measure used to describe average weight of study drug administered (i.e., mg) as shown in Table 11. An information request was sent by the Division to the Applicant requesting clarification of the unit value for the average weight of study drug administered. The Applicant's response is summarized below:

> After finalization and submission of the CSR to the [Agency], the [study]project Biostatistician discovered that the unit of measure associated with compliance assessment (average weight of study drug administered) values (milligrams, mg) found in text Table 8: Average Weight of Study Drug Administered Per Dose Calculated from Dispense and Returned Bottle Weights was incorrect. These compliance assessment values should have been described in grams (g). The erroneous unit does not impact the summaries or conclusions in the CSR therefore, it has been decided not to formally revise the CSR.

The Sponsor's response was adequate.

Primary Efficacy Results

The results for the primary efficacy endpoint, WOMAC pain subscale are displayed in Table 12 using the Applicant's combined LOCF/BOCF imputation method.

Table 12: WOMAC Pain Subscale Score Results by Treatment Group and Study Visit (LOCF/BOCF)

Mean and Mean Change from Baseline	Study Treatment	
	PENNSAID Gel N=130	Vehicle Control N=129
Baseline:		
Mean (SD)	12.4 (3.11)	12.6 (3.41)
Min, Max	4, 20	3, 20
Week 2:		
Mean (SD)	8.8 (4.48)	9.6 (4.41)
Min, Max	0, 19	0, 20
Mean Change (SD)	-3.6 (4.06)	-2.9 (3.79)
Min, Max	-16, 3	-15, 1
Week 4:		
Mean (SD)	7.9 (4.53)	8.9 (4.42)
Min, Max	0, 20	0, 20
Mean Change (SD)	-4.5 (4.49)	-3.6 (4.22)
Min, Max	-15, 4	-17, 4
p-value comparing the Week 4 mean changes in the two treatment groups*	0.040	

Source: NDA 204623, CSR-COV05100031, Table 9, pg. 57 of 106

The Applicant reports that the Pennsaid (diclofenac sodium topical solution) 2% treatment group was statistically superior to the vehicle control for WOMAC™ pain subscale score at Week 4 (least squares [LS] mean change -4.4 versus -3.4, p=0.040) and results were similar (i.e. statistically significant) with the other two imputation approaches (LOCF and BOCF).

Using an alpha of 0.05 the Applicant results (p = 0.040) show that at Week 4 there is a statistically significant difference between Pennsaid (diclofenac sodium topical solution) 2% and placebo control in reducing the pain associated with knee OA. However, this difference may not be clinically meaningful.

Secondary Efficacy Results

(b) (4)

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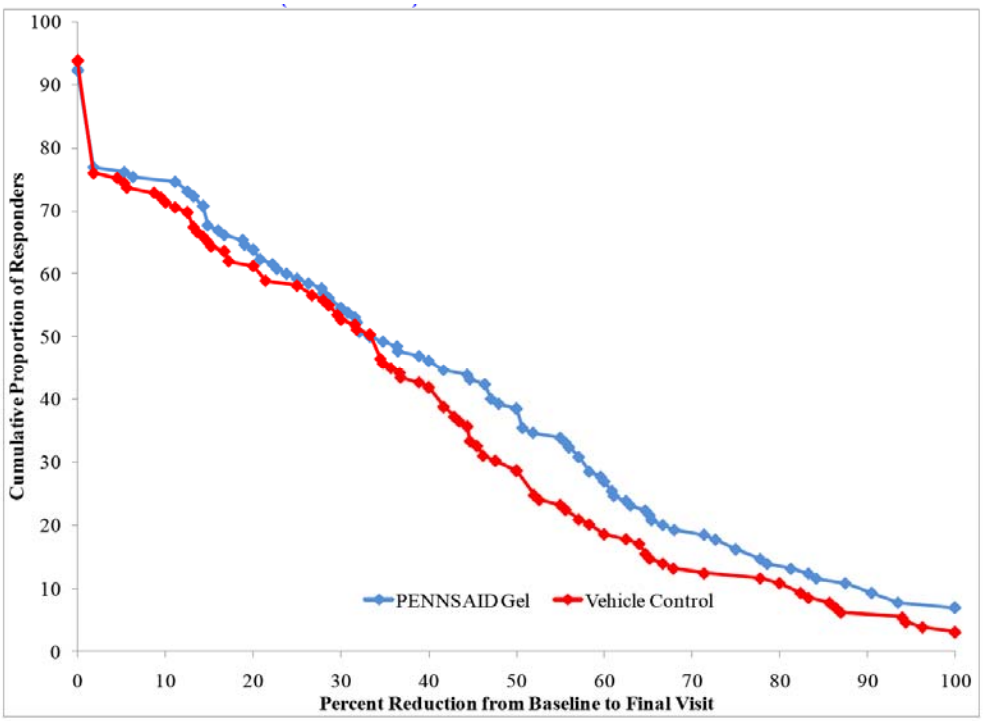
Cumulative Proportion of Responders

Figure 1 shows the cumulative proportion of responders from no response to 100% response using NRS ratings over the last 24 hours at Week 4 in the two treatment groups.

Figure 1: Cumulative Proportion of Responders Analysis: Average Pain During the Last 24 Hours at Final Visit



Source: NDA 204623, CSR-COV05100031, Figure 4, pg. 66 of 106

The Applicant's figure shows that with regards to the reduction of average pain during the last 24 hours at the final visit/Week 4, there is little to no separation between Pennsaid (diclofenac sodium topical solution) 2% and placebo responder curves until the percent reduction is greater than 35%.

SAFETY FINDINGS

A brief summary of the major safety results for this study follows. A complete discussion of safety can be found in Section 7.3.

Exposure

Generally, study patients (regardless of treatment group) received an average of 27.8 days of BID dosing on the study knee, and an average of 27.9 days of BID dosing on the contralateral knee. Mean duration of study drug exposure on the study knee was 28.2 days for the Pennsaid 2%TS arm as compared to 27.4 days for the placebo treatment arm. Overall, mean duration of study drug exposure on the study knee was comparable between treatment groups.

Deaths
There were no deaths reported during the study.

Serious Adverse Events
There were no serious adverse events reported during the study.

Adverse Events leading to Discontinuations
In the Pennsaid (diclofenac sodium topical solution)2% treatment group, the reported adverse events leading to discontinuation included: tachycardia and throat tightness (n=1), upper respiratory infection progressing to bronchitis requiring steroids (n=1), bilateral application site erythema and induration (n=1) and bilateral application site scabbing, erythema, and induration (n=1).

Of note, the case report form (CRF) for the "tachycardia and throat tightness" AE was reviewed. The acute onset of symptoms after Pennsaid (diclofenac sodium topical solution) 2% administration appears to describe an allergic reaction. Please refer to Section 7.3.3 (Dropouts and/or Discontinuations) for further discussion of this AE.

Common Adverse Events (AEs)
The most TEAEs reported at an incidence rate of > 3% in either group included the following: application site dryness, application site exfoliation, application site erythema, urinary tract infection, application site pruritus, and application site pain. Generally, the incidence of these TEAEs was similar between treatment groups.

Clinical labs, Vital signs, Physical exam

- There were no clinically meaningful changes noted between the Pennsaid 2% TS group as compared to the placebo group with respect to labs and vital signs

- Physical exam
    - Application site reactions were the most common AEs
        - Two of the four patients in the Pennsaid 2% group who experienced AEs leading to discontinuation were secondary to application site reactions.

6 Review of Efficacy

Efficacy Summary

(b) (4)

One adequate and well-controlled clinical study was used to support the proposed indication. This study was designed as a Phase 2 exploratory study that enrolled patients with primary osteoarthritis of the knee that had to have experienced a pain flare following

discontinuation of prior analgesic or anti-inflammatory therapy. Of note, one of the principal objectives of the study was to characterize the analgesic effect and to determine the effect size for Pennsaid gel by evaluating multiple efficacy endpoints to assist in planning the Phase 3 program.

The Phase 2 efficacy study evaluated one primary efficacy endpoint: mean change from baseline at Week 4 in WOMAC™ pain subscale score and a number of secondary endpoints (i.e. WOMAC™ physical function subscale score, WOMAC™ stiffness subscale score, patient's global assessment of disease status, pain intensity and use of rescue medication) in order to further characterize the efficacy of Pennsaid 2%.

Pennsaid (diclofenac sodium topical solution) 2% was statistically significant compared to placebo for the reduction of OA knee pain at Week 4, (b) (4)

While analgesic efficacy of Pennsaid (diclofenac sodium topical solution) 2% was supported statistically by reduction of OA knee pain, this reduction may not be clinical meaningful. The treatment difference for reducing OA knee pain was small (approximately 1). (b) (4)

In light of Pennsaid (diclofenac sodium topical sodium) 2% modest efficacy results in reducing OA knee pain, the clinical benefit of this new drug product for the millions of diverse knee OA patients has not been adequately characterized. The cumulative responder analyses was performed for the primary efficacy endpoint by statistical reviewer Feng Li PhD. The results of Dr. Li's analyses paralleled the Applicant's results in that at Week 4, there was a clear separation of Pennsaid (diclofenac sodium topical solution) 2% and placebo responder curves at 30% reduction in pain.

(b) (4)

6.1 Indication

The proposed indication for Pennsaid (diclofenac sodium topical solution) 2% is for the treatment of (b) (4) of OA of the knee.

6.1.1 Methods

The Applicant conducted one Phase 2 efficacy trial (i.e., Study COV5100031) to assess the efficacy and safety of Pennsaid (diclofenac sodium topical solution) 2% topical solution for the treatment of signs and symptoms of the OA of the knee.

Study COV5100031 was a Phase 2, multi-center, randomized, double-blind, vehicle-controlled that evaluated the efficacy and safety of Pennsaid (diclofenac sodium topical solution) 2% at a dose level of 40 (b) (4) mg (i.e. 2 ml) per study knee for the management of signs and symptoms of OA of the knee in men and women aged 40-85 years (inclusive) with a diagnosis of primary OA of the knee who experienced a flare of their OA symptoms following a discontinuation of previous analgesic or anti-inflammatory therapy.

The comparator was vehicle/placebo control (i.e. complete carrier containing DMSO and other ingredients (propylene glycol, alcohol, purified water, and hydroxypropyl cellulose) at the same concentrations as Pennsaid without diclofenac sodium). Patients applied study drugs twice a day for four weeks. For inclusion, patients were to have a baseline minimum pain score of at least 5 using an 11-point NRS and at least a 2- unit worsening from the screening pain score

Study COVO5100031 was initially designed as an exploratory study. The Applicant surmised that the four-week study duration was consistent with the draft guidance for topical diclofenac sodium. Also, the Applicant postulates that there would be no reason to suspect a NSAID which had a treatment effect at Week 4 would not have an treatment effect thereafter.

In my opinion, the Applicant's rationale for the four-week study design is inadequate for the following reasons:

- Pennsaid (diclofenac sodium topical solution) 2% is not a generic drug,
- Pennsaid (diclofenac sodium topical solution) 2% is intended for use as a prescription drug for the treatment (b) (4) of the knee. In prior regulatory meetings, the Applicant has been informed that "for a prescription intending to seen an indication for (b) (4) pain of OA adequate trials must be at least 12 weeks in duration.
- Pennsaid (diclofenac sodium topical solution) 2% is a new drug formulation Superior efficacy established at Week 4 of study treatment does not translate into superior efficacy or sustained treatment benefit at Week 12 and beyond.

The Division has opined that the OGD guidance for Topical Diclofenac may be applied to this NDA.

6.1.2 Demographics

The average age of the total study population was 61 years, and the majority of study patients were female and of White race. Patients treated with Pennsaid (diclofenac sodium topical solution) 2% had an average age of 60 years, 65% were female, and 85% were White.

Overall, the demographic characteristics between Pennsaid (diclofenac sodium topical solution) 2% and placebo treatment groups were similar.

6.1.3 Subject Disposition

A total of 260 patients who were initially randomized, 131 to Pennsaid (diclofenac sodium topical solution) 2% and 129 to placebo control. One patient was randomized to Pennsaid (diclofenac sodium topical solution) 2% in error and did not receive any study drug. Overall, the majority of patients in both treatment groups completed the study: 94% (n=122/130) in the Pennsaid (diclofenac sodium topical solution) 2% arm and 91% (n=117/129) in the placebo arm.

The percentage of patients that discontinued study treatment early secondary to AEs was similar between Pennsaid (diclofenac sodium topical solution) 2% and placebo treatment arms [3.1% (n=4/130) vs. 3.9% (n=5/129)], respectively.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the mean change from baseline to Week 4 in: WOMAC™ pain subscale score. At the EOP2 meeting in September 2006 the Division and the Applicant agreed that the primary endpoints to support efficacy were: WOMAC pain, WOMAC function and PGA. In addition, at a Type B guidance meeting in August 2008, the Division informed the Applicant that three endpoints (i.e. WOMAC pain, WOMAC function, and Patient global assessment) would be required to support the proposed indication for treatment (b) (4) of OA of the knee.

Feng Li PhD , statistical reviewer from the Division of Biometrics 2 repeated the applicant's results for the primary efficacy analyses. Table 16 shows Dr. Li's results for WOMAC assessments from an ANCOVA model with terms including treatment, whether the non-study knee was treated and the baseline value. A negative value of change from baseline indicated an improvement as compared to baseline.

Table 16: Efficacy Results at Week 4

Endpoint		Least Square Means (Standard Error) Diclofenac sodium 2% (N=130)	Vehicle (N=129)	Difference (95% CI)	P-value
WOMAC pain	Baseline mean (SD)	12.4 (3.1)	12.6 (3.4)		
	Change from Baseline	-4.4 (0.4)	-3.4 (0.4)	-1.0 (-2.0, 0.0)	0.04
WOMAC function	Baseline mean (SD)	(b) (4)			
	Change from Baseline				
Patient's global	Baseline mean (SD)				
	Change from Baseline				

SD: standard deviation; CI: confidence interval.
Source: Dr. LI's draft statistical review of NDA 204623, pg. 9 of 13

Dr. Li's review states that while the Pennsaid (diclofenac sodium topical solution) 2% group had a numerically better response in WOMAC pain, function, and PGA than the placebo group only the difference in WOMAC pain achieved statistical significance at level) 0.05.

The results of Dr. Li's analyses confirm the Applicant's results in that after four weeks of study treatment Pennsaid (diclofenac sodium topical solution) 2% was statistically better than placebo in reducing OA knee pain.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary efficacy endpoints included: WOMAC physical function and stiffness subscale scores, PGA of OA in the study knee, daily pain intensity evaluated using NRS, use of rescue medication and cumulative proportion of responders.

Table 16 above summarizes Dr. Li's results for secondary efficacy endpoints WOMAC physical function and PGA. As previously stated, (b) (4)

(b) (4)

(b) (4)

Use of Rescue Medication

Dr. Feng Li, repeated the analyses for the percentage of subjects taking rescue medication at different time periods as seen in Table 17.

Table 17: Percentage of Subjects Using Any Rescue Medication

Period	Diclofenac sodium 2% (N=130)	Vehicle Control (N=129)	P-value [1]
Week 1 and Week 2	89 (68%)	94 (73%)	0.4
Week 3 and Week 4	68 (52%)	82 (64%)	0.07
Overall	95 (73%)	99 (77%)	0.5

Source: Dr. Feng Li's draft statistical review of NDA 204623, Table 4, pg. 9 of 13

A summary from Dr. Li's review regarding the use of rescue medication follows:

> Table [17] presents the percentages of subjects who took rescue during different time periods. Overall, the percentage of subjects who took rescue during the study was similar between the treatment groups. More subjects in the control group than the diclofenac sodium group took rescue after Week 2. I found that approximately 21% of the patients in the control group and 12% of the patients in the diclofenac sodium 2% took rescue within 3 days of Week 4 visit. For these subjects, the Week 4 WOMAC assessments were replaced with baseline values per the pre-specified primary analysis. I found that if the observed WOMAC assessments were used instead of the baseline values the difference between the groups in the primary endpoint would not be significant, indicating that the control group might have had favorable responses after taking rescue.

Overall, the results of the secondary efficacy analyses did not support the primary efficacy analyses.

6.1.6 Other Endpoints

None

6.1.7 Subpopulations

This section is not applicable to this NDA.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This section is not applicable to this NDA.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This section is not applicable to this NDA.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

A total of 189 subjects/patients were exposed to at least one dose of Pennsaid (diclofenac sodium topical solution) 2%. The safety profile of Pennsaid (diclofenac sodium topical solution) 2% was assessed in 130 patients with primary OA of the knee.

There were no serious adverse events (including deaths) reported in clinical studies in the Pennsaid (diclofenac sodium topical solution) 2% clinical development program. Twice as many patients in the placebo treatment arm were discontinued early secondary to a TEAE as compared to patients in the Pennsaid (diclofenac sodium topical solution) 2% treatment arm (6.2% vs. 3.1%, respectively). Of the Pennsaid (diclofenac sodium topical solution) 2% patients who discontinued secondary to a AE, 50% (2/4) of these patients had application site AEs whereas in the placebo group 100% of the patients who were discontinued (n=8/8)

The overall percentage of study patients who experienced any TEAE was 42.9% (n=111/259). The percentage of patients in the Pennsaid (diclofenac sodium topical solution) 2% treatment arm who experienced a TEAE was 40.0% (n=52/130) was lower as compared to the 45.7% (n=59/129) of placebo patients who experienced any TEAE.

The most common adverse events reported in Pennsaid (diclofenac sodium topical solution) 2% patients for the placebo-controlled OA study were: application site dryness, application site exfoliation, application site erythema, and urinary tract infections.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

One randomized, double-blind efficacy and safety study (COV05100031) was completed during the clinical development of Pennsaid (diclofenac sodium topical solution) 2% .

7.1.2 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 12.1

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

For the current NDA, the Applicant did not pool any data to estimate and compare incidence of adverse events.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall Exposure
A total of 189 subjects/patients were exposed to at least one dose of Pennsaid (diclofenac sodium topical solution) 2% in three clinical trials.

- A total of 130 knee OA patients in controlled efficacy/safety study (COV05100031)
- A total of 32 healthy subjects in relative BA/PK study (COV05100075) and
- A total of 27 healthy subjects in relative BA/PK study (COV05100070)

In the efficacy/safety study a total of 129 patients received an average of 28 days of twice daily Pennsaid (diclofenac sodium topical solution) 2% treatment on the study knee. One patient in the Pennsaid (diclofenac sodium topical solution) 2% treatment arm was missing a dose stop date so this patient was dropped from the duration of

treatment calculation. Also, a total of 81 patients received an average of 28 days of twice daily Pennsaid (diclofenac sodium topical solution) 2% on the contralateral knee. The study patients exposed to Pennsaid (diclofenac sodium topical solution) 2% had the following demographics:

- Mean age of 60 years,
- 85% of patients were White, and
- 65% were females

In previous regulatory meetings with the Applicant the size of the safety database was not formally discussed. However, at the EOP2 meeting there was agreement between the Division and Applicant that the NDA for Pennsaid (diclofenac sodium topical solution) could be submitted as a 505(b)(2) application relying on the Agency's finding of safety and efficacy of the initial PENNSAID product (NDA 020947).

According to Dr. Larissa Lapteva's clinical review for NDA 020947 (dated 12-06-06), a total of 911 patients were exposed to PENNSAID® in controlled phase III clinical trials and 793 patients were exposed to PENNSAID® in the open label PEN-03-112E study to form the primary evidence of safety.

The Applicant reports that since its approval in November 2009 through October 31, 2011 IMS data shows (b) (4) prescriptions having been dispensed in the United States using Mallinckrodt's PENNSAID 1.5%, where each prescription is assumed to be equivalent to (b) (4) patient-month.

Taking into account safety data from premarketing controlled clinical trials and postmarketing exposure for PENNSAID 1.5% and current safety data from the Pennsaid (diclofenac sodium topical solution) 2% NDA, the safety database appears adequate.

7.2.2 Explorations for Dose Response

None7.2.3 Special Animal and/or In Vitro Testing

No special animal testing was conducted.

7.2.4 Routine Clinical Testing

The routine testing of subjects was adequate in terms of assessing hematology, serum chemistry and urinalysis laboratory values.

7.2.5 Metabolic, Clearance, and Interaction Workup

None

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Pennsaid (diclofenac sodium topical solution) 2% is classified as a topical NSAID. Special attention was given to AEs commonly seen in patients being treated with topical NSAIDS including those related to application site reactions. In addition, gastrointestinal AEs (e.g., nausea, vomiting) and cardiovascular AEs (e.g., changes in blood pressure) were noted as well.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported during the study.

7.3.2 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse events reported during the study.

7.3.3 Dropouts and/or Discontinuations

The overall incidence of discontinuations secondary to treatment emergent adverse events (TEAEs) was 4.6% (n=12/259). Ten of the 12 discontinuations were due to application site reactions (2 in the Pennsaid group and 8 in the placebo control group). Of note, the placebo control group had a higher rate of discontinuations secondary to TEAEs as compared to the Pennsaid (diclofenac sodium topical solution) 2% group [6.2% (8/129) vs. 3.1% (n=4/130) respectively].

The percentage of patients with TEAEs by SOC leading to study discontinuation is displayed in Table 18.

Table 18: TEAEs Leading to Discontinuation of Study Drug

	Study Treatment		
	PENSAID Gel N=130 n (%)	Vehicle Control N=129 n (%)	Total N=259 n (%)
Number of subjects discontinuing study medication due to TEAE	**4 (3.1%)**	**8 (6.2%)**	**12 (4.6%)**
Cardiac Disorders	**1 (0.8%)**	**0**	**1 (0.4%)**
Tachycardia	1 (0.8%)	0	1 (0.4%)
General Disorders and Administration Site Conditions	**2 (1.5%)**	**8 (6.2%)**	**10 (3.9%)**
Application site dryness	0	3 (2.3%)	3 (1.2%)
Application site erythema	2 (1.5%)	4 (3.1%)	6 (2.3%)
Application site exfoliation	0	1 (0.8%)	1 (0.4%)
Application site induration	2 (1.5%)	0	2 (0.8%)
Application site pain	0	2 (1.6%)	2 (0.8%)
Application site pruritus	0	3 (2.3%)	3 (1.2%)
Application site rash	0	1 (0.8%)	1 (0.4%)
Application site scab	1 (0.8%)	0	1 (0.4%)
Infections and Infestations	**1 (0.8%)**	**0**	**1 (0.4%)**
Upper respiratory tract infection	1 (0.8%)	0	1 (0.4%)
Musculoskeletal and Connective Tissue Disorders	**0**	**1 (0.8%)**	**1 (0.4%)**
Joint swelling	0	1 (0.8%)	1 (0.4%)
Respiratory, Thoracic and Mediastinal Disorders	**1 (0.8%)**	**0**	**1 (0.4%)**
Throat tightness	1 (0.8%)	0	1 (0.4%)

Source: NDA 204623, CSR-COV05100031, Table 23, pg. 82 of 106

The system organ class with the highest frequency of TEAEs leading to discontinuations among both treatment arms includes the general disorders and administration site conditions SOC. However, the placebo control arm had four times the number of patients who discontinued early secondary to application site related AEs as compared to the Pennsaid (diclofenac sodium topical solution) 2% treatment arm [6.2% (n=8/129) vs. 1.5% (n=2/130)].

Cases narratives for Pennsaid arm patients who were permanently discontinued from study drug secondary to a TEAE follow:

Patient 16-003 a 54-year-old female reportedly began Pennsaid (diclofenac sodium topical) 2% study treatment August 3, 2010 for OA of the right and left knees. At the time of study entry the patient's medical history included: OA of bilateral knees, hypertension, acid reflux, intermittent low back pain, vitamin D deficiency, and allergic conditions (i.e., penicillin, keflex and vibramycin allergy, and aspirin sensitivity). Prior surgical history included: partial hysterectomy, and right knee arthroscopy. Concomitant medications included: lisinopril/hydrochlorothiazide, multivitamin, Vitamin D, and acetaminophen (as rescue medication).

The first day Pennsaid (diclofenac sodium topical solution) 2% study treatment administration (i.e., August 3, 2010), the patient experienced a tight throat and

tachycardia. These AEs were reported as mild in severity and no treatment was administered for these AEs. The patient was permanently discontinued from study treatment on August 6, 2010 and the symptoms resolved on August 7, 2010.

While the case report form (CRF) lack further details of this event, the symptoms of tight throat and tachycardia describe symptoms of a possible allergic reaction.

The reported adverse events of a "tight throat and tachycardia" (possibly allergic reaction) leading to this patient's discontinuation were related to Pennsaid (diclofenac sodium topical solution) 2% treatment.

Patient 04-011, a 53-year-old male began Pennsaid (diclofenac sodium topical solution) 2% study treatment on August **1**6**,** 2010 for OA of the left knee and by August 30, 2010 had started study treatment on the contralateral knee. . At the time of study entry the patient's medical history included: OA of the right and left knee. No prior surgical history was reported. Concomitant medications included: acetaminophen (rescue medication).

On August 26, 2010, the patient experienced application site erythema, induration, and scabbing on both the study and contralateral knees. The patient reportedly spent time on his knees laying carpet and applied study drug around the abrasions. These AEs were reported as moderate in severity. No treatment was administered for these AEs. The patient permanently discontinued study treatment on August 30, 2010. The symptoms persisted until September 13, 2010. On August 30, 2010, the patient also reportedly experienced prostatitis and a urinary tract infection, which resolved by September 23, 2010.

The reported adverse events of application site erythema and induration (bilateral) and scabbing leading to this patient's discontinuation were related to Pennsaid (diclofenac sodium topical solution) 2% treatment.

Patient 12-029, a 46-year-old female began Pennsaid (diclofenac sodium topical) 2% study treatment on November 23, 2010. At the time of study entry the patient's medical history included: OA of the right and left knee, obesity, and menorrhagia. Prior surgical history included: vaginal ablation, tubal ligation, and lap band surgery. Concomitant medications included: acetaminophen (rescue medication).

On December 6, 2010, the patient experienced application site erythema and induration on both the study and contralateral knees reported as moderate in severity. No treatment was administered for these AEs The patient permanently discontinued study treatment on December 8, 2010, and the symptoms reportedly resolved by December 12, 2010.

The reported adverse events of application site erythema and induration (bilateral) leading to this patient's discontinuation were related to Pennsaid (diclofenac sodium topical solution) 2% treatment.

Patient 24-017 a 68-year-old male began Pennsaid (diclofenac sodium topical) 2% study treatment on October 14, 2010 for OA of the left knee. At the time of study entry the patient's medical history included: OA of the right and left knee, OA of the right hip, degenerative joint disease, gastroesophageal reflux disease, benign prostatic hypertrophy, hypertension, hyperlipidemia, erectile dysfunction, and left ankle edema. Prior surgical history included: right hip resurfacing. Concomitant medications included: esomeprazole, doxazosin, mesylate, simvastatin, aspirin, tadalafil and acetaminophen (rescue medication)

On October 17, 2010, the patient reportedly developed an upper respiratory infection that progressed to bronchitis. The subject was prescribed protocol-prohibited corticosteroids, dexamethasone and methylprednisolone, for the infection; as well as clarithromycin this was considered a major protocol deviation. The patient was also prescribed clarithromycin and albuterol inhaler for their bronchitis. The AE was assessed as moderate in severity. . The patient was permanently discontinued from study treatment October 22, 2010. The bronchits infection was reported as resolved on January 4, 2011.

The reported adverse event of bronchitis leading to this patient's discontinuation was not related to Pennsaid (diclofenac sodium topical solution) 2% treatment.

7.3.4 Significant Adverse Events

All significant AEs are discussed in **Sections 7.3 and 7.4.**

7.3.5 Submission Specific Primary Safety Concerns

A potential safety concern specific to this NDA was skin reactions at the application site. Skin irritation was assessed using an ordinal scale (0-4 where 0 represented no visible reaction and 4 represented erythema with induration and bullae. Skin irritation assessments were performed pre and post-treatment during Day 1 (Visit 2) of the study and once at 2 weeks (Visit 3) and 4 weeks (Visit 4) after start of study drug treatment.

Table 19 contains the results of application site skin evaluations of the study knee.

Table 19: Application Site Skin Evaluation of Study Knee

Visit/Knee	Skin Irritation Assessment	Study Treatment		
		PENSAID Gel N=130 n (%)*	Vehicle Control N=129 n (%)*	Total N=259 n (%)*
Day 1, Pre-treatment	0 (no visible reaction)	127 (98.4%)	124 (97.6%)	251 (98.0%)
	0.5 (dryness or flaking)	2 (1.6%)	3 (2.4%)	5 (2.0%)
	1 (erythema)	0	0	0
	2 (erythema with induration)	0	0	0
	3 (erythema with induration and vesiculation)	0	0	0
	4 (erythema with induration and bullae)	0	0	0
	Total non-missing	129 (99.2%)	127 (98.4%)	256 (98.8%)
Day 1, Post-treatment	0 (no visible reaction)	129 (99.2%)	122 (95.3%)	251 (97.3%)
	0.5 (dryness or flaking)	1 (0.8%)	2 (1.6%)	3 (1.2%)
	1 (erythema)	0	4 (3.1%)	4 (1.6%)
	2 (erythema with induration)	0	0	0
	3 (erythema with induration and vesiculation)	0	0	0
	4 (erythema with induration and bullae)	0	0	0
	Total non-missing	130 (100%)	128 (99.2%)	258 (99.6%)
Week 2 (+/- 2 Days)	0 (no visible reaction)	104 (81.9%)	107 (84.9%)	211 (83.4%)
	0.5 (dryness or flaking)	20 (15.7%)	14 (11.1) %	34 (13.4%)
	1 (erythema)	1 (0.8%)	5 (4.0) %	6 (2.4%)
	2 (erythema with induration)	2 (1.6%)	0	2 (0.8%)
	3 (erythema with induration and vesiculation)	0	0	0
	4 (erythema with induration and bullae)	0	0	0
	Total non-missing	127 (97.7%)	126 (97.7%)	253 (97.7%)
Week 4 (+/- 5 Days)	0 (no visible reaction)	98 (79.7%)	95 (80.5%)	193 (80.1%)
	0.5 (dryness or flaking)	21 (17.1%)	20 (16.9%)	41 (17.0%)
	1 (erythema)	4 (3.3%)	2 (1.7%)	6 (2.5%)
	2 (erythema with induration)	0	1 (0.8%)	1 (0.4%)
	3 (erythema with induration and vesiculation)	0	0	0
	4 (erythema with induration and bullae)	0	0	0
	Total non-missing	123 (94.6%)	118 (91.5%)	241 (93.1%)

*Percentages calculated using the total number of reported scores as the denominator

Source: NDA 204623, CSR-COV05100031, Table 26, pg. 88 of 106

The Applicant assessed a score greater than 0 as an AE and score >2 required withdrawal from the study. At Week 4, a higher percentage of Pennsaid (diclofenac sodium topical solution) 2% patients had dryness or flakiness (17.1% vs. 16.9%m respectively) and erythema with induration (3.3% vs. 2.7% respectively).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The review of common adverse events encompasses all TEAEs reported in Study COV051000031 unless otherwise stated.

A summary of the most common TEAEs by preferred term reported for ≥ 3% in any treatment group is displayed Table 20.

Table 20: Incidence of Common TEAEs by System Organ Class and Preferred Term

System Organ Class and Preferred Term	Study Treatment		
	PENSAID Gel N=130 n (%)	Vehicle Control N=129 n (%)	Total N=259 n (%)
General Disorders and Administration Site Conditions	**41 (31.5%)**	**50 (38.8%)**	**91 (35.1%)**
Application site dryness	28 (21.5%)	28 (21.7%)	56 (21.6%)
Application site exfoliation	9 (6.9%)	11 (8.5%)	20 (7.7%)
Application site erythema	5 (3.8%)	15 (11.6%)	20 (7.7%)
Application site pruritus	3 (2.3%)	18 (14.0%)	21 (8.1%)
Application site pain	2 (1.5%)	4 (3.1%)	6 (2.3%)
Infections or Infestations	**7 (5.4%)**	**6 (4.7%)**	**13 (5.0%)**
Urinary tract infection	4 (3.1%)	1 (0.8%)	5 (1.9%)

*Most common defined as incidence of > 3% in either treatment group

Source: NDA 204623, CSR-COV05100031, Table 20, pg. 77 of 106

Overall, TEAES reported at an incidence >3% reported by system organ class (SOC) occurred most frequently in the General Disorders and Administration Site Conditions SOC (31%, n=91/259). TEAEs reported at an incidence rate of > 3% in either group included the following: application site dryness, application site exfoliation, application site erythema, urinary tract infection, application site pruritus, and application site pain. The incidence of the skin related AEs was lower in the Pennsaid (diclofenac sodium topical solution) 2% treatment arm as compared to the placebo treatment arm. The anti-inflammatory action of diclofenac in the active study drug, in theory, may have been a contributory factor in the decreased incidence of skin related adverse reactions.

7.4.2 Laboratory Findings

Overview of laboratory testing in the development program

Clinical laboratory tests included hematology, clinical chemistry and urinalyses. Laboratory assessments were obtained at screening and Visit 4 (Week 4). In addition pregnancy tests for women of childbearing age were performed at screening (serum), before start of treatment at Visit 2/baseline (urine) and at Visit 4 (urine)

Hematology analysis

Results for hematologic lab values included: erythrocytes, leukocytes, hemoglobin (Hgb), hematocrit (Hct), platelets, neutrophils, lymphocytes, eosinophils, and monocytes.

Analysis focused on measures of central tendency
Overall, there were no clinically relevant changes from baseline in mean hematologic values over time.

Analysis focused on shifts from normal to abnormal
A higher percentage of patients in the Pennsaid 2% treatment group (9.4%) had shifts from normal to low in hematocrit. as compared to the control treatment group (4.9%)

Outliers Determined to be Clinically Significant and Dropouts for Hematology Abnormalities
Clinical significance was determined by the Investigator. One patient (#23-019) in the Pennsaid 2% treatment arm had hematology values (i.e. low erythrocytes, low hemoglobin and low hematocrit) that were deemed to be clinical significant [4.06 X10^12/L {normal range 4.5-5.9,) 0.355 L/L (normal range 0.416-0.541) and 124 g/L (normal range 130-175) respectively} at an unscheduled visit after Week 4 of the study. There were no dropouts for hematology abnormalities.

Chemistry analysis
Results for clinical chemistry lab values included: sodium, potassium, chloride, bicarbonate, glucose, bilirubin, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl transferase (GGT).

Analysis focused on measures of central tendency
Overall, there were no clinically relevant changes from baseline in mean chemistry values over time.

Analysis focused on shifts from normal to abnormal
A higher percentage of patients in the Pennsaid 2% treatment group (8.5%, n=11/130) had shifts from normal to high in BUN as compared to the control treatment group (4.1%, n=5/129)

Outliers Determined to be Clinically Significant and Dropouts for Chemistry Abnormalities
Clinical significance was determined by the investigator. One patient (#08-017) in the Pennsaid treatment arm with a history of diabetes had elevated blood glucose [13.8 mmol/L normal range (3.3-7.8)] at the Week 4 study visit. There were no dropouts for chemistry abnormalities.

7.4.3 Vital Signs

Vital sign assessments included sitting systolic and diastolic blood pressure, (mmHg) after 5 minutes of rest in the nondominant arm, pulse rate (beats per minute), respiratory rate (breaths per minute), and body temperature (°C). Vital signs were

assessed at screening, before and after study treatment at Visit 2 (Day 1) and at Visit 3 and Visit 4.

Analyses focused on measures of central tendency
Overall, there were no clinically relevant changes from baseline in mean vital signs values over time.

Analysis focused on shifts from normal to abnormal
Vital sign shift tables were not provided by the Applicant.

Outliers Determined to be Clinically Significant and Dropouts for Vital Sign Abnormalities
One patient (#16-003) in the Pennsaid 2% treatment arm experienced tachycardia along with throat tightness on Day 1 of study treatment. The pulse rates recorded on the CRF at screening, pre-and post-dose on Day 1 were all recorded as 72 bpm, respectively. The patient was permanently discontinued from study participation secondary to adverse events of

7.4.4 Electrocardiograms (ECGs)

No ECG assessments were conducted in Study COV05100031.

7.4.5 Special Safety Studies/Clinical Trials

No additional safety studies were conducted to support the NDA.

7.4.6 Immunogenicity

No immunogenicity studies were conducted to support the NDA.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Study COV05100031 evaluated one dosage form of Pennsaid (diclofenac sodium topical solution) 2%, therefore there was no evaluation of dose dependency for AEs by the Applicant.

7.5.2 Time Dependency for Adverse Events

As previously discussed, application site reactions were the most common reported AEs in Study COV05100031. The Applicant performed skin irritation assessments at the application site at both pre and post-treatment during Day 1 and once at 2 and 4 weeks after study treatment initiation. Skin irritation was scored on a scale of 0-4, with scores greater than zero being reported as AEs. The mean time to first skin irritation AE reported (for study knee) was 18.1 days for the Pennsaid (diclofenac sodium topical solution) 2% treatment group as compared to 14.7 days for the placebo control treatment group.

7.5.3 Drug-Demographic Interactions

Drug-demographic (i.e. age, sex, race and ethnicity factors) interactions were not formally evaluated by the Applicant in Study COV05100031.

7.5.4 Drug-Disease Interactions

The safety of repeat doses of Pennsaid (diclofenac sodium topical solution) 2% was not formally evaluated in patients special disease states such as hepatic or renal impairment.

7.5.5 Drug-Drug Interactions

No additional data on drug interactions was obtained from clinical trial, COV05100031 using Pennsaid (diclofenac sodium topical solution) 2%. The Applicant intends to use identical language regarding DDI from the Pennsaid 1.5% topical solution package insert.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No formal human carcinogenicity studies have been conducted with Pennsaid (diclofenac sodium topical solution) 2%.

7.6.2 Human Reproduction and Pregnancy Data

No formal human reproduction and pregnancy studies have been conducted with Pennsaid (diclofenac sodium topical solution) 2%.

7.6.3 Pediatrics and Assessment of Effects on Growth

No formal studies have been conducted with Pennsaid (diclofenac sodium topical solution) 2% in the pediatric population. The Applicant has submitted a Pediatric Waiver based on their rationale that OA does not occur in the pediatric population, which appears reasonable This waiver will be reviewed by PeRC on January 30, 2013.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose
No cases of overdose were reported during clinical development of Pennsaid (diclofenac sodium topical solution) 2% .

Drug Abuse Potential
No formal animal or human abuse potential studies were conducted during clinical development of Pennsaid (diclofenac sodium topical solution) 2% .

Withdrawal/Rebound
No cases of withdrawal or rebound were reported clinical development of Pennsaid (diclofenac sodium topical solution) 2% .

7.7 Additional Submissions / Safety Issues

There were no additional safety submissions (including the 120-day safety update) made by the Applicant.

Two submissions were made in response to queries from the clinical team.

Submission Date	Information Submitted
October 31, 2012	Clarification regarding Table 8 (i.e., Average Weight of Study Drug Administered per Dose Calculated from Dispensed and Returned Bottle Weights) located in Clinical Study Report COV05100031 ,the wide variability of dosing at Weeks 2 and 6 and whether attempts were made to correct the wide variability of dosing among subjects in both treatment groups
January 18, 2013	Clarification regarding the unit of measure associated with the average weight of study drug administered of located in Table 8 (i.e., Average Weight of Study Drug Administered per Dose Calculated from Dispensed and Returned Bottle Weights) of the CSR COV05100031.

The Applicant's responses to both information requests were deemed adequate.

8 Postmarket Experience

Pennsaid (diclofenac sodium topical solution) 2% has not been marketed in either the United States or elsewhere. However, PENNSAID is currently approved and marketed in the United States and worldwide.

The Applicant provided a postmarketing safety summary for approved PENNSAID. The adverse reactions that have been reported during the postapproval use of PENNSAID appear similar to adverse events reported in premarketing controlled clinical trials with PENNSAID.

9 Appendices

9.1 Literature Review/References

]1http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm

2Bhandari M, Smith J, Miller LE, Block JE. Clinical and Economic Burden of Revision Knee Arthoroplasty. Clinical Medicine insights: Arthritis and Musculoskeletal Disorders. 2012;5:89-94.

9.2 Labeling Recommendations

The Division of Medication Error Prevention and Analysis (DMEPA) completed a review of the Applicant's initial proprietary name "PENNSAID (b) (4)". DMEPA determined that the (b) (4) was unnecessary and did not convey the difference between the proposed Pennsaid (diclofenac sodium topical solution) 2% and the currently marketed PENNSAID product. DMEPA's denial of the proprietary name was conveyed to the Applicant during a teleconference on July 26, 2012. Malincrokdt subsequently withdrew the proprietary name review for (b) (4) On December 11, 2012 the Applicant submitted an additional proprietary name review for (b) (4) and DMEPA's review of this name is ongoing.

The proposed Pennsaid (diclofenac sodium topical solution) 2% w/w label is similar to the approved PENNSAID 1.5% with changes in the description of the drug product, dosing, and other clinical studies section.

A preliminary review of the proposed labeling identified the following issues:

(b) (4)

9.3 Advisory Committee Meeting

There was no advisory committee meeting associated with this NDA.

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

/s/

JACQUELINE A SPAULDING
01/28/2013

ELLEN W FIELDS
01/28/2013